Online Document: Active Links
Saved pdf: Active Bookmarks

MUSCULOSKELETAL & CONNECTIVE TISSUE

NEUROLOGY

OBSTETRICS & GYNECOLOGY

OVER THE COUNTER (OTC) & HERBAL MEDICATIONS

Objective, Comparative Drug Information. www.RxFiles.ca

PSYCHIATRY

RESPIRATORY

SMOKING CESSATION

MISCELLANEOUS

INDICES

TOP

Other Online EBM Resources/Links:

EBM Portal Links (SK): http://web.mac.com/malees/Primary_Care_Portal/EBM.html; Evidence Updates service: http://plus.mcmaster.ca/EvidenceUpdates/Default.aspx

General: U of T: http://www.cebm.utoronto.ca/; Oxford: http://www.cebm.net/?o=1011; McMasters: How to teach evidence based clinical practice – Links: http://hsl.mcmaster.ca/ebcp/. Dynamed: *www.ebscohost.com/dynamed/*

User's Guide: UofA, Centre for Health Evidence: http://www.cche.net/usersguides/main.asp; UBC: http://www.ti.ubc.ca/; Grey Literature Searching: http://www.cadth.ca/index.php/en/cadth/products/grey-matters

ScHARR Intro to Evidence Based Practice (Sheffield, UK) http://www.shef.ac.uk/scharr/ir/netting/; BMJ – Clinical Evidence Links: http://clinicalevidence.bmj.com/ceweb/resources/useful_links.jsp; NNTs http://www.thennt.com/

Clinical significance CALCULATORS: UBC: http://spph.ubc.ca/sites/healthcare/files/calc/clinsig.html; Wisconsin: http://intsmain.is.mcw.edu/clincalc/bayes.html. Essential Evidence Plus: http://www.essentialevidenceplus.com/

Dalhousie Katie Clinical Significance Calculator: http://ktcalc.cme.dal.ca/site/login.php

RxFiles – Select Trial Summaries (more available online at www.RxFiles.ca)

Diabetes: Landmark Trials Summary: Glucose: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

Landmark Trials Summary: NON-Glucose: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-DIABETES-Landmark-Trials-Non-Glucose.pdf

ACCORD-ADVANCE Comparison: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-A1C-ACCORD-vs-ADVANCE-COMPARISON.pdf

ACCORD-BP & LIPID: http://www.rxfiles.ca/rxfiles/uploads/documents/ACCORD-BP-Lipid-Trial-Overview.pdf

ACCORD: Glucose http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf

ADVANCE: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-ADVANCE-trial.pdf

AVANDIA & CV risk – Meta-analysis: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Avandia-CV-Meta-Comments.pdf

DREAM: http://www.rxfiles.ca/rxfiles/uploads/documents/Dream-QandA.pdf

RECORD:http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-RECORD-Trial-Summary.pdf

Hypertension: Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/HTNLandmarkHypertensionTrials.pdf

ACCOMPLISH: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-Accomplish.pdf

ALLHAT: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-Update-2003-Final.pdf

ANBP2: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-ANBP2.pdf

ASCOT-BPLA: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-ASCOT.pdf

Trial Summary table - abridged: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-HTN-trial-summary.pdf

HF: CHARM: http://www.rxfiles.ca/rxfiles/uploads/documents/CHARM-Comments.pdf

Hirsutism: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Hirsutism%20Trial%20Summary.pdf

HRT: WHI: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT Post-WHI-2002-Header.pdf

WHI & Age: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-Age-and-the-WHI.pdf ;

WHI & Extras/Perspectives on NNTs, NNHs: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-WHI-Extras-Perspectives.pdf

Lipid: Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid agents-major trials.pdf

& Q&A 2004: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Update-Oct04.pdf

AIM-HIGH: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-AIM-HIGH-nicotinic-acid-Niaspan-trial.pdf

ASCOT-LLA: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-ASCOT.pdf

CARDS: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-CARDS.pdf

ENHANCE: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-ENHANCE trial overview.pdf

IDEAL: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-IDEAL.pdf

JUPITER: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-Jupiter-trial-overview.pdf

PROVE-IT: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Prove-It.pdf

SHARP: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-Sharp-CKD-trial.pdf

SPARCL: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-SPARCL.pdf

Thrombotic (antithrombotics: ASA, clopidogrel, anticoagulants: warfarin) :

ACTIVE-A & ACTIVE-W trials http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf

Antithrombotics Summary Chart:: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf

CHARISMA: http://www.rxfiles.ca/rxfiles/uploads/documents/Charisma-Q&A.pdf

Clopidogrel-PPI drug interaction: http://www.rxfiles.ca/rxfiles/uploads/documents/Clopidogrel-PPI-interaction-QandA.pdf

RE-LY: Dabigatran vs warfarin in Atrial Fibrillation http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf

ROCKET-AF: Rivaroxaban vs warfarin in A Fib: http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf

ARISTOTLE: Apixaban vs warfarin in A Fib: http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE-AF-Apixaban.pdf

MISC.:

Catie-AD: Atypical Antipsychotics in Patients with Alzheimer's http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-CATIE-AD-trial-summary.pdf

Meloxicam: SELECT, MELISSA; *celecoxib* CLASS, *rofecoxib* VIGOR,: http://www.rxfiles.ca/rxfiles/uploads/documents/QandA-Meloxicam-2.pdf

OAB: Darifenacin-Oxybutynin Memory Trial : http://www.rxfiles.ca/rxfiles/uploads/documents/UI-Darifenacin-Kay-Trial-QandA.pdf

RxFiles: Evidence Based Medicine (EBM) Overview - References

[1] Sackett D, Straus S, Richardson WS, Rosenberg, Haynes R. Evidence-Based Medicine: how to practice and teach EBM. Churchill Livinstone. 2000.

[2] Dawes M, Davies P, Gray A, Mant J, Seers K, Snowball. Evidence-based Practice; a primer for health care professionals. Elsevier, 2nd edition 2005.

[3] Allen J. Pharmacist's Letter / Prescriber's Letter. Applying Study Results to Patient Care. June 2005, 21;1-14.

[4] Jadad A, Enkin M. Randomized Controlled Trials: Questions, Answers and Musings 2nd edition. Blackwell Publishing 2007; BMJ Books

[5] Edited by: Geyman J, Deyo R, Ramsey S. Evidence-Based Clinical Practice: Concepts and Approaches. Butterworth Heinemann 2000.

[6] Centre for Evidence Based Medicine (CEBM) Oxford: EBM Tools accessed online 31Jul08 at: http://www.cebm.net/index.aspx?o=1157

[7] Centre for Evidence Based Medicine, University Health Network, Toronto. Critical Appraisal tools; accessed online 31Jul08: http://www.cebm.utoronto.ca/teach/materials/caworksheets.htm

[8] Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995 Feb 1;273(5):408-12. {Compared with trials in which authors reported adequately concealed treatment allocation, trials in which concealment was either inadequate or unclear (did not report or incompletely reported a concealment approach) yielded larger estimates of treatment effects (P < .001). Odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials (adjusted for other aspects of quality). Trials in which participants had been excluded after randomization did not yield larger estimates of effects, but that lack of association may be due to incomplete reporting. Trials that were not double-blind also yielded larger estimates of effects (P = .01), with odds ratios being exaggerated by 17%.}

[9] Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998 Aug 22;352(9128):609-13. {FINDINGS: The quality of trials was low. Masked assessments provided significantly higher scores than unmasked assessments (mean 2.74 [SD 1.10] vs 2.55 [1.20]). Low-quality trials (score < or = 2), compared with high-quality trials (score > 2), were associated with an increased estimate of benefit of 34% (ratio of odds ratios [ROR] 0.66 [95% CI 0.52-0.83]). Trials that used inadequate allocation concealment, compared with those that used adequate methods, were also associated with an increased estimate of benefit (37%; ROR=0.63 [0.45-0.88]). The average treatment benefit was 39% (odds ratio [OR] 0.61 [0.57-0.65]) for all trials, 52% (OR 0.48 [0.43-0.54]) for low-quality trials, and 29% (OR 0.71 [0.65-0.77]) for high-quality trials. Use of all the trial scores as quality weights reduced the effects to 35% (OR 0.65 [0.59-0.71]) and resulted in the least statistical heterogeneity. INTERPRETATION: Studies of low methodological quality in which the estimate of quality is incorporated into the meta-analyses can alter the interpretation of the benefit of intervention, whether a scale or component approach is used in the assessment of trial quality.}

[10] Fletcher J. Subgroup analyses: how to avoid being misled. BMJ. 2007 Jul 14;335(7610):96-7.

[11] Centre for Evidence Based Medicine (CEBM) Oxford: EBM Tools accessed online 31Jul08 at: http://www.cebm.net/index.aspx?o=1039

[12] Oleckno WA. Essential Epidemiology Principles and Applications. Long Grove IL: Waveland Press Inc, 2002. (page 108)

[13] http://www.cochrane.org/ ; http://www.cfp.ca/cgi/content/full/55/11/1155?etoc

[14] http://www.campbellcollaboration.org/ ; http://www.campbellcollaboration.org/library.php

[15] Centre for Evidence Based Medicine (CEBM) Oxford: EBM Tools accessed online 31Jul08 at: http://www.cebm.net/index.aspx?o=1025

[16] Barratt A, Wyer PC, Hatala R, McGinn T, Dans AL, Keitz S, Moyer V, For GG; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ. 2004 Aug 17;171(4):353-8.

[17] Bandolier; Number Needed to Treat. Accessed online 31Jul08 at: http://www.medicine.ox.ac.uk/bandolier/band59/NNT1.html

[18] Finlay A. McAlister. The "number needed to treat" turns 20 — and continues to be used and misused. CMAJ 2008; 179: 549-553. http://www.cmaj.ca/cgi/content/full/179/6/549

[19] James P McCormack. NNT misses the mark on baseline risks. Electronic Letter, CMAJ online. (17 September 2008) http://www.cmaj.ca/cgi/eletters/179/6/549#20357

[20] Centre for Evidence Based Medicine (CEBM) Oxford: NNT calculator tool. Accessed online 31Jul08 at http://www.cebm.net/index.aspx?o=1044 .

[21] Montori VM, Kleinbart J, Newman TB, Keitz S, Wyer PC, Moyer V, Guyatt G; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 2. Measures of precision (confidence intervals). CMAJ. 2004 Sep 14;171(6):611-5.

[22] Hatala R, Keitz S, Wyer P, Guyatt G; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results. CMAJ. 2005 Mar 1;172(5):661-5.

[23] Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. 2005 Aug 6;331(7512):321-7. http://www.bmj.com/cgi/reprint/331/7512/321 {A systematic review by Kaduszkiewicz and colleagues (p 321) included 22 double blind randomised controlled trials with the follow-up ranging from six weeks to three years, but the trials scored poorly on a predefined checklist of criteria of methodological quality. Further, the outcomes measuring cognition did show beneficial effects of cholinesterase inhibitors, but these effects were minimal (ranging from 1.5 points to 3.9 points on a 70 point Alzheimer's disease assessment scale).}

[24] Regier L. RxFiles Trial Summary: Darifenacin (ENABLEX) vs Oxybutynin ER extended release (DITROPAN XL) vs Placebo: Effects On Memory / Cognitive Impairment. Accessed at: http://www.rxfiles.ca/rxfiles/uploads/documents/UI-Darifenacin-Kay-Trial-QandA.pdf

[25] Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. BMJ. 2007 Apr 28;334(7599):882-4.

[26] Montori VM. Treat the Target or Treat the Patient. Aust Prescr 2011;34:94-5. Accessed online Aug 2, 2011 at http://www.australianprescriber.com/magazine/34/4/94/5.

[27] Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing treatments: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):848-56. Summary for patients in: Ann Intern Med. 2007 Jun 19;146(12):I50.

[28] Anonymous. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and the risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

[29] Regier L. HRT in Light of the WHI – Data in Perspective. Sept 2002. Available online at: http://www.rxfiles.ca/rxfiles/uploads/documents/HRT-WHI-Extras-Perspectives.pdf

[30] Ross JS, Mulvey GK, Hines EM, et al. Trial publication after registration in ClinicalTrials.Gov: A cross-sectional analysis. PLoS Med 2009; DOI:10.1371/journal.pmed.1000144.

[31] Mathieu S, Boutron I, Moher D, et al. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA 2009; 302: 977-984.

[32] McNutt Robert A.; Livingston Edward H. Evidence-Based Medicine Requires Appropriate Clinical Context.JAMA. 2010;303(5):454-455.

Reviewer Acknowledgments: G Michael Allen MD, CCFP, Associate Professor, Director of EBM, Dept of Fam Med, U of A. Michael Allen MD, Associate Professor, Director Evidence-based Programs, Dalhousie University CME, Pam Maclean-Veysey, Drug Eval Unit, Halifax. Derek Jorgenson, PharmD, U of S. Darcy Lamb, C of Pharmacy, U of S. David Blackburn, C of Pharmacy, U of S. G. Turcotte MD, FM/EBM teaching, Gatineau, Quebec.

TOP

2009 Canadian -10yr risk of Cardiovascular (CVD) disease (based on Framingham Heart Study).

RISK*	MEN									
AGE	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
Age points	0	2	5	7	8	10	11	12 or 13	14	15
TOTAL CHOL										
<4.1 mmol/l						0				
4.1-5.2						1				
5.2-6.2						2				
6.2-7.2						3				
≥ 7.2						4				
HDL mmol/l	<0.9		0.9-1.2		1.2-1.3	1.3-1.6		≥1.6		
	+2		+1		0	-1		-2		
SYSTOLIC BP mmHg	Not Treated					Treated				
	<120	-2				<120	0			
	120-129	0				120-129	2			
	130-139	1				130-139	3			
	140-159	2				140-159	4			
	≥160	3				≥160	5			
SMOKER										
No						0				
Yes						4				
Diabetic										
No						0				
Yes						3				
TOTAL POINTS										

Guidelines use "13" but this appears to be an error; should be "12" .based on reference.

POINTS	MEN: actual 10yr CVD risk %												
<3	-2-1	2-3	4-5	6	7	8	9	10	11	12	13-14	15-16	>17
<1% (10yr % Risk→)	1	2	3	4	5	6	7	9	11	13	15-18	21-25	>29

WOMEN										
30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
0	2	4	5	7	8	9	10	11	12
				0					
				1					
				3					
				4					
				5					
<0.9		0.9-1.2		1.2-1.3		1.3-1.6		≥1.6	
+2		+1		0		-1		-2	
Not Treated						Treated			
<120	-3					<120	-1		
120-129	0					120-129	2		
130-139	1					130-139	3		
140-149	2					140-149	5		
150-159	4					150-159	6		
>160	5					>160	7		
				0					
				3					
				0					
				4					

POINTS	WOMEN actual 10yr CVD risk %												
<-2	-1-2	3-5	6-7	8-9	10	11	12	13	14-15	16-17	18-20	≥21
<1% (10yr % Risk→)	1	2	3	4-5	6	7	8	10	11-13	15-18	21-27	≥30

Key: Low risk <10% Moderate risk 10-19% High risk ≥ 20%

*Risk assessments based on Framingham data; other risk factors such as **family history** of CAD (2x CAD 10yr risk %=actual risk %), physical inactivity, obesity & left ventricular hypertrophy should also be considered.

Patients with **High risk→ ALL pts with CAD,CVD,PAD; most with DIABETES ♂>45yr,♀>50yr, younger with risk factors & chronic renal dx GFR <30ml/min** regardless of risk score.

Cardiac Risk Tools: 1) www.statcoder.com 2) www.nhlbi.nih.gov/guidelines **3) http://www.framinghamheartstudy.org/**

4) Reynold Risk Score (also incorporates family cardiac history & CRP results, but is based on non-diabetic individuals) **http://www.reynoldsriskscore.org/**

5) Cardiovascular Life Expectancy Model Risk Score (also incorporates family cardiac history) **http://www.chiprehab.com/**

For suggested lipid targets, see bottom of page 15 on the RxFiles Lipid chart.

Comparative 10yr CAD % risks by AGE		30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74yr
Males	Low risk % →	2%	3	4	4	6	7	9	11	14
	Average risk % →	3%	5	7	11	14	16	21	25	30
Females	Low risk % →	<1%	<1	2	3	5	7	8	8	8
	Average risk % →	<1%	<1	2	5	8	12	12	13	14

[1] Jackson R. Updated New Zealand cardiovascular disease risk-benefit prediction guide. BMJ 2000;320:709-10.

[2] Campbell NRC, Drouin D, Feldman RD, for the Canadian Hypertension Recommendations Working Group. The 2001 Canadian hypertension recommendations take-home messages. CMAJ 2002:167(6):661-8.

[3] Canadian Hypertension Society -2011 Canadian Hypertension Recommendations Working Group-downloadable Summary & Slides; www.hypertension.ca
Canadian Hypertension Education Program. 2011 CHEP recommendations for the management of hypertension.
http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf
ACCF American College of Cardiology Foundation / AHA American Heart Association 2011 – Hypertension in the Elderly: http://circ.ahajournals.org/cgi/reprint/CIR.0b013e31821daaf6

[4] Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol. 2009 Oct;25(10):567-79.
McPherson R, Frohlich J, Fodor G, Genest J. Canadian 2006 Cardiovascular Society position statement -- Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol. 2006 Sep;22(11):913-27. (Genest J, Frohlich J, Fodor G, McPherson R; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the Canadian 2003 update. CMAJ. 2003 Oct 28;169(9):921-4. http://www.cmaj.ca/cgi/data/169/9/921/DC1/1 Full Report.)

[5] Canadian 2008 Guidelines (Sept 2008): http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
Canadian 2003 Diabetes Guidelines http://www.diabetes.ca/cpg2003/download.aspx (Meltzer S, Leiter L, Daneman D, et al 1998. Clinical practice guidelines for the management of diabetes in Canada. CMAJ 1998;159 (8 Suppl).)

TOP

[6] Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc. 2003 May;51(5 Suppl Guidelines):S265-80.

Additonal articles of interest for CV Risk:

Adabag S, Lopez F, Alonso A, et al. Risk of sudden cardiac death in **obese** individuals: The Atherosclerosis Risk in Communities (ARIC) study. Heart Rhythm Society 2012 Scientific Sessions; May 9, 2012.

Ahmadi N, Hajsadeghi F, Mirshkarlo HB, et al. **Post-traumatic stress disorder, coronary atherosclerosis, and mortality**. Am J Cardiol. 2011 Jul 1;108(1):29-33.

Ahmed HM, Blaha MJ, Nasir K, et al. Effects of **Physical Activity** on Cardiovascular Disease. Am J Cardiol. 2011 Oct 17.

Allan, G. Michael, Mallery, Laurie, Ivers, Noah. Treating hypertension in the **very elderly**. Can Fam Physician 2010 56: 1141.

Allen N, Berry J, Ning H, et al. **Impact of blood pressure** and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease the cardiovascular lifetime risk pooling project. Circulation 2012;

Alpert JS. Cardiology **patient page**. What you need to know if you have **coronary artery disease**. Circulation. 2011 Aug 9;124(6):e176-8.

Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Et al. **Ankle brachial index combined with Framingham** Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008 Jul 9;300(2):197-208. Measurement of the ABI may improve the accuracy of cardiovascular risk prediction beyond the FRS.

Arbab-Zadeh A, Miller JM, Rochitte CE, et al. Diagnostic accuracy of **computed tomography coronary angiography** according to pre-test probability of coronary artery disease and severity of coronary arterial calcification: The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) international multicenter

Armstrong AW, Harskamp CT, Ledo L et al. Coronary Artery Disease in Patients With **Psoriasis** Referred for Coronary Angiography. Am J Cardiol. 2012 Jan 3.

Arsenault, Benoit J., Lemieux, Isabelle, Despres, Jean-Pierre, et al. The **hypertriglyceridemic-waist phenotype** and the risk of coronary artery disease: results from the EPIC-Norfolk Prospective Population Study. CMAJ 2010 182: 1427-1432.

Artinian NT, Fletcher G, Mozaffarian D, et al on behalf of the American Heart Association (AHA) Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote **physical activity and dietary lifestyle** changes for cardiovascular risk factor reduction in adults; a scientific statement from the American Heart Association. Circulation 2010; DOI: 10.1161/CIR.0b013e3181e8edf1.

Ashley EA, Hershberger RE, Caleshu C, et al. **Genetics and cardiovascular disease**. A policy statement from the American Heart Association. Circulation 2012.

Auer R, Bauer DC, Marques-Vidal P, et al. **Association of major and minor ECG abnormalities** with coronary heart disease events.JAMA 2012; 307:1497-1505.

Baggish, Aaron L. Hutter, Jr Adolph M.., Wang, Francis Et al. Cardiovascular Screening in College **Athletes** With and Without Electrocardiography: A Cross-sectional Study. Ann Intern Med March 2, 2010 152:269-275

Bandosz P, O'Flaherty M, Drygas W, et al. **Decline in mortality from coronary heart disease in Poland** after socioeconomic transformation: modelling study. BMJ 2012;344:d8136.

Blaha M, Budoff M, DeFilippis A, et al. Association between **C-reactive protein**, **coronary artery calcium**, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011; 378: 684-692.

Baker PRA, Francis DP, Soares J, Weightman AL, Foster C. **Community wide interventions for increasing physical activity**. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD008366. DOI: 10.1002/14651858.CD008366.pub2.

Bangalore S, Kumar S, Lobach I, et al. **Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose**: Observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011.

Baron SL, Hein MJ, Lehman E et al. Body Mass Index, Playing Position, Race, and the Cardiovascular Mortality of Retired **Professional Football Players**. (NFL) Am J Cardiol. 2012 Jan 13.

Barton P, Andronis L, Briggs A, et al. Effectiveness and cost effectiveness of **cardiovascular disease prevention in whole populations**: modelling study. BMJ. 2011 Jul 28;343:d4044.

Bhaskaran K, Hajat S, Armstrong B, Haines A, Herrett E, Wilkinson P, et al. The effects of hourly differences in **air pollution** on the risk of myocardial infarction: case crossover analysis of the MINAP database. BMJ 2011;343:d5531.

Bayturan Ozgur; Tuzcu E. Murat; Lavoie Andrea; et al. The **Metabolic Syndrome**, Its **Component Risk Factors**, and Progression of Coronary Atherosclerosis. *Arch Intern Med*. 2010;170(5):478-484.

Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, et al.; the **HYVET** Study Group. Treatment of Hypertension in Patients 80 Years of Age or Older.N Engl J Med. 2008 Mar 31; [Epub ahead of print].

Berry JD et al. **Lifetime risks** of cardiovascular disease. N Engl J Med 2012 Jan 26; 366:321.

Bhatt Deepak L.; Eagle Kim A.; Ohman E. Magnus; et al. for the **REACH** Registry Investigators. Comparative Determinants of 4-Year Cardiovascular Event **Rates in Stable Outpatients** at Risk of or With Atherothrombosis. JAMA. 2010;0(2010):jama.2010.1322.

Bibbins-Domingo, Kirsten, Chertow, Glenn M., Coxson, Pamela G., et al. Projected Effect of Dietary **Salt Reductions** on Future Cardiovascular Disease. N Engl J Med 2010 0: NEJMoa0907355.

Blumenthal James A.; Babyak Michael A.; Hinderliter Alan; et al. Effects of the **DASH Diet** Alone and in Combination With Exercise and Weight Loss on Blood Pressure and Cardiovascular Biomarkers in Men and Women With High Blood Pressure: The **ENCORE** Study. *Arch Intern Med*. 2010;170(2):126-135.

Bluemke DA, Achenbach S, Budoff M, et al. Noninvasive Coronary Artery Imaging. **Magnetic Resonance Angiography and Multidetector Computed Tomography Angiography**. A Scientific Statement From the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. Circulation. 2008 Jun 27. [Epub ahead of print]

Bouchard C, Blair SN, Church TS, et al. **Adverse metabolic response to regular exercise**: Is it a rare or common occurrence? PLoS ONE 2012.

Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term **androgen suppression for prostate cancer** with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066-73.

Bonow, Robert O. Should **Coronary Calcium Screening** Be Used in Cardiovascular Prevention Strategies? N Engl J Med 2009 361: 990-997.

Bosner, Stefan, Haasenritter, Jorg, Becker, Annette, et al. Ruling out coronary artery disease in **primary care**: development and validation of a **simple prediction rule**. CMAJ 2010 0: cmaj.100212.

Brett T, Arnold-Reed D, Phan C, et al. The **Fremantle** Primary Prevention Study: a multicentre randomised trial of **absolute cardiovascular risk reduction**. Br J Gen Pract. 2012;e22-28.

Brewer N, Wright CS, Travier N, Cunningham CW, Hornell J, Pearce N, Jeffreys M. A New Zealand linkage study examining the associations between A1C concentration and mortality. Diabetes Care. 2008 Jun;31(6):1144-9. Epub 2008 Feb 25. This is the largest study to date of **A1C** levels and subsequent mortality risk. It confirms previous findings that A1C levels are strongly associated with subsequent mortality in both men and women without a prior diabetes diagnosis.

Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart. 2006 Dec;92(12):1752-9. Epub 2006 Apr 18. For CHD, the predicted to observed ratios ranged from an underprediction of 0.43 (95% CI 0.27 to 0.67) in a high-risk population to an overprediction of 2.87 (95% CI 1.91 to 4.31) in a lower-risk population.

Buckley D. I., Fu R., Freeman M., et al. **C-Reactive Protein** as a Risk Factor for Coronary Heart Disease: A Systematic Review and Meta-analyses for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; 483-495.

Buitrago-Lopez A, Sanderson J, Johnson L, et al. **Chocolate consumption** and cardiometabolic disorders: systematic review and meta-analysis. BMJ 2011; DOI:10.1136/bmj.d4488.

Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is **diabetes** a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009;26:142-8. {InfoPOEMs Apr09: This meta-analysis found no evidence to support the contention that diabetes alone is a coronary heart disease (CHD) risk equivalent to a history of prior myocardial infarction (MI). The blanket use of aspirin and statins for patients with type 2 diabetes, regardless of their lipid levels, is not supported by the evidence. (LOE = 2a)}

Byberg L, Melhus H, et al. Total mortality after changes in leisure time **physical activity** in 50 year old men: 35 year follow-up of population based cohort. BMJ. 2009 Mar 5;338:b688. doi: 10.1136/bmj.b688. Increased physical activity in middle age is eventually followed by a reduction in mortality to the same level as seen among men with constantly high physical activity. This reduction is comparable with that associated with smoking cessation.

Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I et al. Cardiovascular mortality in **women with obstructive sleep apnea** with or without continuous positive airway pressure treatment: a cohort study. Ann Intern Med. 2012 Jan 17;156(2):115-22.

Canto JG, Kiefe CI, Roger WJ, et al; NRMI Investigators. **Number of coronary heart disease risk factors and mortality** in patients with first myocardial infarction. JAMA. 2011;306(19):2120-2127.

Capewell S, O'Flaherty M. Rapid **mortality falls after risk-factor changes** in populations. Lancet. 2011 Mar 15.

Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. **Sleep duration predicts cardiovascular outcomes**: a systematic review and meta-analysis of prospective studies. Eur Heart J 2011; online 7 February.

Cappuccio FP, Capewell S, Lincoln P, McPherson K. Policy options to reduce population **salt** intake. BMJ 2011; DOI:10.1136/bmj.d4995.

CDC Sep/11 **Million Hearts**: Strategies to Reduce the Prevalence of Leading Cardiovascular Disease Risk Factors --- United States, 2011 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm60e0913a1.htm?s_cid=mm60e0913a1_x

CDC. Feb 2012 Vital Signs: Food Categories Contributing the Most to **Sodium Consumption** — United States, 2007–2008. Early Release. February 7, 2012 / 61(Early Release);1-7. http://www.cdc.gov/mmwr/pdf/wk/mm61e0207.pdf
Overall, the mean daily sodium consumption (excluding table salt) was 3266 mg, well above recommendations to keep intake below 2300 mg. The top 10 food categories contributing to sodium consumption were, in descending order: bread and rol

TOP

poultry, soups, sandwiches, cheese, pasta mixed dishes, meat mixed dishes, and savory snacks.
Chamnan Parinya, Simmons Rebecca K, Khaw Kay-Tee, et al. Estimating the population impact of screening strategies for identifying and treating people at high risk of cardiovascular disease: modelling study. BMJ 2010;340:c1693, (Pub 25 April 2010)
Chamnan P, Simmons RK, Hori H, Sharp S, Khaw KT, Wareham NJ, Griffin SJ. A simple risk score using routine data for predicting cardiovascular disease in primary care. Br J Gen Pract. 2010 Aug;60(577):e327-34.
Charchar FJ, Bloomer LDS, Barnes TA, et al. Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. Lancet 2012; published online Feb 9.
Chatterjee A, Harris SB, Leiter LA, et al. Managing cardiometabolic risk in primary care: summary of the 2011 consensus statement. Can Fam Physician. 2012 Apr;58(4):389-93, e196-201.
Chen L, Caballero B, Mitchell DC, et al. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure. A prospective study among United States adults. Circulation 2010.
Chen ST, Maruthur NM, Appel LJ. The effect of dietary patterns on estimated coronary heart disease risk: results from the Dietary Approaches to Stop Hypertension (DASH) trial. Circ Cardiovasc Qual Outcomes. 2010;3:484 – 489.
Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation. 2011 Nov 29;124(22):2423-32, 1-8.
Chiuve SE, Fung TT, Rexrode KM, et al. Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women. JAMA 2011; 306:62-69.
Chou R, Arora B, Dana T, Fu R, et al. Screening asymptomatic adults with resting or exercise electrocardiography (ECG): a review of the evidence for the U.S. Preventive Services Task Force. (USPSTF) Ann Intern Med. 2011; 155:375-85.
Chow CK, Pell AC, Walker A, O'Dowd C, Dominiczak AF, Pell JP. Families of patients with premature coronary heart disease: an obvious but neglected target for primary prevention. BMJ. 2007 Sep 8;335(7618):481-5.
Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation. 2010 Feb 16;121(6):750-8.
Chow CK, Islam S, Bautista L, et al. Parental history and myocardial infarction risk across the world: The INTERHEART study. J Am Coll Cardiol 2011; 57:619-627.
Chow BJ, Freeman MR, Bowen JM, et al. Ontario Multidetector Computed Tomographic Coronary Angiography Study: Field Evaluation of Diagnostic Accuracy. Arch Intern Med. 2011 Mar 14.
Christoffersen M, Frikke-Schmidt R, Schnohr P, Jensen GB, Nordestgaard BG, Tybjærg-Hansen A. Xanthelasmata, arcus corneae, and ischaemic vascular disease and death in general population: prospective cohort study. BMJ 2011;343:d5497
Clase CM, Gao P, Tobe SW, et al. on behalf of the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in Angiotensin-Converting-Enzyme-Inhibitor Intolerant Subjects with Cardiovascular Disease). Estimated Glomerular Filtration Rate and Albuminuria as Predictors of Outcomes in Patients With High Cardiovascular Risk: A Cohort Study. Ann Intern Med. 2011 Mar 1;154(5):310-318.
Clarke R, Peden JF, Hopewell JC, et al. PROCARDIS Consortium. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009 Dec 24;361(26):2518-28.
Clarke R, Bennett DA, Parish S, et al. Homocysteine and coronary heart disease: meta-analysis of MTHFR case-control studies, avoiding publication bias. PLoS Med 2012
Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006 Mar 23;354(12):1264-72. These data indicate that moderate lifelong reduction in the plasma level of LDL cholesterol is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non-lipid-related cardiovascular risk factors.
Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. BMJ. 2009 Jul 7;339:b2584. doi: 10.1136/bmj.b2584.
Collins GS, Altman DG. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. BMJ. 2010 May 13;340:c2442. doi: 10.1136/bmj.c2442.
Collins GS, Altman DG. External validation of QDSCORE((R)) for predicting the 10-year risk of developing Type 2 diabetes. Diabet Med. 2011 May;28(5):599-607. doi: 10.1111/j.1464-5491.2011.03237.x
Conen David, Chae Claudia U., Glynn Robert J., et al. Risk of Death and Cardiovascular Events in Initially Healthy Women With New-Onset Atrial Fibrillation. JAMA. 2011;305(20):2080-2087.doi:10.1001/jama.2011.659
Cook NR, Obarzanek E, Cutler JA, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK; Trials of Hypertension Prevention Collaborative Research Group. Joint effects of sodium and potassium intake on subsequent Cardiovascular disease: the Trials of Hypertension Prevention follow-up study. Arch Intern Med. 2009 Jan 12;169(1):32-40. A higher sodium to potassium excretion ratio is associated with increased risk of subsequent CVD, with an effect stronger than that of sodium or potassium alone.
Cook NR, Paynter NP, Eaton CB, et al. Comparison of the Framingham and Reynolds Risk Scores for Global Cardiovascular Risk Prediction in the Multiethnic Women`s Health Initiative. Circulation. 2012 Mar 7.
Cooney Marie Therese, Dudina Alexandra, D'Agostino Ralph, et al. Cardiovascular Risk-Estimation Systems in Primary Prevention: Do They Differ? Do They Make a Difference? Can We See the Future? Circulation 122: 300-310.
Cooper Rachel, Kuh Diana, Hardy Rebecca, Mortality Review Group . Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 341:doi:10.1136/bmj.c4467 (Published 9 September 2010).
Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a Collaborative meta-analysis. Lancet. 2010 Jun 12;375(9731):2073-81.
Crowson CS, Matteson EL, Roger VL, et al. Usefulness of Risk Scores to Estimate the Risk of Cardiovascular Disease in Patients With Rheumatoid Arthritis. Am J Cardiol. 2012 Apr 20.
Danaei G, Finucane MM, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. Lancet 2011.
Daniels SR, Pratt CA, Hayman LL. Reduction of risk for cardiovascular disease in children and adolescents. Circulation. 2011 Oct 11;124(15):1673-86.
De Caterina Raffaele. n–3 Fatty Acids in Cardiovascular Disease. N Engl J Med 2011; 364:2439-2450.
de Gonzalez Amy Berrington, Hartge Patricia, Cerhan James R., et al. Body-Mass Index and Mortality among 1.46 Million White Adults. N Engl J Med 2010; 363:2211-2219.
de Koning L, Malik VS, Kellogg MD et al. Sweetened beverage consumption, incident coronary heart disease and biomarkers of risk in men. Circulation 2012; DOI: 10.1161/CIRCULATIONAHA.111.067017
de Lemos JA., Drazner MH., Omland T, et al. Association of Troponin T Detected With a Highly Sensitive Assay and Cardiac Structure and Mortality Risk in the General Population. JAMA. 2010;304(22):2503-2512.
de Oliveira C, Watt R, Hamer M. Toothbrushing, inflammation, and risk of cardiovascular disease: results from Scottish Health Survey. BMJ. 2010 May 27;340:c2451. doi: 10.1136/bmj.c2451.
Deo Rajat; Vittinghoff Eric; Lin Feng; et al. Risk Factor and Prediction Modeling for Sudden Cardiac Death in Women With Coronary Artery Disease. Arch Intern Med. 2011;0(2011):archinternmed.2011.328.
De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343(8911):1454-59.
De Ruijter W, et al. Use of Framingham risk score and new biomarkers (homocysteine) to predict cardiovascular mortality in older people: population-based observational cohort study. BMJ 2009; DOI: 10.1136/bmj.a3083.
Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008; 358:1336-1345.
Di Angelantonio Emanuele, Chowdhury Rajiv, Sarwar Nadeem, et al. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. BMJ 341:doi:10.1136/bmj.c4986 (30 Sept 2010).
Dietary Guidelines for Americans (DGA) 2010. Full Guideline: http://www.health.gov/dietaryguidelines/dga2010/DietaryGuidelines2010.pdf, Summary: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/ExecSumm.pdf
Do R, Xie C, Zhang X, et al. INTERHEART investigators. The Effect of Chromosome 9p21 Variants on Cardiovascular Disease May Be Modified by Dietary Intake: Evidence from a Case/Control and a Prospective Study. PLoS Med. 2011 Oct;9(10):e1001106.
Dong JY, Zhang YH, Wang P, Qin LQ. Meta-analysis of dietary glycemic load and glycemic index in relation to risk of coronary heart disease. Am J Cardiol. 2012 Jun 1;109(11):1608-13.
Dong C, Rundek T, Wright CB, et al. Ideal Cardiovascular Health Predicts Lower Risks of Myocardial Infarction, Stroke, and Vascular Death across Whites, Blacks and Hispanics: the Northern Manhattan Study. Circulation. 2012 May 22.
Drozda J. Jr., Messer JV, Spertus J, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. J Am Coll Cardiol 2011;58:xxx–xxx. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.05.002v1.pdf
Dumurgier Julien, Elbaz Alexis, , et al. **Slow walking speed** and cardiovascular death in well functioning older adults: prospective cohort study. BMJ 2009;339:b4460, doi: 10.1136/bmj.b4460 (Published 10 November 2009).
Ebrahim S, Taylor F, Ward K, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD001561. DOI: 10.1002/14651858.CD001561.pub3. Interventions using counselling and education aimed at behaviour change do not reduce total or CHD mortality or clinical events in general populations but may be effective in reducing mortality in high-risk hypertensive and diabetic populations. Risk factor declines were modest but owing to marked unexplained heterogeneity between trials, the pooled estimates are of dubious validity. Evidence suggests that health promotion interventions have limited use in general populations.
Ekelund U, Luan J, Sherar LB, et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. JAMA 2012; 307:704-712.
Elkind MS, Luna JM, Moon YP, Liu KM, Spitalnik SL, Paik MC, Sacco RL. High-sensitivity C-reactive protein predicts mortality but not stroke: The Northern Manhattan Study. Neurology. 2009 Oct 20;73(16):1300-7.
Elizabeth Dunford MPH, Jacqueline Webster PhD, Mark Woodward PhD, et al. The variability of reported salt levels in fast foods across six countries: Opportunities for salt reduction. CMAJ 2012

TOP

Elliott P, Chambers JC, Zhang W, et al. Genetic Loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA. 2009 Jul 1;302(1):37-48.
Elsayed EF, et al. Waist-to-hip ratio, body mass index, and subsequent kidney disease and death. Am J Kidney Dis. 2008 Jul;52(1):29-38. Epub 2008 May 29. WHR, but not BMI, is associated with incident CKD and mortality. Assessment of CKD risk should use WHR rather than BMI as an anthropomorphic measure of obesity.
Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke and mortality: an individual participant meta-analysis. Lancet 2009; DOI:10.1016/S0140-6736(09)61717-7.
Emerging Risk Factors Collaboration, Diabetes mellitus, fasting blood glucose concentration, & risk of vascular disease: a collaborative meta-analysis of 102 prospective studies, Lancet, Volume 375, Issue 9733, 26 June 2010-2 July 2010, Pages 2215-2222.
Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies.Lancet 2011;online Mar11.DOI:10.1016/S0140-6736(11)60105-0.
Esposito K, Maiorino MI, Ciotola M, Di Palo C, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med* 2009;151(5):306-14.
Fang J, Shaw KM, Keenan NL, Centers for Disease Control and Prevention. Prevalence of coronary heart disease—United States, 2006-2010. MMWR Morb Mortal Wkly Rep 2011; 60:1377-1381.
Farzadfar F, Finucane MM, Danaei G, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 2011.
Ferket Bart S.; Colkesen Ersen B.; Visser Jacob J.; et al. Systematic Review of Guidelines on Cardiovascular Risk Assessment: Which Recommendations Should Clinicians Follow for a Cardiovascular Health Check? *Arch Intern Med*. 2010;170(1):27-40.
Fihn SD, Bucher JB, McDonell M, et al. Collaborative care intervention for stable ischemic heart disease. Arch Intern Med. 2011 Sep 12;171(16):1471-9.
Finucane MM, Stevens GA, Cowan MJ. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011.
Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Ann Intern Med. 2010 Jan 5;152(1):26-35.
Ford ES. Trends in mortality from all causes and cardiovascular disease among hypertensive and nonhypertensive adults in the United States. Circulation. 2011 Apr 26;123(16):1737-44.
Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. Circulation 2012
Fradley MG, Larson MG, Cheng S, et al. Reference Limits for N-Terminal-pro-B-Type Natriuretic Peptide in Healthy Individuals (from the Framingham Heart Study). Am J Cardiol. 2011 Aug 23.
Freedman ND, Park Y, Abnet CC, et al. Association of coffee drinking with total and cause-specific mortality. N Engl J Med. 2012 May 17;366(20):1891-904.
Fulton Janet E.; Simons-Morton Denise G.; Galuka Deborah A. Physical Activity: An Investment That Pays Multiple Health Dividends: Comment on "Combined Effects of Cardiorespiratory Fitness, Not Smoking, and Normal Waist Girth on Morbidity and Mortality in Men," "Physical Activity and Survival in Male Colorectal Cancer Survival," "Effects of a Television Viewing Reduction on Energy Intake and Expenditure in Overweight and Obese Adults," and "Physical Activity and Rapid Decline in Kidney Function Among Older Adults". Arch Intern Med. 2009;169(22):2124-2127.
Fung Teresa T., van Dam Rob M., Hankinson, Susan E. Low-Carbohydrate Diets and All-Cause and Cause-Specific Mortality: Two Cohort Studies. *Ann Intern Med* September 7, 2010 153:289-298.
Galan P, Kesse-Guyot E, Czernichow S, et al. , for the SU.FOL.OM3 Collaborative Group. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ 341:doi:10.1136/bmj.c6273 (29 Nov 2010).
García-Almagro FJ, Gimeno JR, Villegas M, et al. Prognostic value of the Thrombolysis in Myocardial Infarction risk score in a unselected population with chest pain. Construction of a new predictive model. Am J Emerg Med. 2008 May;26(4):439-45. In this developmental study, a modified Thrombolysis in Myocardial Infarction (TIMI) risk score was better at predicting coronary events 6 months after patients present with chest pain suspected to be ischemic in origin. Since models generally perform better in developmental studies than in subsequent testing, the new score needs independent validation. (LOE = 2b-)
Gardener H, Rundek T, Wright CB, Elkind MSV, Sacco RL. Dietary sodium and risk of stroke in the Northern Manhattan Study. Stroke. 2012;43:1200 –1205.
Garovic VD, Bailey KR, Boerwinkle E, et al. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. J Hypertens. 2010 Jan 16. [Epub ahead of print]
Gaziano TA, Young CR, Fitzmaurice G, et al. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. Lancet. 2008 Mar 15;371(9616):923-31. Cardiovascular prediction models that do not require laboratory testing perform as well as models that use laboratory testing. (LOE = 2b)
Gogebakan O, Kohl A, Osterhoff MA, et al. Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the Diet, Obesity, and Genes (DiOGenes) study, a randomized controlled trial. Circulation. 2011;124:2829 –2838.
Goel K, Lennon RJ, Tilbury RT, et al. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. Circulation. 2011 May 31;123(21):2344-52.
Gore FM, Bloem PJN, Patton GC, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. Lancet 2011; published online June 7. DOI:10.1016/S0140-6736(11)60512-6.
Gordon-Larsen P, Boone-Heinomen J, Sidney S, et al. Active commuting and cardiovascular disease risk. Arch Intern Med 2009; 169: 1216-1223.
Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database of Systematic Reviews 2011, Issue 11. Art. No.: CD004022. DOI: 10.1002/14651858.CD004022.pub3. Sodium reduction resulted in a 1% decrease in blood pressure in normotensives, a 3.5% decrease in hypertensives, a significant increase in plasma renin, plasma aldosterone, plasma adrenaline and plasma noradrenaline, a 2.5% increase in cholesterol, and a 7% increase in triglyceride. In general, these effects were stable in studies lasting for 2 weeks or more.
Gray L, Lee I-M, Sesso HD, Batty GD. Blood pressure in early adulthood, hypertension in middle age, and future cardiovascular disease mortality: HAHS (Harvard Alumni Health Study). J Am Coll Cardiol 2011; 58:2396-2403.
Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA Guideline: Assessment of Cardiovascular Risk in Asymptomatic Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Dec 14;56(25):e50-e103. http://content.onlinejacc.org/cgi/reprint/56/25/e50.pdf
Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet. 2011 Dec 22.
Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among US adults with and without diabetes between 1997 and 2006. Diabetes Care 2012; 35:1252-1257.
Grunwald JE, Ying GS, Maguire M, et al. Association Between Retinopathy and Cardiovascular Disease in Patients With Chronic Kidney Disease (from the Chronic Renal Insufficiency Cohort [CRIC] Study). Am J Cardiol. 2012 Apr 18.
Guallar-Castillón P, Rodriguez-Artalejo F, Lopez-Garcia E, et al. Consumption of fried foods and risk of coronary heart disease: Spanish cohort of the European Prospective Investigation into Cancer and Nutrition study. BMJ 2012;344;e363.
Gulliksson Mats; Burell Grundy SM, Barlow CE, Farrell SW, et al. Cardiorespiratory Fitness and Metabolic Risk. Am J Cardiol. 2012 Jan 3.
Gunilla; Vessby Bengt; et al. Randomized Controlled Trial of Cognitive Behavioral Therapy vs Standard Treatment to Prevent Recurrent Cardiovascular Events in Patients With Coronary Heart Disease: Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM). *Arch Intern Med*. 2011;171(2):134-140.
Gunderson EP, Jacobs DR Jr, Chiang V, et al. Duration of Lactation and Incidence of the Metabolic Syndrome in Women of Reproductive Age According to Gestational Diabetes Mellitus Status: A 20-Year Prospective Study in CARDIA--The Coronary Artery Risk Development in Young Adults Study. Diabetes. 2009 Dec 3.
Hackam DG, Shojania KG, Spence JD, et al. Influence of Noninvasive Cardiovascular Imaging in Primary Prevention: Systematic Review and Meta-analysis of Randomized Trials. Arch Intern Med. 2011 Mar 14.
Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. Circulation 2009; DOI: 10.1161/CIRCULATIONAHA.109.876383.
Hankey GJ. Nutrition (salt, overeating etc…) and the risk of stroke. Lancet Neurol 2012; 11:66-81.
Hardoon SL, Morris RW, Whincup PH, et al. Rising adiposity curbing decline in the incidence of myocardial infarction: 20-year follow-up of British men and women in the Whitehall II cohort. Eur Heart J 2011.
Harmon KG, Asif IM, Klossner D, et al. Incidence of sudden cardiac death in national collegiate athletic association athletes. Circulation. 2011 Apr 19;123(15):1594-600.
Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, et al. Omega-6 Fatty Acids and Risk for Cardiovascular Disease. A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. Circulation. 2009 Jan 26. [Epub ahead of print] In summary, the AHA supports an omega-6 PUFA intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD.

TOP

He FJ, Marciniak M, Visagie E, et al. Effect of Modest Salt Reduction on Blood Pressure, Urinary Albumin, and Pulse Wave Velocity in White, Black, and Asian Mild Hypertensives. Hypertension. 2009 Jul 20. [Epub ahead of print]
Health Canada Sep/11 GnRH Agonists: Heart-related Risk in Men Treated for Prostate Cancer. Health Canada is informing health professionals and patients about a possible increased risk of certain heart-related events in men being treated for prostate cancer with a type of prescription drug known as a Gonadotropin-Releasing Hormone (GnRH) agonist.
Heitmann Berit L, Frederiksen Peder. Thigh circumference and risk of heart disease and premature death: prospective cohort study. BMJ 2009;339:b3292, doi: 10.1136/bmj.b3292 (Published 3 September 2009)
Held C, Iqbal R, Lear SA, et al. Physical activity levels, ownership of goods promoting sedentary behavior and risk of myocardial infarction: results of the INTERHEART study. Eur Heart J 2012
Hemmelgarn Brenda R.; Manns Braden J.; Lloyd Anita; et al. for the Alberta Kidney Disease Network. Relation Between Kidney Function, Proteinuria, and Adverse Outcomes. JAMA. 2010;303(5):423-429.
Henney JE, Taylor CL, and Boon CS, eds. Institute of Medicine. Strategies to Reduce Sodium Intake in the United States; Washington, DC: National Academies Press, 2010. Available here.
Hess EP, Agarwal D, Chandra S, et al. Diagnostic accuracy of the TIMI risk score in patients with chest pain in the emergency department: a meta-analysis. CMAJ. 2010 Jul 13;182(10):1039-44. Epub 2010 Jun 7.
Hippisley-Cox J, et al. Performance of the QRISK cardiovascular risk prediction algorithm in an independent UK sample of patients from general practice: a validation study. Heart. 2008 Jan;94(1):34-9. Epub 2007 Oct 4.
This analysis demonstrated that QRISK is better calibrated to the UK population than Framingham and has better discrimination. www.qrisk.org
Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008 Jun 23. [Epub ahead of print]
Incorporating ethnicity, deprivation, and other clinical conditions into the QRISK2 algorithm for risk of cardiovascular disease improves the accuracy of identification of those at high risk in a nationally representative population. At the 20% threshold, QRISK2 is likely to be a more efficient and equitable tool for treatment decisions for the primary prevention of cardiovascular disease. As the validation was performed in a similar population to the population from which the algorithm was derived, it potentially has a "home advantage." Further validation in other populations is therefore advised. www.qrisk.org
Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 341:doi:10.1136/bmj.c6624 (Published 9 Dec 2010)
Hooper L, Summerbell CD, Thompson R, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD002137. DOI: 10.1002/14651858.CD002137.pub2. The findings are suggestive of a small but potentially important reduction in cardiovascular risk on modification of dietary fat, but not reduction of total fat, in longer trials. Lifestyle advice to all those at risk of cardiovascular disease and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates. The ideal type of unsaturated fat is unclear.
Horne BD, May HT, Muhlestein JB, et al. Exceptional mortality prediction by risk scores from common laboratory tests. Am J Med. 2009 Jun;122(6):550-8.
Hsia J, Larson JC, Ockene JK, Sarto GE, Allison MA, et al.; Women's Health Initiative Research Group. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. BMJ. 2009 Feb 3;338:b219. doi: 10.1136/bmj.b219. Resting heart rate, a low tech and inexpensive measure of autonomic tone, independently predicts myocardial infarction or coronary death, but not stroke, in women.
Huffman MD, Capewell S, Ning H, et al. Cardiovascular health behavior and health factor changes (1988 –2008) and projections to 2020: results from the National Health and Nutrition Examination Surveys. Circulation. 2012;125:2595–2602.
Hurst RT, Nelson MR, Kendall CB, et al. Carotid Intimal-Medial Thickness in Active Professional American Football Players Aged 23 to 35 Years. Am J Cardiol. 2011 Dec 21.
Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011; DOI: DOI:10.1016/S0140-6736(11)60781-2.
ICSI: Institute for Clinical Systems Improvement. Primary prevention of chronic disease risk factors. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 May.
IL6R Genetics Consortium and Emerging Risk Factors Collaboration IL-6 (Interleukin-6) pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet 2012.
lina MV, Kepron CA, Taylor GP, et al. Undiagnosed Heart Disease Leading to Sudden Unexpected Death in Childhood: A Retrospective Study. Pediatrics. 2011 Aug 8.
Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA 2007; 298:776-785. In this large, population-based cohort, the overall performance of apo B:apo A-I ratio for prediction of CHD was comparable with that of traditional lipid ratios but did not offer incremental utility over total cholesterol:HDL-C. These data do not support measurement of apo B or apo A-I in clinical practice when total cholesterol and HDL-C measurements are available. Measurement of the apolipoprotein B:apolipoprotein A-I ratio is comparable with, but does not offer any incremental utility to, standard lipid level ratios in predicting coronary heart disease (CHD). Routine measurement of apolipoprotein levels in clinical practice should be discouraged. (LOE = 1b)
Jabre P, Jouven X, Adnet F, et al. Atrial Fibrillation and Death After Myocardial Infarction: A Community Study. Circulation. 2011 May 2.
Jackson Andrew S.; Sui Xuemei; Hebert James R.; et al. Role of Lifestyle and Aging on the Longitudinal Change in Cardiorespiratory Fitness. *Arch Intern Med*. 2009;169(19):1781-1787.
Jacobs Eric J.; Newton Christina C.; Wang Yiting; et al. Waist Circumference and All-Cause Mortality in a Large US Cohort. Arch Intern Med. 2010;170(15):1293-1301.
James Matthew T, Hemmelgarn Brenda R, Wiebe N. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. The Lancet, Early Online, 22 November 2010 doi:10.1016/S0140-6736(10)61271-8.
JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008; 31:2115–2127. (n=4418 over 2yrs)
Ji J, Zöller B, Sundquist K, Sundquist J. Increased risks of coronary heart disease and stroke among spousal caregivers of cancer patients. Circulation. 2012 Apr 10;125(14):1742-7.
Jobs E, Ingelsson E, Risérus U, et al. Association Between Serum Cathepsin S and Mortality in Older Adults. JAMA. 2011 Aug 29.
Johnson KM, Dowe DA, Brink JA. Traditional clinical risk assessment tools do not accurately predict coronary atherosclerotic plaque burden: a CT angiography study. AJR Am J Roentgenol. 2009 Jan;192(1):235-43.
Johnson KM, Dowe DA. The detection of any coronary calcium outperforms Framingham risk score as a first step in screening for coronary atherosclerosis. AJR Am J Roentgenol 2010; 194:1235-1243.
Johnson CM, Angell SY, Lederer A, et al. Sodium content of lunchtime fast food purchases at major US chains. Arch Intern Med 2010; 170:732-734.
Juonala M, Magnussen CG, Venn A, et al. Influence of age and associations between childhood risk factors and carotid IMT in adulthood. The Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. Circulation 2010; DOI:10.1161/CIRCULATIONAHA.110.966465.
Kaczorowski Janusz, Chambers LW, Dolovich Lisa, et al. Improving cardiovascular health at population level: 39 community cluster randomised trial of Cardiovascular Health Awareness Program (CHAP). BMJ 2011;342:doi:10.1136/bmj.d442 (7 Feb 2011)
Kahn HS, Cheng YJ, Thompson TJ, Imperatore G, Gregg EW. Two risk-scoring systems for predicting incident diabetes mellitus in U.S. adults age 45 to 64 years. Ann Intern Med. 2009 Jun 2;150(11):741-51. Basic information identified adults at high risk for diabetes. Additional data from fasting blood tests better identified those at extreme risk.
Kaltman JR, Thompson PD, Lantos J, et al. Screening for sudden cardiac death in the young: report from a national heart, lung, and blood institute working group. Circulation. 2011 May 3;123(17):1911-8.
Kasiman K, Lundholm C, Sandin S, et al. Familial Effects on Ischemic Stroke: The Role of Sibling Kinship, Sex and Age of Onset. Circ Cardiovasc Genet. 2012 Mar 9.
Karthikeyan G, Moncur RA, Levine O, et al. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. J Am Coll Cardiol. 2009 Oct 20;54(17):1599-606.
Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, et al. Evaluation of newer risk markers for coronary heart disease risk classification. A cohort study. Ann Intern Med. 2012;156:438-44
Kerr AJ, Broad J, Wells S, et al. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease?. Heart. 2009 Feb;95(2):125-9. Epub 2008 Apr 1. Patients with prior CVD have five-year CVD risks approximately 20% higher, in absolute terms than patients without prior CVD, after accounting for standard risk factors. Almost half the CVD events occurred in those with prior CVD. These patients should be the highest priority for intensive preventive management in primary care.
Khan KM, Weiler R, Blair SN. Prescribing exercise in primary care. BMJ. 2011 Jul 15;343:d4141. doi: 10.1136/bmj.d4141.
Kharazmi E, Dossus L, Rohrmann S, Kaaks R. Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). Heart. 2010 Dec 1.
Kim JH, Malhotra R, Chiampas G et al, Cardiac arrest during long-distance running races. N Engl J Med 2012; 366:130-140.
Kivimäki Mika, Batty G. David, Hamer Mark, et al. Using Additional Information on Working Hours to Predict Coronary Heart Disease: A Cohort Study. *Ann Intern Med* April 5, 2011 154:457-463.
Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009 May 20;301(19):2024-35. Better CRF was associated with lower risk of all-cause mortality and CHD/CVD. Participants with a MAC of 7.9 METs or more had substantially lower rates of all-cause mortality and CHD/CVD events compared with those with a MAC of less 7.9 METs.

TOP

Kshirsagar AV, Bang H, Bomback AS, et al. A simple algorithm to predict incident kidney disease. Arch Intern Med. 2008 Dec 8;168(22):2466-73. In the simplified model, age, anemia, female sex, hypertension, diabetes mellitus, peripheral vascular disease, and history of congestive heart failure or cardiovascular disease were associated with the development of a GFR less than 60 mL/min/1.73 m(2).
Kuo H-K, Fujise K. Human papillomavirus and cardiovascular disease among US women in the National Health and Nutrition Examination Survey, 2003 to 2006. J Am Coll Cardiol 2011; 58: 2001-2006.
Kurth T, Schürks M, Logroscino G, Gaziano JM, et al. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. BMJ. 2008 Aug 7;337:a636. doi: 10.1136/bmj.a636. The association between migraine with aura and cardiovascular disease varies by vascular risk status. Information on history of migraine and vascular risk status might help to identify women at increased risk for specific future cardiovascular disease events.
Kurth T, de Jong PE, Cook NR, Buring JE, Ridker PM. Kidney function and risk of cardiovascular disease and mortality in women: a prospective cohort study. BMJ. 2009 Jun 29;338:b2392. doi: 10.1136/bmj.b2392.
Kvaavik Elisabeth; Batty G. David; Ursin Giske; et al. Influence of Individual and Combined Health Behaviors on Total and Cause-Specific Mortality in Men and Women: The United Kingdom Health and Lifestyle Survey. Arch Intern Med. 2010;170(8):711-718.
Kwak SM, Myung SK, Lee YJ, et al. Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials. Arch Intern Med. 2012 Apr 9.
Labarthe DR, Dunbar SB. Global cardiovascular health promotion and disease prevention: 2011 and beyond. Circulation. 2012 May 29;125(21):2667-76.
Laitinen TT, Pahkala K, Magnussen CG, et al. Ideal cardiovascular health in childhood and cardiometabolic outcomes in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation. 2012;125: 1971–1978.
Lavie CJ, Milani RV, Mehra MR, et al. Omega-3 polyunsaturated fatty acids and cardiovascular disease. J Am Coll Cardiol 2009; 54: 585-594.
Lee Chong-Do; Sui Xuemei; Blair Steven N. Combined Effects of Cardiorespiratory Fitness, Not Smoking, and Normal Waist Girth on Morbidity and Mortality in Men. Arch Intern Med. 2009;169(22):2096-2101.
Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men. Circulation 2011
Lee Meng, Saver Jeffrey L, Chang Kuo-Hsuan, et al. Low glomerular filtration rate and risk of stroke: meta-analysis. BMJ 341:doi:10.1136/bmj.c4249 (Published 30 September 2010). Leunissen RW, Kerkhof GF, Stijnen T, et al. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA. 2009 Jun 3;301(21):2234-42. Rapid weight gain in the first 3 months of life is associated with several determinants of cardiovascular disease and type 2 diabetes in early adulthood.
Lee DC et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics center longitudinal study. Circulation. 2011 Dec 6;124(23):2483-90.
Lee DC, Sui X, Church TS, et al. Changes in fitness and fatness on the development of cardiovascular disease risk factors. J Am Coll Cardiol 2012; 59:665-672.
Leslie LK, Cohen JT, Newburger JW, et al. Costs and benefits of targeted screening for causes of sudden cardiac death in children and adolescents. Circulation. 2012;125:2621–2629.
Levine Glenn N., D'Amico Anthony V., Berger Peter, et al. and on behalf of the American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association. Androgen-Deprivation Therapy in Prostate Cancer and Cardiovascular Risk. A Science Advisory From the American Heart Association, American Cancer Society, and American Urological Association. Circulation published February 1, 2010, doi:10.1161/CIRCULATIONAHA.109.192695
Lewis JR, Prince RL, Zhu K, Devine A, Thompson PL, Hodgson JM. Habitual chocolate intake and vascular disease: a prospective study of clinical outcomes in older women. Arch Intern Med. 2010 Nov 8;170(20):1857-8.
Li Chaoyang; Ford Earl S.; Zhao Guixiang; et al. Serum {alpha}-Carotene Concentrations and Risk of Death Among US Adults: The Third National Health and Nutrition Examination Survey Follow-up Study. *Arch Intern Med*. 2010;0(2010):archinternmed.2010.440. (Higher fruit & vegetable consumption)
LIFE Study Investigators, Pahor M, Blair SN, Espeland M, et al. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. J Gerontol A Biol Sci Med Sci. 2006 Nov;61(11):1157-65.
Lim LS, Haq N, Mahmood S, Hoeksema L, ACPM Prevention Practice Committee, American College of Preventive Medicine. Atherosclerotic cardiovascular disease screening in adults: American College of Preventive Medicine position statement on preventive practice. Am J Prev Med 2011 Mar;40(3):381.e1-10.
Lin JS, O'Connor E, Whitlock EP, Beil TL. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the u.s. Preventive services task force. Ann Intern Med. 2010 Dec 7;153(11):736-50.
Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011 Mar 9.
Ling CH, Taekema D, de Craen AJ, Gussekloo J, Westendorp RG, Maier AB. Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study. CMAJ. 2010 Feb 8. [Epub ahead of print]
Link MS, Estes NA 3rd. Sudden cardiac death in the athlete: bridging the gaps between evidence, policy, and practice. Circulation. 2012 May 22;125(20):2511-6.
Liu K, Daviglus ML, Loria CM, et al. Healthy Lifestyle Through Young Adulthood and the Presence of Low Cardiovascular Disease Risk Profile in Middle Age: The Coronary Artery Risk Development in (Young) Adults (CARDIA) Study. Circulation. 2012 Feb 28;125(8):996-1004.
Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008; DOI: 10.1161/CIRCULATIONAHA.108.191261. Available at: http://circ.ahajournals.org.
Lockhart P B, Bolger AF, Papapanou PN, et al Periodontal disease and atherosclerotic vascular disease: Does the evidence support an independent association? A scientific statement from the American Heart Association. Circulation 2012
Look AHEAD Research Group. Long-term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals With Type 2 Diabetes Mellitus: Four-Year Results of the Look AHEAD Trial. Arch Intern Med. 2010;170(17):1566-1575.
Lorenz MW, Polak JF, Kavousi M, et al, on behalf of the PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet 2012
Loria CM, Mussolino ME, Cogswell ME, et al. Usual sodium intakes (salt) compared with current dietary guidelines—United States, 2005-2008. MMWR Morb Mortal Wkly Rep 2011; 60:1413-1417.
Lp-PLA(2) Studies Collaboration, Thompson A, Gao P, Orfei L et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet. 2010 May 1;375(9725):1536-44.
Ludvigsson JF, James S, Askling J, et al. Nationwide cohort study of risk of ischemic heart disease in patients with celiac disease. Circulation. 2011 Feb 8;123(5):483-90.
Magnus P, Bakke E, Hoff DA, et al. Controlling for high-density lipoprotein cholesterol does not affect the magnitude of the relationship between alcohol and coronary heart disease. Circulation. 2011;124:2296 –2302.
Mancia G, Schumacher H, Redon J, Verdecchia P, et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). Circulation. 2011;124:1727–1736.
Maron BJ, Thompson PD, Ackerman MJ, et al. American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the AHA Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2007 Mar 27;115(12):1643-455. Epub 2007 Mar 12.
May AL, Kuklina EV, Yoon PW. Prevalence of Cardiovascular Disease Risk Factors Among US Adolescents, 1999-2008. Pediatrics. 2012 May 21.
McCullough Peter A.; Chinnaiyan Kavitha M. Annual Progression of Coronary Calcification (CAC) in Trials of Preventive Therapies: A Systematic Review. Arch Intern Med. 2009;169(22):2064-2070.
McCullough ML, Peterson JJ , Patel R, et al. Flavonoid (chocolate, wine) intake and cardiovascular disease mortality in a prospective cohort of US adults. Am J Clin Nutr 2012; 95:454-464.
McEvoy John W.; Blaha Michael J.; Nasir Khurram; et al. Impact of Coronary Computed Tomographic Angiography Results on Patient and Physician Behavior in a Low-Risk Population. Arch Intern Med. 2011;0(2011):archinternmed.2011.204.
McGeechan K, Liew G, Macaskill P, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. Ann Intern Med. 2009 Sep 15;151(6):404-13.
McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, Steyn K, Sanderson JE, Hasani M, Volkova E, Kazmi K, Yusuf S; INTERHEART study investigators. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet. 2008 Jul 19;372(9634):224-33. The non-fasting ApoB/ApoA1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, and it should be introduced into worldwide clinical practice.
Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA. 2009 Jul 1;302(1):49-57.
Mellerio H, Alberti C, Druet C, et al. Novel modeling of reference values of cardiovascular risk factors in children aged 7 to 20 years. Pediatrics. 2012 Apr;129(4):e1020-9.

TOP

Melzer D, Osborne NJ, Henley WE, et al. Urinary bisphenol: A concentration and risk of future coronary artery disease in apparently healthy men and women. Circulation 2012.
Mente A, de Koning L, Shannon HS, et al. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med 2009*; 169:659-669.
Mente A, Yusuf S, Islam S, et al. Metabolic syndrome and risk of acute myocardial infarction. A case-control study of 26 903 subjects from 52 countries. J Am Coll Cardiol 2010; 55:2390-2398.
Meyers DG, Neuberger JS, He J et al. Cardiovascular effect of bans on smoking in public places. A systematic review and meta-analysis. J Am Coll Cardiol 2009; 54: 1249-1255.
Michos ED, Blumenthal RS. How Accurate Are 3 Risk Prediction Models in US Women? Circulation. 2012 Apr 10;125(14):1723-6.
Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008 Nov 27;359(22):2324-36. December 3, 2008
Min J, Lin F, Gidseg D, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: What is the "warranty period" for remaining normal? J Am Coll Cardiol 2010 55:1110-1117.
Minassian C, D'Aiuto F, Hingorani AD, Smeeth L. Invasive dental treatment and risk for vascular events: a self-controlled case series. Ann Intern Med. 2010 Oct 19;153(8):499-506.
Möhlenkamp S, Lehmann N, Moebus S, et al. Quantification of coronary atherosclerosis and inflammation (CRP) to predict coronary events and all-cause mortality. J Am Coll Cardiol 2011; 57:1455-1464
Morrison JA, Glueck CJ, Wang P. The Child as Proband for Future Parental Cardiometabolic Disease: The 26-Year Prospective Princeton Lipid Research Clinics Follow-Up Study. J Pediatr. 2012 Jan 12.
Morrow DA. Cardiovascular risk prediction in patients with stable and unstable coronary heart disease. Circulation. 2010 Jun 22;121(24):2681-91.
Mosca Lori, Benjamin Emelia J., Berra Kathy, et al. Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update: A Guideline From the American Heart Association. Circulation published Feb 14, 2011.
Mosca L, Aggarwal B, Mochari-Greenberger H, et al. Association Between Having a Caregiver and Clinical Outcomes 1 Year After Hospitalization for Cardiovascular Disease. Am J Cardiol. 2011 Sep 29.
Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2010;7:e1000252.
Mozaffarian Dariush, Shi Peilin, Morris J. Steven, et al. Mercury Exposure and Risk of Cardiovascular Disease in Two U.S. Cohorts. N Engl J Med. 2011;364:1116-1125.
Mulrooney Daniel A, Yeazel Mark W, Kawashima Toana, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009;339:b4606, doi: 10.1136/bmj.b4606 (Published 8 December 2009).
Murabito JM, Pencina MJ, Nam BH, et al. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. JAMA. 2005 Dec 28;294(24):3117-23.
Murphy A W, Cupples M E, Smith S M, et al., for the SPHERE study team. Effect of tailored practice and patient care plans on secondary prevention of heart disease in general practice: cluster randomised controlled trial. BMJ 2009;339:b4220, doi: 10.1136/bmj.b4220 (Published 29 October 2009)
Nafiu OO, Burke C, Lee J, Voepel-Lewis T, Malviya S, Tremper KK. Neck Circumference as a Screening Measure for Identifying Children With High Body Mass Index. Pediatrics. 2010 Jul 5.
Nanda A, Chen MH, et al. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA. 2009 Aug 26;302(8):866-73.
Nawrot TS, Perez L, Künzli N, et al. Public health importance of triggers of myocardial infarction: A comparative risk assessment. Lancet 2011; DOI: 10.1016/S0140-6736(10)62296-9. A comparative risk assessment of various triggers for MI suggests that cocaine is most likely to trigger an event in an individual, but traffic and exposure to air pollution has the greatest effect on triggering an MI at the population level.
NaumanJ, Janszky I, Vatten LJ, Wisløff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA2011; 306:2579-2587.
Nilsson G, Holmberg L, Garmo H, et al. Distribution of Coronary Artery Stenosis After Radiation for Breast Cancer. J Clin Oncol. 2011 Dec 27.
Nordestgaard BG, Palmer TM, Benn M, et al. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a mendelian randomisation approach. PLoS Med. 2012 May;9(5):e1001212.
Nordmann AJ, Suter-Zimmermann K, Bucher HC, et al. Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. Am J Med. 2011;124:841-51.
Norheim Ole Frithjof, Gjelsvik Bjørn, Klemsdal Tor Ole, et al. Norway's new principles for primary prevention of cardiovascular disease: age differentiated risk thresholds. BMJ 2011;343:doi:10.1136/bmj.d3626 (Published 13 July 2011)
Odegaard AO, Koh WP, Gross MD, Yuan JM, Pereira MA. Combined lifestyle factors and cardiovascular disease mortality in Chinese men and women: the Singapore Chinese health study. Circulation. 2011 Dec 20;124(25):2847-54.
O'Donnell MJ, Xavier D, Liu Lisheng, et al; and on behalf of the INTERSTROKE investigators, Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study, The Lancet, Online 17 June 2010
O'Donnell MJ, Yusuf S, Mente A, et al. Urinary **sodium and potassium excretion** and risk of cardiovascular events. JAMA 2011; 306:2229-2238.
O'Hare Ann M.; Hailpern Susan M.; Pavkov Meda E.; et al. Prognostic Implications of the **Urinary Albumin to Creatinine Ratio** in Veterans of Different Ages With Diabetes. *Arch Intern Med*. 2010;170(11):930-936.
Omland T, de Lemos JA, et al. the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial. A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease. N Engl J Med. 2009 Nov 25.
O'Neil AE, Sanderson K. The use of cognitive behavioral therapy for secondary prevention in patients with coronary heart disease. Arch Intern Med. 2011 Sep 12;171(16):1506.
Otten Jennifer J.; Jones Katherine E.; et al. Effects of Television Viewing Reduction on Energy Intake and Expenditure in Overweight and Obese Adults: A Randomized Controlled Trial. Arch Intern Med. 2009;169(22):2109-2115.
Pahkala K, Heinonen OJ, Simell O, et al. Association of physical activity with vascular endothelial function and intima-media thickness. Circulation. 2011 Nov 1;124(18):1956-63.
Papadakis M, Whyte G, Sharma S. Preparticipation screening for cardiovascular abnormalities in young competitive athletes. BMJ. 2008 Sep 29;337:a1596. doi: 10.1136/bmj.a1596.
Park K. How low to go with glucose control? http://www.australianprescriber.com/magazine/32/2/30/1
Park Yikyung; Subar Amy F.; Hollenbeck Albert; et al. Dietary Fiber Intake and Mortality in the NIH-AARP Diet and Health Study. Arch Intern Med. 2011;171(12):1061-1068.
Parker BA, Augeri AL, Capizzi JA, et al. Effect of Marathon Run and Air Travel on Pre- and Post-Run Soluble D-Dimer, Microparticle Procoagulant Activity, and P-Selectin Levels. Am J Cardiol. 2012 Feb 17.
Pavey TG, Taylor AH, Fox KR, et al. Effect of exercise referral schemes in primary care on physical activity and improving health outcomes: systematic review and meta-analysis. BMJ 2011;343:d6462.
Paynter NP, Chasman DI, Paré G, Buring JE, Cook NR, Miletich JP, Ridker PM. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA. 2010 Feb 17;303(7):631-7.
Paynter NP, Mazer NA, Pradhan AD, Gaziano JM, Ridker PM, Cook NR. Cardiovascular risk prediction in diabetic men and women using haemoglobin A1c vs diabetes as a high-risk equivalent. Arch Intern Med. 2011.
Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation. 2009 Jun 23;119(24):3078-84. Epub 2009 Jun 8.
Persell SD.; Zei C; Cameron KA.; et al. Potential Use of 10-Year and Lifetime Coronary Risk Information for Preventive Cardiology Prescribing Decisions: A Primary Care Physician Survey. *Arch Intern Med*. 2010;170(5):470-477.
Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2009 Sep 22.
Pickett CA, et al. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. Lancet. 2008 May 10;371(9624):1587-94. Auscultation for carotid bruits in patients at risk for heart disease could help select those who might benefit the most from an aggressive modification strategy for cardiovascular risk.
Pikula A, Beiser AS, Decarli C, et al. Multiple biomarkers and risk of clinical and subclinical vascular brain injury:the framingham offspring study. Circulation. 2012 May 1;125(17):2100-7.
Pimenta E, Gaddam KK, Oparil S, et al. Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension. Results From a Randomized Trial. Hypertension. 2009 Jul 20. [Epub ahead of print]
Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008 Nov 13;359(20):2105-20. These data suggest that both general adiposity and abdominal adiposity are associated with the risk of death and support the use of waist circumference or waist-to-hip ratio in addition to BMI in assessing the risk of death.
Polonsky Tamar S.; McClelland Robyn L.; Jorgensen Neal W.; et al. Coronary Artery Calcium Score and Risk Classification for Coronary Heart Disease Prediction. JAMA. 2010;303(16):1610-1616.
Prasad V, Vandross A. Cardiovascular primary prevention: How high should we set the bar? Arch Intern Med 2012; 172:656-659.
Preis SR, Massaro JM, Hoffmann U, et al. Neck Circumference as a Novel Measure of Cardiometabolic Risk: The Framingham Heart Study. J Clin Endocrinol Metab. 2010 May 19.
Qureshi N, Armstrong S, Dhiman P, et al. Effect of adding systematic family history enquiry to cardiovascular disease risk assessment in primary care. Ann Intern Med 2012; 156:253-262.
Rana JS, Gransar H, Wong ND, et al. Comparative Value of Coronary Artery Calcium and Multiple Blood Biomarkers for Prognostication of Cardiovascular Events. Am J Cardiol. 2012 Mar 15.
Rankin P, Morton DP, Diehl H, et al. Effectiveness of a Volunteer-Delivered Lifestyle Modification Program for Reducing Cardiovascular Disease Risk Factors. Am J Cardiol. 2011 Sep 23.
Reddigan JI, Ardern CI, Riddell MC, Kuk JL. Relation of Physical Activity to Cardiovascular Disease Mortality and the Influence of Cardiometabolic Risk Factors. Am J Cardiol. 2011 Aug 17.
Retnakaran, Ravi, Shah, Baiju R. Mild glucose intolerance in pregnancy and risk of cardiovascular disease: a population-based cohort study. CMAJ 2009 0: cmaj.090569
Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds risk score for men. Circulation. 2008 Nov 25;118(22):2243-51. Epub 2008 Nov 9. As previously

TOP

shown in women, a prediction model in men that incorporates high-sensitivity C-reactive protein and parental history significantly improves global cardiovascular risk prediction.
Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med. 2008 Nov 10;168(20):2212-8. Rapid decline in eGFR is associated with an increased risk of cardiovascular and all-cause mortality in older adults, independent of baseline eGFR and other demographic variables.
Ripatti S, Tikkanen E, Orho-Melander M, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. Lancet. 2010 Oct 23;376(9750):1393-400.
Rockwood, Kenneth, Song, Xiaowei, Mitnitski, Arnold. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ 2011 183: E487-494
Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 2011; DOI:10.1136/bmj.d671.
Rozanski A, Gransar H, Shaw LJ, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing. J Am Coll Cardiol 2011; DOI:10.1016/j.jacc.2011.01.019.
Ruidavets Jean-Bernard, Ducimetière Pierre, Evans Alun, et al. Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME) . BMJ 341:doi:10.1136/bmj.c6077 (Published 23 Nov 2010)
Ruiz JR, Sui X, Lobelo F, Morrow JR Jr, Jackson AW, Sjöström M, Blair SN. Association between muscular strength and mortality in men: prospective cohort study. BMJ. 2008 Jul 1;337:a439. doi: 10.1136/bmj.a439. Muscular strength is inversely and independently associated with death from all causes and cancer in men, even after adjusting for cardiorespiratory fitness and other potential confounders.
Sabanayagam C; Shankar A. Sleep duration and cardiovascular disease: Results from the National Health Interview Survey. Sleep 2010; 33:1037-1042.
Sacco Ralph L.. Achieving Ideal Cardiovascular and Brain Health: Opportunity Amid Crisis: Presidential Address at the American Heart Association (AHA)2010 Scientific Sessions. Circulation 123: 2653-2657, doi:10.1161/CIR.0b013e318220dec1
Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS; and the Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493-500.
Sallis JF, Floyd MF, Rodríguez DA et al. Role of built environments in physical activity, obesity, and cardiovascular disease. Circulation. 2012 Feb 7;125(5):729-37.
Santschi V, Chiolero A, Burnand B, et al. Impact of Pharmacist Care in the Management of Cardiovascular Disease Risk Factors: A Systematic Review and Meta-analysis of Randomized Trials. Arch Intern Med. 2011 Sep 12;171(16):1441-53.
Sattelmair JR, Kurth T, Buring JE, et al. Physical activity and risk of stroke in women. Stroke 2010; 41:1243-1250.
Sattelmair J, Pertman J, Ding EL, et al. Dose response between physical activity and risk of coronary heart disease. A meta-analysis. Circulation 2011; DOI: 10.1161/CIRCULATIONAHA.110.010710.
Scherrer U, Rimoldi SF, Rexhaj E, Stuber T, Duplain H, et al. Systemic and pulmonary vascular dysfunction in children conceived by assisted reproductive technologies. Circulation. 2012;125:1890 –1896.
Schmidt M, Jacobsen JB, et al. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. BMJ 2012;344:e356.
Shah AS, Dolan LM, Gao Z, Kimball TR, Urbina EM. Clustering of Risk Factors: A Simple Method of Detecting Cardiovascular Disease in Youth. Pediatrics. 2011 Jan 17.
Shay CM, Ning H, Allen NB et al. Status of Cardiovascular Health in US Adults: Prevalence Estimates From the National Health and Nutrition Examination Surveys (NHANES) 2003-2008. Circulation. 2012 Jan 3;125(1):45-56.
Shemesh J, Motro M, Morag-Koren N et al. Relation of Coronary Artery Calcium to Cardiovascular Risk in Patients With Combined Diabetes Mellitus and Systemic Hypertension. Am J Cardiol. 2011 Dec 21.
Sheridan Stacey L.; Viera Anthony J.; Krantz Mori J.; et al. for the Cardiovascular Health Intervention Research and Translation Network Work Group on Global Coronary Heart Disease Risk. The Effect of Giving Global Coronary Risk Information to Adults: A Systematic Review. Arch Intern Med. 2010;170(3):230-239.
Sheridan SL. Global risk of coronary heart disease: assessment and application. Am Fam Physician. 2010 Aug 1;82(3):265-74.
Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. JAMA. 2011;306(19):2128-2136
Sieri S, Krogh V, Berrino F, et al. Dietary glycemic load and index and risk of coronary heart disease in a large italian cohort: the EPICOR study. Arch Intern Med. 2010 Apr 12;170(7):640-7.
Simmons RK, Sharp S, Boekholdt SM, et al. Evaluation of the Framingham risk score in the European Prospective Investigation of Cancer-Norfolk cohort: does adding glycated hemoglobin improve the prediction of coronary heart disease events? Arch Intern Med. 2008 Jun 9;168(11):1209-16. The Framingham risk score predicts CHD in this cohort. The addition of HbA(1c) made a small but statistically significant improvement to discrimination in men but not in women, without significant improvement in reclassification of risk category.
Singh RB, Dubnov G, Niaz MA, Ghosh S, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. *Lancet* 2002;360(9344):1455-61.
Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A. Meat intake and mortality: a prospective study of over half a million people. Arch Intern Med. 2009;169:562-71.
Siontis GCM, Tzoulaki I, Siontis KC, Ioannidis JPA. Comparisons of established risk prediction models for cardiovascular disease: systematic review. BMJ 2012;344:3318
Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. (SOS) JAMA. 2012;307(1):56-65.
Smith S, Benjamin E, Bonow R, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011; DOI:10.1161/CIR.0b013e318235eb4d.
Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Ad herence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008;337:a1344.
Sofi F, Capalbo A, Pucci N, et al. Cardiovascular evaluation, including resting and exercise electrocardiography, before participation in competitive sports: cross sectional study. BMJ. 2008 Jul 3;337:a346. doi: 10.1136/bmj.a346. Among people seeking to take part in competitive sports, exercise ECG can identify those with cardiac abnormalities. Follow-up studies would show if disqualification of such people would reduce the incidence of CV events among athletes.
Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010 Nov;92(5):1189-96.
Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. BMJ 2012;344:d8059.
Sniderman AD, Thanassoulis G, Lawler PR, et al. Comparison of Coronary Calcium Screening Versus Broad Statin Therapy for Patients at Intermediate Cardiovascular Risk. Am J Cardiol. 2012 May 9.
Stamatakis E, Hamer M, Dunstan DW et al. Screen based entertainment time (TV etc), all-cause mortality, and cardiovascular events. Population based study with ongoing mortality and hospital events follow-up. J Am Coll Cardiol 2011; 57: 292-299.
Stenestrand U, Wijkman M, Fredrikson M, et al. Association between admission supine systolic blood pressure and 1-year mortality in patients admitted to the intensive care unit for acute chest pain. JAMA. 2010 Mar 24;303(12):1167-72.
Stessman Jochanan; Hammerman-Rozenberg Robert; Cohen Aaron; et al. Physical Activity, Function, and Longevity Among the Very Old. Arch Intern Med. 2009;169(16):1476-1483.
Stolarz-Skrzypek K, Kuznwtsova T, Thijs L et al. Fatal and nonfatal outcomes, incidence of hypertension, and BP changes in relation to urinary **sodium excretion**. JAMA 2011; 305: 1777-1785.
Stone GW et al. for the PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011 Jan 20; 364:226.
Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364:226 –235.
Strazzullo Pasquale, D'Elia Lanfranco, et al. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567, doi: 10.1136/bmj.b4567 (24 November 2009).
Ström M, Halldorsson TI, Mortensen EL, et al. Fish, n-3 fatty acids and cardiovascular diseases in women of reproductive age. A prospective study in a large national cohort. Hypertension 2011
Suckling RJ, He FJ, MacGregor GA. Altered dietary **salt intake** for preventing and treating diabetic kidney disease. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD006763.
Sun Qi; Townsend Mary K.; Okereke Olivia I.; et al. Physical Activity at Midlife in Relation to Successful Survival in Women at Age 70 Years or Older. (Nurses' Health Study) *Arch Intern Med*. 2010;170(2):194-201.
Sun Q, Townsend MK, Okereke OI, et al. Alcohol consumption at midlife and successful ageing in women: a prospective cohort analysis in the nurses' health study. PLoS Med. 2011 Sep;8(9)
Taylor RS, Ashton KE, Moxham T, et al. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD009217. DOI: 10.1002/14651858.CD009217. Despite collating more event data than previous systematic reviews of randomised controlled trials (665 deaths in some 6,250 participants), there is still insufficient power to exclude clinically important effects of reduced dietary salt on mortality or cardiovascular morbidity in normotensive or hypertensive populations. Further RCT evidence is needed to confirm whether restriction of sodium is harmful for people with heart failure. Our estimates of benefits from dietary salt restriction are consistent with the predicted small effects on clinical events attributable to the small blood pressure reduction achieved.
Thomas Mathew, Haas Tammy S., Doerer Joseph J., et al. Epidemiology of Sudden Death in Young, Competitive Athletes Due to Blunt Trauma. Pediatrics 2011; 128:1 e1-e8; doi:10.1542/peds.2010-2743
Tirosh A et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. N Engl J Med 2011 Apr 7; 364:1315.

TOP

Tobe SW, Stone JA, Brouwers M, et al. Harmonization of guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE Initiative. CMAJ. 2011 Sep 12.
Ton TG, Fogg TT, Fong CT, et al. Knowledge, perception, and behaviors of relatives of people with premature heart disease: a systematic literature review. Circulation. 2011 Aug 23;124(8):958-64.
Traiperm N, Gatterer H, Wille M, Burtscher M. Cardiac Troponins in Young Marathon Runners. Am J Cardiol. 2012 May 9.
Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. BMJ. 2009 Jun 23;338:b2337. doi: 10.1136/bmj.b2337. Some food groups in the Mediterranean diet are more important than others in promoting health and longer life, according to this prospective cohort study from the Greek segment of the European Prospective Investigation into Cancer and nutrition (EPIC). The researchers investigated the importance of individual components of the diet and found that eating more vegetables, fruits, nuts, pulses, and olive oil, and drinking moderate amounts of alcohol is linked to people living longer, whereas following a Mediterranean diet high in seafood and cereals and low in dairy products was not an indicator of longevity.
Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010 May 8;375(9726):1634-9.
Tucker Andrew M.; Vogel Robert A.; Lincoln Andrew E.; et al. Prevalence of Cardiovascular Disease Risk Factors Among National Football League Players. JAMA. 2009;301(20):2111-2119.
Tzoulaki Ioanna; Liberopoulos George; A. Ioannidis John P.. Assessment of Claims of Improved Prediction Beyond the Framingham Risk Score. JAMA. 2009;302(21):2345-2352.
Tzoulaki I, Siontis KCM, Ioannidis JPA. Prognostic effect size of cardiovascular biomarkers in datasets from observational studies versus randomised trials: meta-epidemiology study. BMJ 2011;343:d6829.
Uberoi A, Stein R, Freeman J, et al. Interpretation of the electrocardiogram of young athletes. Circulation. Circulation 2011; 124:746-757.
Umpierre D, Ribeiro P. B., Kramer CK., et al. Physical Activity Advice Only or Structured Exercise Training and Association With HbA1c Levels in Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA. 2011;305(17):1790-1799.
Unverzagt FW, McClure LA, Wadley VG, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. Neurology. 2011 Nov 8;77(19):1729-36.
U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009 Oct 6;151(7):474-82.
Vaidya D, Becker DM, Bittner V, et al. Ageing, menopause, and ischaemic heart disease mortality in England, Wales, and the United States: modeling study of national mortality data. BMJ 2011; 343: DOI:10.1136/bmj.d5170.
van der Heijden AA, Ortegon MM, Niessen LW, et al. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. Diabetes Care. 2009 Nov;32(11):2094-8. The use of the Framingham function for prediction of the first CHD event is likely to overestimate an individual`s absolute CHD risk. In CHD prevention, application of the SCORE and UKPDS functions might be useful in the absence of a more valid tool.
van der Ploeg HP, Chey T, Korda RJ, Banks E, Bauman A. Sitting time and all-cause mortality risk in 222 497 Australian adults. Arch Intern Med. 2012; 172(6):494-500.
Van Hemelrijk M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelson A, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer; results from the Population-based PCBaSe Sweden. J Clin Oncol 2010;28:3448-56.Viera AJ,
Van Kempen BJH, Spronk S, Koller M, et al. Comparative effectiveness and cost-effectiveness of computed tomography screening for coronary artery calcium in asymptomatic individuals. J Am Coll Cardiol 2011; 58:1690-701.
Van Vliet BN, Campbell NR; Canadian Hypertension Education Program. Efforts to reduce sodium intake in Canada: why, what, and when? Can J Cardiol. 2011 Jul-Aug;27(4):437-45.
Veeranna V, Zalawadiya SK, Niraj A, et al. Homocysteine and reclassification of cardiovascular disease risk. J Am Coll Cardiol2011; 58:1025-1033.
Viner RM, Coff ey C, Mathers C, et al. 50-year mortality trends in children and young people: a study of 50 low-income, middle-income, and high-income countries. Lancet 2011; 377: 1162–74.
Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein (a) levels and cardiovascular outcomes in African Americans and Caucasians: The atherosclerosis risk in communities (ARIC) study. Circulation 2011.
Virtanen M, Ferrie JE, Singh-Manoux A, Shipley MJ, Vahtera J, Marmot MG, Kivimäki M. Overtime work and incident coronary heart disease: the Whitehall II prospective cohort study. Eur Heart J. 2010 May 11.
Wannamethee SG, Shaper AG, Lennon L, et al. Metabolic Syndrome vs Framingham Risk Score for Prediction of Coronary Heart Disease, Stroke, and Type 2 Diabetes Mellitus. Arch Intern Med. 2005 Dec 26;165(22):2644-50.
Wannamethee S. Goya; Shaper A. Gerald; Whincup Peter H.; et al. Impact of Diabetes on Cardiovascular Disease Risk and All-Cause Mortality in Older Men: Influence of Age at Onset, Diabetes Duration, and Established and Novel Risk Factors. Arch Intern Med. 2011;171(5):404-410.
Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ. 2007 Sep 22;335(7620):599. Epub 2007 Sep 13. The proposed strategy of screening children and parents for familial hypercholesterolaemia could have considerable impact in preventing the medical consequences of this disorder in two generations simultaneously.
Walldius G, Aastveit AH, Jungner I. Stroke mortality and the apoB/apoA-I ratio: results of the AMORIS prospective study. J Intern Med. 2006 Mar;259(3):259-66.
Wannamethee SG, Welsh P, Lowe GD, et al. N-terminal pro-brain natriuretic peptide is a more useful predictor of cardiovascular disease risk than C-reactive protein in older men with and without preexisting cardiovascular disease. J Am Coll Cardiol 2011; 58:56-64.
Wang TJ et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006 Dec 21; 355:2631-9. Ware JH. (The limitations of risk factors as prognostic tools. N Engl J Med 2006 Dec 21; 355:2615-7.) After adjustment for traditional cardiovascular risk factors, five biomarkers -- BNP, CRP, albumin/creatinine ratio, homocysteine, and renin -- were associated with higher risk of death from any cause, and two – BNP and albumin/creatinine ratio -- with risk of first major cardiovascular events. However, statistically, these biomarkers added only moderately to the predictive ability of conventional risk factors.
Wang NY, Young JH, et al. Blood pressure change and risk of hypertension associated with parental hypertension: the johns hopkins precursors study. Arch Intern Med. 2008 Mar 24;168(6):643-8. Hypertension in both mothers and fathers has a strong independent association with elevated BP levels and incident hypertension over the course of adult life.
Weinstein AR, Sesso HD, Lee IM, Rexrode KM, et al. The joint effects of physical activity and body mass index on coronary heart disease risk in women. Arch Intern Med. 2008 Apr 28;168(8):884-90. The risk of CHD associated with elevated body mass index is considerably reduced by increased physical activity levels. However, the risk is not completely eliminated, reinforcing the importance of being lean and physically active.
Welsh JA, Sharma A, Cunningham SA, Vos MB. Consumption of Added Sugars and Indicators of Cardiovascular Disease Risk Among US Adolescents. Circulation. 2011 Jan 25;123(3):249-57.
Weintraub WS, Daniels SR, Burke LE, et al. Value of primordial and primary prevention for cardiovascular disease: A policy statement from the American Heart Association (AHA). Circulation 2011. DOI: 10.1161/CIR.0b013e3182285a81.
Whelton PK. Urinary sodium and cardiovascular disease risk. Informing guidelines for sodium consumption. JAMA 2011; 306:2262-2264.
Wen CP, Wai JPM, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011. (15min a day or 90 min a week of moderate intensity exercise)
Weustink AC, Mollet NR, Neefjes LA, et al. Diagnostic accuracy and clinical utility of noninvasive testing for coronary artery disease. Ann Intern Med. 2010 May 18;152(10):630-9.
Wijeysundera DN, Beattie WS, Austin PC, et al. Non-invasive cardiac stress testing before elective major non-cardiac surgery: population based cohort study. BMJ 2010;340:b5526, doi: 10.1136/bmj.b5526 (Published 28 Jan 2010)
Wijeysundera Harindra C.; Machado Marcio; Farahati Farah et al; Association of Temporal Trends in Risk Factors and Treatment Uptake With Coronary Heart Disease Mortality, 1994-2005. JAMA. 2010;303(18):1841-1847.
Wheeler, Matthew T. Heidenreich, Paul A. Froelicher, Victor F. Et al. Cost-Effectiveness of Preparticipation Screening for Prevention of Sudden Cardiac Death in Young Athletes. Ann Intern Med March 2, 2010 152:276-286.
Yancy William S Jr; Westman Eric C.; McDuffie Jennifer R.; et al. A Randomized Trial of a Low-Carbohydrate Diet vs Orlistat Plus a Low-Fat Diet for Weight Loss. Arch Intern Med. 2010;170(2):136-145.
Yang Lin, Sahlqvist Shannon, McMinn Alison, et al. Interventions to promote cycling: systematic review. BMJ 341:doi:10.1136/bmj.c5293 (Published 18 October 2010)
Yang Q, Liu T, Kuklina EV, et al. Sodium and potassium intake and mortality among US adults: prospective data from the Third National Health and Examination Survey. Arch Intern Med. 2011;171(13):1183-1191.
Yang Q, Cogswell ME, Flanders WD, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults [published online March 16, 2012]. JAMA. doi:10.1001/jama.2012.339.
Yarur AJ, Deshpande AR, Pechman DM, et al. Inflammatory Bowel Disease Is Associated With an Increased Incidence of Cardiovascular Events. Am J Gastroenterol. 2011 Mar 8.
Young LH, Wackers FJ, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA. 2009 Apr 15;301(15):1547-55. Screening for coronary artery disease (CAD) in adults with type 2 diabetes and no indication of existing CAD does not improve outcomes more than standard care. This should come as no surprise -- screening for asymptomatic CAD with electron beam tomography (JAMA 2003; 289:2215-23.) and carotid intima-thickness (Stroke 2001;32:1532-8) also did not improve outcomes. Knowing with additional certainty that a patient is "at risk" for CAD does not result in different medication use nor improved compliance. (LOE = 1b-)
Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med. 2008 Oct 30;359(18):1897-908.
Zethelius B, Berglund L, Sundström J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med. 2008 May 15;358(20):2107-16. (troponin I, N-terminal pro-brain natriuretic

TOP

peptide, cystatin C, and C-reactive protein, respectively) Our data suggest that in elderly men with or without prevalent cardiovascular disease, the simultaneous addition of several biomarkers of cardiovascular and renal abnormalities substantially improves the risk stratification for death from cardiovascular causes beyond that of a model that is based only on established risk factors.
Zhang Y, Tuomilehto J, Jousilahti P, et al. Lifestyle Factors on the Risks of Ischemic and Hemorrhagic Stroke. Arch Intern Med. 2011 Sep 12.
Zheng W, McLerran DF, and Rolland B. Association between BMI and risk of death in more than one million Asians. New Engl J Med 2011; 364:719-729.
Zipes DP. Sudden Cardiac Arrest and Death Following Application of Shocks From a TASER Electronic Control Device. Circulation. 2012 May 22;125(20):2417-22.
Zomer E, Owen A, Magliano DJ, et al. The effectiveness and cost effectiveness of dark chocolate consumption as prevention therapy in people at high risk of cardiovascular disease: Best case scenario analysis using a Markov model. BMJ 2012.

Additional Links:

AHA: Beneficial & Harmful Fats 1 pager – Jan 2009: http://americanheart.mediaroom.com/file.php/290/Fats+--+beneficial+vs+harmful%282%29.pdf

TOP

ACE INHIBITOR (ACEI) / ANGIOTENSIN II RECEPTOR BLOCKER (ARB): Comparison Chart

[1] Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.

[2] 2001 Canadian Hypertension Recommendations: What's New & What's Not so New but is Still Important. CJHP 2002;55:4651.

[3] FA McAlister, M Levine, KB Zarnke, et al. The 2000 recommendations for the management of hypertension. Can J Cardiol 2001; 17(5):543-559.

[4] 1999 Canadian recommendations for the management of hypertension. CMAJ 1999;161(Suppl):S1-S16.

[5] **1999 World Health Organization**–International Society of Hypertension Guidelines:Management of Hypertension. J Hypertens 1999;17:151-183.

[6] 6th Report-Joint National Committee on Prevention,Detection,Evaluation & Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413-46.

[7] Drugs for hypertension. Med Lett Drugs Ther 2001;43:17-22.

[8] Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD.2011.

[9] Micromedex 2010 online

[10] Hansten & Horn's Drug Interactions: Analysis & Management-Facts & Comparisons 2008.

[11] Treatment Guidelines: Drugs for Hypertension from The Medical Letter Feb 2003, repeated June 2005, January 2009, and updated January 2012.

[12] The **2012** Canadian Hypertension Education Program **Recommendations** www.hypertension.ca
Canadian Hypertension Education Program. **2011 CHEP recommendations** for the management of **hypertension**. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf .

[13] ALLHAT Working Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (**ALLHAT**). JAMA 2000;283:1967-75.

[14] Liu P, Arnold JM, Belenkie I, et al. The 2002/3 Canadian Cardiovascular Society consensus guideline update for the diagnosis and management of **heart failure**. Can J Cardiol. **2003** Mar 31;19(4):347-56.

[15] **Treatment Guidelines**: Drugs for Treatment of **Heart Failure** from The Medical Letter April **2003** & Jan **2006.**

[16] Jessup M, Brozena S. Heart Failure. N Engl J Med 2003;348:2007-18.

[17] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (The **JNC 7**); JAMA. **2003** May;289(19):2560-72.

[18] Pfeffer Marc A, Swedberg Karl, Granger Christopher B. et al, Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the **CHARM**-Overall programme. Lancet 2003 **362:** 759-66. (Granger BB, Swedberg K, Ekman I, et al.; for the CHARM investigators. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet. 2005 Dec 10;366(9502):2005-2011.) (Hillege HL, et al. Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006 Feb 7;113(5):671-8.)(Ducharme A, et al. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J. 2006 May;151(5):985-91.)

[19] The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the **EUROPA** study). Lancet 2003; 362: 782-88.

[20] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both.(the **VALIANT** study). N Engl J Med. 2003 Nov 10
(McMurray J, et al. The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol. 2006 Feb 21;47(4):726-33. Epub 2006 Jan 26.)

[21] Chobanian AV, Bakris GL, Black HR, et al.; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003 Dec;42(6):1206-52. Epub 2003 Dec 01.

[22] Strippoli GF, et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ. 2004 Oct 9;329(7470):828.

[23] Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 1. A meta-analysis of randomised clinical trials. Diabetes Metab. 2004 Dec;30(6):487-96.

[24] Diagnosis and Management of Chronic **Heart Failure** in the Adult: **ACC/AHA 2005 Guideline Update** for the (J Am Coll Cardiol 2005) http://www.acc.org/clinical/guidelines/failure/index.pdf

[25] **PROGRESS** Collaborative Group. Randomised trial of perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack.Lancet 2001 Sep29;358(9287):1033-41.
(Arima H, et al.; for the PROGRESS Collaborative Group. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens. 2006 Jun;24(6):1201-1208.)
Patel A; **ADVANCE** Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40.

[26] Yusuf S, Sleight P, et al. The Heart Outcomes Prevention Evaluation (**HOPE**) Study Investigators, Effects of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. N Engl J Med 2000 342: 145-153.

[27] Palmer, B. Managing Hyperkalemia Caused by Inhibitors of the Renin-Angiotensin-Aldosterone System. N Engl J Med 2004;351:585-92.

Additional references:

Abuissa H, Jones PG, Marso SP, et al. **ACE or ARB** for **prevention of type 2 diabetes** a meta-analysis of randomized clinical trials. J Am Coll Cardiol. 2005 Sep 6;46(5):821-6. CONCLUSIONS: The use of an ACE inhibitor or ARB should be considered in patients with pre-diabetic conditions such as metabolic syndrome, hypertension, impaired fasting glucose, family history of diabetes, obesity, congestive heart failure, or coronary heart disease.

ACCF/AHA 2011 Focused Update of the Guidelines for the Management of Patients With **Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011 0: j.jacc.2011.02.009. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.02.009v1.pdf

ACTIVE I Investigators. Irbesartan in Patients with Atrial Fibrillation. N Engl J Med 2011; 364:928-938. (Not reduce CV events)

Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of **new-onset diabetes mellitus** : an emerging theme. Drugs. 2006;66(9):1169-77.

Ahimastos AA, et al. Brief communication: ramipril markedly improves walking ability in patients with **peripheral arterial disease**: a randomized trial. Ann Intern Med. 2006 May 2;144(9):660-4.

Ahimastos AA, Aggarwal A, D'Orsa KM, et al. Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. JAMA. 2007 Oct 3;298(13):1539-47.
Perindopril reduced both aortic stiffness and aortic root diameter in patients with **Marfan syndrome** taking standard beta-blocker therapy, possibly through attenuation of TGF-beta signaling. Large clinical trials are needed to assess the clinical benefit of angiotensin II blockade in Marfan syndrome.

Al-Mallah MH, et al. Angiotensin-converting enzyme inhibitors in coronary artery disease and **preserved left ventricular** systolic function: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2006 Apr 18;47(8):1576-83. Epub 2006 Mar 29. Treatment of 100 patients for an average duration of 4.4 years prevents either of the adverse outcomes (one death, or one nonfatal myocardial infarction, or one cardiovascular death or one coronary revascularization procedure). CONCLUSIONS: The cumulative evidence provided by this meta-analysis shows a modest favorable effect of ACEIs on the outcome of patients with CAD and preserved LV systolic function.

Andersen NH, et al. Long-term dual blockade with candesartan and lisinopril in hypertensive patients with diabetes: the **CALM II** study. Diabetes Care. 2005 Feb;28(2):273-7.

Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor **zofenopril** on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (**SMILE**) Study Investigators. N Engl J Med. 1995 Jan 12;332(2):80-5.

TOP

American College of Cardiology Foundation, , American Heart Association Task Force on Practice Guidelines, , American Association for Thoracic Surgery, , Society of Cardiovascular Anesthesiologists, , Society of Thoracic Surgeons, Hillis, L. David, Smith, Peter K., Anderson, Jeffrey L., et al. **2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery**: Executive Summary. J Am Coll Cardiol 2011 0: j.jacc.2011.08.008. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.08.008v1.pdf

Anand IS, Rector TS, et al. Effect of baseline blood pressure and changes in systolic blood pressure over time on the effectiveness of valsartan in the Valsartan Heart Failure Trial (**Val-HeFT**). Circ Heart Fail 2008; 1: 34-42.

Appel LJ, Wright JT Jr, Greene T, et al.; for the African American Study of Kidney Disease and Hypertension Collaborative Research Group. (**AASK** trial) Long-term Effects of Renin-Angiotensin System-Blocking Therapy and a Low Blood Pressure Goal on Progression of Hypertensive Chronic Kidney Disease in African Americans. Arch Intern Med. 2008 Apr 28;168(8):832-839. Despite the benefits of renin-angiotensin system-blocking therapy on CKD progression, most African Americans with hypertensive CKD who are treated with currently recommended BP therapy continue to progress during the long term.

ARB Trialists Collaboration. Effects of **telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers** in 15 trials enrolling 138 769 individuals. J Hypertens 2011; 29:623-635.

Arnold JM, et al.; Canadian Cardiovascular Society. **Canadian** Cardiovascular Society consensus conference recommendations on **heart failure 2006**: diagnosis and management. Can J Cardiol. 2006 Jan;22(1):23-45. Erratum in: Can J Cardiol. 2006 Mar 1;22(3):271. http://www.ccs.ca/download/consensus_conference/consensus_conference_archives/Arnold_CCS_final.pdf (Arnold JM, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure **update 2007**: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol. 2007 Jan;23(1):21-45.)

Asselbergs FW, et al. Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004 Nov 2;110(18):2809-16. Epub 2004 Oct 18. In microalbuminuric subjects, treatment with fosinopril had a significant effect on urinary albumin excretion. In addition, fosinopril treatment was associated with a trend in reducing cardiovascular events. Treatment with pravastatin did not result in a significant reduction in urinary albumin excretion or cardiovascular events.

Baguet JP, et al. A placebo-controlled comparison of the efficacy and tolerability of candesartan cilexetil, 8 mg, and losartan, 50 mg, as monotherapy in patients with essential hypertension, using 36-h ambulatory blood pressure monitoring.Int J Clin Pract. 2006 Apr;60(4):391-8.

Baker WL, Coleman CI, et al. Effectiveness of therapies for **stable ischemic heart** disease. Systematic review comparative effectiveness of **ACE inhibitors or ARBs** for ischemic heart disease. *Annals Internal Med* 2009

Bangalore Sripal, Kumar Sunil, Kjeldsen Sverre E et al. Antihypertensive drugs and **risk of cancer**: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. *The Lancet Oncology* - 30 November 2010 DOI: 10.1016/S1470-2045(10)70260-6. (Combo of ACEI & ARB possible higher risk)

Bangalore Sripal, Kumar Sunil, Wetterslev Jørn, et al. **Angiotensin receptor blockers and risk of myocardial infarction**: meta-analyses and trial sequential analyses of 147□020 patients from randomised trials. BMJ 2011;342:doi:10.1136/bmj.d2234 (Published 26 April 2011). –no increase in MI.

Barnett AH, Bain SC, Bouter P, ET AL. Angiotensin-Receptor Blockade versus Converting-Enzyme Inhibition in Type 2 Diabetes and Nephropathy (**DETAIL**). N Engl J Med. 2004 Oct 31

Beavers Craig James, Dunn Steven P, Macaulay Tracy E. The Role of Angiotensin Receptor Blockers in Patients with Angiotensin-Converting Enzyme Inhibitor–**Induced Angioedema**. Articles Ahead of Print published on 1 April 2011, DOI 10.1345/aph.1P630. Ann Pharmacother ;45:520-524.

Beckett NS, Peters R, Fletcher AE, et al. the **HYVET** Study Group. Treatment of Hypertension in Patients 80 Years of Age or Older. N Engl J Med. 2008 Mar 31; [Epub ahead of print] The results provide evidence that antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older is beneficial.

Berger AK, Duval S, Manske C, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. Am Heart J. 2007 Jun;153(6):1064-73. ACE inhibitors & ARB are underused in patients with heart failure with chronic kidney disease. Given the reduction in 30-day & 1-year mortality, these medications should be considered in most patients with heart failure, independent of underlying renal function. Among patients on hemodialysis, further investigation is warranted.

Bhaskaran K, Douglas I, Evans S, et al. Angiotensin receptor blockers and **risk of cancer**: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. BMJ. 2012 Apr 24;344:e2697.

Bhatia RS, et al. Outcome of **heart failure with preserved ejection fraction** in a population-based study. N Engl J Med. 2006 Jul 20;355(3):260-9.

Bilous R, Chaturvedi N, Sjølie AK, et al. Effect of Candesartan on Microalbuminuria and Albumin Excretion Rate in Diabetes: Three Randomized Trials (**DIRECT**). Ann Intern Med. 2009 May 18. [Epub ahead of print]. Candesartan, 32 mg/d, for 4.7 years did not prevent microalbuminuria in mainly normotensive patients with type 1 or type 2 diabetes.

Borghi C, et al. on behalf of the Survival of Myocardial Infarction Long-Term Evaluation (**SMILE**) Study. Effects of early angiotensin-converting enzyme inhibition in patients with non-ST-elevation acute anterior myocardial infarction. Am Heart J. 2006 Sep;152(3):470-7.

Bosch J, Lonn E, Pogue J, Arnold JM, Dagenais GR, Yusuf S; **HOPE/HOPE-TOO** Study Investigators. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension. Circulation. 2005 Aug 30;112(9):1339-46.

Braunwald E, et al. Rosenberg YD, Rouleau JL; **PEACE** Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004 Nov 11;351(20):2058-68. Epub 2004 Nov 7. In patients with stable coronary heart disease and preserved left ventricular function who are receiving "current standard" therapy and in whom the rate of cardiovascular events is lower than in previous trials of ACE inhibitors in patients with vascular disease, there is no evidence that the addition of an ACE inhibitor provides further benefit in terms of death from cardiovascular causes, myocardial infarction, or coronary revascularization. (Solomon SD, et al; Prevention of Events with ACE inhibition (PEACE) Investigators. **Renal function** and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. Circulation. 2006 Jul 4;114(1):26-31. Epub 2006 Jun 26.)

Brener SJ, Ivanc TB, Poliszczuk R, et al. Antihypertensive therapy and regression of coronary artery disease: insights from the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (**CAMELOT**) and Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation (NORMALISE) trials. Am Heart J. 2006 Dec;152(6):1059-63.

Brooke BS, Habashi JP, Judge DP, et al. Angiotensin II blockade (**losartan**) and aortic-root dilation in **Marfan's** syndrome. N Engl J Med. 2008 Jun 26;358(26):2787-95. In a small cohort study, the use of ARB therapy in patients with Marfan's syndrome significantly slowed the rate of progressive aortic-root dilation.

Brown MJ, McInnes GT, Papst CC, et al. **Aliskiren** and the calcium channel blocker **amlodipine combination** as an initial treatment strategy for hypertension control (**ACCELERATE**): a randomised, parallel-group trial. Lancet. 2011 Jan 12.

Burgess E, Muirhead N, de Cotret PR, Chiu A, Pichette V, Tobe S; the **SMART** (Supra Maximal Atacand Renal Trial) Investigators. Supramaximal Dose of Candesartan in Proteinuric Renal Disease. J Am Soc Nephrol. 2009 Feb 11. [Epub ahead of print] The authors randomly assigned 269 patients who had persistent proteinuria (>/=1 g/d) despite 7 wk of treatment with the highest approved dosage of candesartan (16 mg/d) to 16, 64, or 128 mg/d candesartan for 30 wk. In conclusion, proteinuria that persists despite treatment with the maximum recommended dosage of candesartan can be reduced by increasing the dosage of candesartan further, but serum potassium levels should be monitored during treatment.

Caton AR, Bell EM, Druschel CM, Werler MM, Lin AE, Browne ML, et al. **Antihypertensive medication use during pregnancy** and the risk of cardiovascular malformations. Hypertension 2009;54:63-70.

Casas JP, et al. Effect of inhibitors of the **renin-angiotensin system** and other antihypertensive drugs on **renal outcomes**: systematic review and meta-analysis. Lancet. 2005 Dec 10;366(9502):2026-2033. INTERPRETATION: The benefits of ACE inhibitors or ARBs on renal outcomes in placebo-controlled trials probably result from a blood-pressure-lowering effect. In patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain unproven, and there is uncertainty about the greater renoprotection seen in non-diabetic renal disease.

Chang CH, Lin JW, Wu LC, Lai MS. Angiotensin receptor blockade and risk of **cancer** in type 2 diabetes mellitus: A nationwide case-control study. J Clin Oncol 2011; DOI 10.1200/JCO.2011.35.1908. The results did not show an effect of ARBs as a class on increasing cancer incidence in patients with diabetes. However, there was a negative association of losartan but a positive one of candesartan and telmisartan with the overall occurrence of cancer.

Charles JA, et al. Prevention of migraine with **olmesartan** in patients with hypertension/prehypertension. Headache. 2006 Mar;46(3):503-7. Tronvik E, et al. Prophylactic treatment of migraine with an angiotensin II receptor blocker (**candesartan**): a randomized controlled trial. JAMA. 2003 Jan 1;289(1):65-9.

Chaturvedi N, Porta M, Klein R, et al. for the **DIRECT** Programme Study Group. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (**DIRECT-Protect 1**) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet. 2008 Sep 25. [Epub ahead of print]

Cheung BM, Cheung GT, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large outcome trials of angiotensin receptor blockers in hypertension. J Hum Hypertens. 2005 Aug 25; [Epub ahead of print] In conclusion, the reduction in new-onset diabetes partly offsets any increase in the risk of myocardial infarction. Most hypertensive patients require more than one class of drugs. Small differences in treatment outcome should not over-ride the importance of good blood pressure control.

Choi HK, Soriano LC, Zhang Y, Rodríguez LAG. **Calcium channel blockers, losartan**, and the risk of **incident gout** among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.

Chrysostomou A, Pedagogos E, MacGregor L.. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist **spironolactone** in patients who have persistednt proteinuria and are on long-term angiotension-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. Clin J Am Soc Nephrol. 2006 Jan 3;1:256-62.

TOP

Cice G, Di Benedetto A, D'Isa S, et al. Effects of **telmisartan** added to angiotensin-converting enzyme inhibitors on mortality and morbidity in **hemodialysis patients with chronic heart failure**: a double-blind, placebo-controlled trial. J Am Coll Cardiol. 2010;56:1701-8.

Cleland JG, et al. The perindopril 4mg od in elderly people ≥70yr with chronic heart failure (**PEP-CHF**) study. Eur Heart J. 2006 Oct;27(19):2338-45. Epub 2006 Sep 8.

Cohn JN, Tognoni G . A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure (**Val-HeFT**); Valsartan Heart Failure Trial Investigators. N Engl J Med 2001 Dec 6;345(23):1667-75.

Cooper WO, et al. Major congenital malformations after **first-trimester exposure to ACE** inhibitors. (pregnancy) N Engl J Med. 2006 Jun 8;354(23):2443-51. (see also Pharmacist's Letter July 2006)

Cooperate: The Editors Of The Lancet. **Retraction**-Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (**COOPERATE**): a randomised controlled trial. Lancet. 2009 Oct 10;374(9697):1226.

Dagenais GR, et al. Angiotensin-converting-enzyme inhibitors in **stable vascular disease without left ventricular** systolic dysfunction or heart failure:a combined analysis of three trials. Lancet. 2006 Aug 12;368(9535):581-8.

Dahlof B, et al. LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (**LIFE**): a randomised trial against atenolol. Lancet. 2002 Mar 23;359(9311):995-1003. (Lindholm LH, et al.; LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002 Mar 23;359(9311):1004-10.)(Ibsen H, et al. Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. Diabetes Care. 2006 Mar;29(3):595-600.)

Danchin N, et al. Angiotensin-Converting Enzyme Inhibitors in Patients With Coronary Artery Disease and **Absence of Heart Failure** or Left Ventricular Systolic Dysfunction: An Overview of Long-term Randomized Controlled Trials. Arch Intern Med. 2006 Apr 10;166(7):787-96. Angiotensin-converting enzyme inhibitors reduce total mortality and major cardiovascular end points in patients who have CAD and no left ventricular systolic dysfunction or heart failure. (InfoPOEMs: Angiotensin-converting enzyme (ACE) inhibitors decrease overall mortality, cardiovascular mortality, myocardial infarction risk, and stroke risk in patients with coronary artery disease (CAD) but without signs or symptoms of heart failure. The benefit is not pronounced, with only 1 death prevented in more than **400** patients treated for 2 years. (LOE = 1a))

Davies NM, Kehoe PG, Ben-Shlomo T, Martin RM. Associations of anti-hypertensive treatments (**ARBS**) with **Alzheimer's disease**, vascular dementia, and other dementias. J Alzheimer's Dis 2011; 26:699-708.

Demers C, McMurray JJ, Swedberg K; **CHARM** Investigators. Impact of candesartan on nonfatal myocardial infarction and cardiovascular death in patients with heart failure. JAMA. 2005 Oct 12;294(14):1794-8.

Dicpinigaitis PV. **Angiotensin-converting enzyme inhibitor**-induced **cough**: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):169S-173S.

Dufouil C, Chalmers J, Coskun O, et al. Effects of Blood Pressure Lowering on Cerebral White Matter Hyperintensities in Patients With Stroke. The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. Circulation. 2005 Sep 6; [Epub ahead of print]

Effect of Ramipril on the Incidence of Diabetes. (**DREAM**) N Engl J Med. 2006 Sep 15; [Epub ahead of print]

Eklind-Cervenka M, Benson L, Dahlstro¨m U, et al. Association of **candesartan vs losartan** with all-cause mortality in patients with **heart failure**. JAMA. 2011;305(2):175-182.

Elder DHJ, Wei L, Szwejkowski BR, et al. The impact of renin-angiotensin-aldosterone system blockade on heart failure outcomes and mortality in patients identified to have **aortic regurgitation**. A large population cohort study. J Am Coll Cardiol 2011; 58:2084-2091.

EMA: European Medicines Agency. European Medicines Agency Oct/11 concludes that benefit-risk balance of **angiotensin II receptor antagonists remains positive** (**cancer** etc) [press release]. October 20, 2011.

European Medicines Agency, 2011. Questions and answers on the review of **angiotensin II receptor antagonists and the risk of cancer** [online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2011/10/WC500116862.pdf [Accessed 22 December 2011].

EXPERT PANEL ON INTEGRATED GUIDELINES FOR CARDIOVASCULAR HEALTH AND RISK REDUCTION IN CHILDREN AND ADOLESCENTS. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011 Nov 14. [Epub ahead of print]

Evangelista A, Tornos P, Sambola A, et al.. Long-term vasodilator therapy in patients with severe aortic regurgitation. N Engl J Med. 2005 Sep 29;353(13):1342-9. (InfoPOEMs: This small study does not find that vasodilators such as nifedipine (Procardia) or enalapril (Vasotec) delay the need for aortic valve replacement (AVR) in patients with asymptomatic but severe aortic regurgitation. The study was quite small, and although it is possible that a small but clinically important benefit was not detected, this seems unlikely since the trends actually run against active treatment. (LOE = 1b-))

FDA June/10 June 14, 2010 (Washington, DC) — The FDA is conducting a safety review of the angiotensin receptor blocker **olmesartan** (Benicar, Daiichi Sankyo) after determining that diabetic patients taking the drug in two completed phase 3 trials may have had an excess risk of **cardiovascular death**, the regulatory body has announced [1].The safety announcement says that the FDA's review is "ongoing, and the agency has not concluded that Benicar increases the risk of death. FDA currently believes that the benefits of Benicar in patients with high blood pressure continue to outweigh its potential risks." The agency also notes that "other controlled clinical trials evaluating Benicar and other ARBs have not suggested an increased risk of cardiovascular-related death."The primary end points of the two trials were dominated by measures of renal function.In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, conducted in Europe, 4447 patients with diabetes and at least one additional cardiovascular risk factor, but no evidence of renal dysfunction, were randomized to receive either olmesartan at 40 mg/day (n=2232) or placebo (n=2215). The trial, sponsored by Sankyo Pharma, ended in July 2009 [2]. In the Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT), conduced in Japan and Hong Kong, 566 patients with diabetes and renal dysfunction were randomized to receive olmesartan at 10 mg/day to 40 mg/day (n=282) or placebo (n=284).

FDA June/11 Food and Drug Administration drug safety: **No increase in risk of cancer** with certain blood pressure drugs—**angiotensin receptor blockers (ARBs).** June 2, 2011. http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm

FDA Apr/12 notified healthcare professionals of possible risks when using blood pressure medicines containing aliskiren with other drugs called angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with diabetes or kidney (renal) impairment. (Altitude study)

Ferrari R; Perindopril and Remodeling in Elderly with Acute Myocardial Infarction Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (**PREAMI**) Study. Arch Intern Med. 2006 Mar 27;166(6):659-66.

Fitzharris P, Jordan A. Investigating **recurrent angio-oedema**. BMJ. 2011 Oct 24;343:d6607.

Gillespie EL, White CM, Kardas M, et al. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. Diabetes Care. 2005 Sep;28(9):2261-6. CONCLUSIONS: ACEIs or ARBs may decrease patients' odds of developing new-onset type 2 diabetes but does not reduce the odds of mortality, cardiovascular, or cerebrovascular outcomes over the study follow-up periods among patients with hypertension.

GISSI-AF Investigators, Disertori M, Latini R, Barlera S, et al. Valsartan for prevention of recurrent **atrial fibrillation**. N Engl J Med. 2009 Apr 16;360(16):1606-17. Treatment with valsartan was not associated with a reduction in the incidence of recurrent atrial fibrillation.

Gliddon AE, Doré CJ, Black CM, et al. Prevention of vascular damage in **scleroderma** and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. Arthritis Rheum. 2007 Nov;56(11):3837-46. Administration of quinapril for up to 3yrs had no demonstrable effects on the occurrence of upper limb digital ulcers or on other vascular manifestations of lcSSc in this pt population.

Goldenberg I, et al. **Polymorphism** in the angiotensinogen gene, hypertension, and ethnic differences in the risk of recurrent coronary events. Hypertension. 2006 Oct;48(4):693-9. Epub 2006 Aug 28.

Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of **Raynaud's phenomenon**. BMJ. 2012 Feb 7;344:e289.

Guertin JR, Jackevicius CA, Cox JL, et al. The potential economic impact of **restricted access to angiotensin-receptor blockers** (ARBs). *CMAJ* 2011; DOI: 10.1503/cmaj.100787ARBs.

Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and **aortic rupture**: a population-based case-control study. Lancet. 2006 Aug 19;368(9536):659-665.

Haller H, Ito S, Izzo JL Jr, et al. **Olmesartan** for the delay or prevention of microalbuminuria in type 2 diabetes. (**ROADMAP**) N Engl J Med 2011;364:907-17. (n=4447 over 3.2yr. Improved microalbuminuria, but increased fatal CV events)

Harel Z et al. The effect of combination treatment with **aliskiren and blockers of the renin-angiotensin system** on hyperkalaemia and acute kidney injury: systematic review and meta-analysis. BMJ. 2012 Jan 9;344:e42.

Haymore BR, Yoon J, et al. Risk of **angioedema** with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Ann Allergy Ast

TOP

2008 Nov;101(5):495-9. Limited evidence suggests that for patients who develop angioedema when taking an ACE-I, the risk of development of any subsequent angioedema when taking an ARB is between 2% and 17%; for confirmed angioedema, the risk is 0% to 9.2%.
Heinze G, et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal **transplantation**. J Am Soc Nephrol. 2006 Mar;17(3):889-99. Epub 2006 Feb 15.
Health Canada Jan/12 **RASILEZ** (aliskiren) and RASILEZ HCT (aliskiren/hydrochlorothiazide) - Potential Risks of Cardiovascular and Renal Adverse Events in Patients with Type 2 Diabetes - Novartis Pharmaceuticals Canada Inc. The combination of **aliskiren with ACE inhibitors and ARBs is now contraindicated in patients with type 2 diabetes**. The Product Monograph will be updated accordingly.

Heart Failure Society Of America. **HFSA 2006** Comprehensive Heart Failure Practice Guideline. J Card Fail. 2006 Feb;12(1):e1-2.
Heran BS, et al. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD003822. The evidence from this review suggests that there are no clinically meaningful BP lowering differences between available ARBs. The BP lowering effect of ARBs is modest and similar to ACE inhibitors as a class; the magnitude of average trough BP lowering for ARBs at maximum recommended doses and above is -8/-5 mmHg. Furthermore, 60 to 70% of this trough BP lowering effect occurs with recommended starting doses. The review did not provide a good estimate of the incidence of harms associated with ARBs because of the short duration of the trials and the lack of reporting of adverse effects in many of the trials.
Heran BS, Musini VM, Bassett K, et al. Angiotensin receptor blockers for heart failure. Cochrane Database Syst Rev. 2012 Apr 18;4:CD003040. In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity. ARBs are better tolerated than ACEIs but do not appear to be as safe and well tolerated as placebo in terms of withdrawals due to adverse effects. Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.
Hippisley-Cox J., Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. BMJ 2005;330:1059-1063 (7 May), doi:10.1136/bmj.330.7499.1059. Conclusions: Combo of statins, aspirins, & beta-blockers improve survival in high risk pts with cardiovascular dx, although the addition of an angiotensin converting enzyme inhibitor conferred no additional benefit despite the analysis being adjusted for congestive cardiac failure.
Ho JM, Juurlink DN. Considerations when prescribing **trimethoprim-sulfamethoxazole**. CMAJ. 2011 Oct 11.
Hou FF, Zhang X, Zhang GH, et al. Efficacy & safety of **benazepril** for advanced chronic renal (**CKD pts**) insufficiency. N Engl J Med. 2006 Jan 12;354(2):131-40. (InfoPOEMs: In a group of nondiabetic patients with serum creatinine levels between 3.0 & 5.0 mg/dL, benazepril slows the progression of renal disease. These pts were carefully monitored for any changes in renal function during the first 8 weeks, and were carefully screened & monitored to detect any early adverse effects on renal function. (LOE = 1b))
Huang CC, Chan WL, Chen YC, Chen TJ, Lin SJ, Chen JW, Leu HB. Angiotensin II Receptor Blockers and **Risk of Cancer** in Patients With Systemic Hypertension. Am J Cardiol. 2011 Jan 20.
Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. (**ACCOMPLISH**)N Engl J Med. 2008 Dec 4;359(23):2417-2428. The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.
Julius S, et al.; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the **VALUE** randomised trial. Lancet. 2004 Jun 19;363(9426):2022-31. (Kjeldsen SE, et al.; for the VALUE Trial. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertens. 2006 Jul;24(7):1405-1412.)(Julius S, et al. The Valsartan Antihypertensive Long-Term Use Evaluation (**VALUE**) trial: outcomes in patients receiving monotherapy. Hypertension. 2006 Sep;48(3):385-91. Epub 2006 Jul 24.)
Julius S, et al.; Trial of Preventing Hypertension (**TROPHY**) Study. Feasibility of treating prehypertension with an ARB.(candesartan) N Engl J Med. 2006 Apr 20;354(16):1685-97. Epub 2006 Mar 14. (see also PharmLetter May06.) (InfoPOEMs: This study tells us what we already know (that is, that blood pressure medications reduce blood pressure), but says nothing about what really matters: Does intervention in patients with prehypertension improve patient-oriented outcomes? The choice to study such an expensive drug is also disappointing, but not surprising. Given that the number needed to treat [NNT] to prevent 1 stroke, heart attack, or death in patients with mild hypertension is 140 for 5 years (http://www.jr2.ox.ac.uk/bandolier/index.html), it is likely that the actual clinical benefit of treating prehypertension is even smaller. (LOE = 1b))
Kalavrouziotis D, Buth KJ, Cox JL, and Baskett RJ. Should all patients be treated with an angiotensin converting enzyme inhibitor after **coronary artery bypass graft surgery**? The impact of angiotensin converting enzyme inhibitors, statins, and beta blockers after coronary artery bypass graft surgery. Am Heart J 2011.
Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (**HEAAL** study): a randomised, double-blind trial. *Lancet* 2009; DOI:10.1016/S0140-6736(09)61913-9.
Korniyenko A, Alviar CL, Cordova JP, Messerli FH. **Visceral angioedema** due to angiotensin-converting enzyme inhibitor therapy. Cleve Clin J Med. 2011 May;78(5):297-304.
Kjeldsen SE, et al. **VALUE** Trial Investigators. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertens. 2006 Jul;24(7):1405-12.
Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (**TRACE**) Study Group. N Engl J Med. 1995 Dec 21;333(25):1670-6.
Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of **angioedema** associated with enalapril. Arch Intern Med. 2005 Jul 25;165(14):1637-42. RESULTS: Angioedema occurred in 86 of 12 557 (0.68%) of the subjects.
Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; on behalf of the Guideline Development Group. **Management of hypertension**: summary of **NICE** guidance. BMJ. 2011 Aug 25;343:d4891.
Ku E, Park J, Vidhun J, Campese V. The **hazards of dual renin-angiotensin blockade** in chronic kidney disease. Arch Intern Med. 2009 Jun 8;169(11):1015-8.
Kuenzli A, Bucher HC, Anand I, et al. **Meta-analysis** of combined therapy with angiotensin receptor antagonists versus ACE inhibitors alone in patients with **heart failure**. PLoS One. 2010 Apr 1;5(4):e9946.
Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: Effect of **Monotherapy and Combination** Therapy with Inhibitors of the Renin Angiotensin System on Proteinuria in Renal Disease. Ann Intern Med. 2007 Nov 5; [Epub ahead of print] ARBs reduce **proteinuria**, independent of the degree of proteinuria and of underlying disease, to a similar degree as placebo or calcium-channel blocker. Reduction in proteinuria from ARB and ACE inhibitors is similar, but their combination is more effective than either drug alone.
Kurnik D, Vesterman-Landes J, Bialik M, et al. **Hyperkalemia and renal function during monotherapy and dual Renin-Angiotensin blockade** in the community setting. Clin Ther. 2011 Apr;33(4):456-64.
Lacourcière Y, Poirier L, Lefebvre J, et al. Increasing the doses of both **diuretics and angiotensin receptor blockers** is beneficial in subjects with uncontrolled systolic hypertension. Can J Cardiol. 2010 Oct;26(8):313-9.
Latini R, Tognoni G, Maggioni AP, et al. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of **aspirin**: systematic overview of individual data from 96,712 randomized patients. Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group. J Am Coll Cardiol. 2000 Jun;35(7):1801-7.
Lee VC, Rhew DC, Dylan M, Badamgarav E, et al. Meta-Analysis: Angiotensin-Receptor Blockers in Chronic Heart Failure and High-Risk Acute Myocardial Infarction. Ann Intern Med. 2004 Nov 2;141(9):693-704.
Lee HY, Hong BK, Chung WJ, et al. Phase IV, 8-week, multicenter, randomized, active treatment-controlled, parallel group, efficacy, and tolerability study of **high-dose candesartan** cilexetil combined with hydrochlorothiazide in Korean adults with stage II hypertension. Clin Ther. 2011 Aug;33(8):1043-56.
Lennestal R, Olausson PO, Kallen B. **Maternal use of antihypertensive drugs in early pregnancy** and delivery outcome, notably the presence of heart defects in the infants. Eur J Clin Pharmacol 2 009;65:615-25.
Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, Burns K, Manns B, White C, Madore F, Moist L, Klarenbach S, Barrett B, Foley R, Jindal K, Senior P, Pannu N, Shurraw S, Akbari A, Cohn A, Reslerova M, Deved V, Mendelssohn D, Nesrallah G, Kappel J, Tonelli M; Canadian Society of Nephrology. Guidelines for the management of **chronic kidney disease**. CMAJ. 2008 Nov 18;179(11):1154-62. http://www.cmaj.ca/cgi/data/179/11/1154/DC1/1
Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of **dementia** in a predominantly male population: prospective cohort analysis. BMJ. 2010 Jan 12;340:b5465. doi:10.1136/bmj.b5465.
Li DK, Yang C, Andrade S, et al. Maternal exposure to **angiotensin converting enzyme inhibitors** in the **first trimester and risk of malformations** in offspring: A retrospective cohort study. BMJ 2011.
Madison JR, Spies C, Schatz IJ, Masaki K, Chen R, et al. **Proteinuria** and risk for stroke and coronary heart disease during 27 years of follow-up: the Honolulu Heart Program. Arch Intern Med. 2006 Apr 24;166(8):884-9.
Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. **Val-HeFT** Investigators (Valsartan Heart Failure Trial). J Am Coll Cardiol 2002 Oct 16;40(8):1414-21.

TOP

Makani H, Bangalore S, Romero J, et al. Effect of Renin-Angiotensin system blockade (ACEI/ARB) on calcium channel blocker-associated **peripheral edema**. Am J Med. 2011 Feb;124(2):128-35.
Makani H, Messerli FH, Romero J, et al. Meta-Analysis of Randomized Trials of **Angioedema** as an Adverse Event of Renin-Angiotensin System Inhibitors. Am J Cardiol. 2012 Apr 20.
Massie BM, Carson PE, McMurray JJ, et al.; the **I-PRESERVE** Investigators. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N Engl J Med. 2008 Nov 11. [Epub ahead of print]
Matchar DB, McCrory DC, Orlando LA, et al. **Systematic Review**: Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers for Treating Essential Hypertension. Ann Intern Med. 2007 Nov 5; [Epub ahead of print] Available evidence shows that ACE inhibitors and ARBs have similar effects on blood pressure control, and that ACE inhibitors have higher rates of cough than ARBs. Data regarding other outcomes are limited.
Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of **enalapril and losartan in type 1** diabetes. N Engl J Med. 2009 Jul 2;361(1):40-51. Early blockade of the renin-angiotensin system in patients with type 1 diabetes did not slow nephropathy progression but slowed the progression of retinopathy.
McAlister, Finlay A., Zhang, Jianguo, Tonelli, Marcello, et al. The safety of **combining angiotensin-converting-enzyme inhibitors with angiotensin-receptor blockers** in elderly patients: a population-based longitudinal analysis. CMAJ 2011 0: cmaj.101333.
McAlister FA; for the Renin Angiotension System Modulator Meta-Analysis Investigators. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in **normotensive atherosclerotic** patients: a collaborative meta-analysis of randomized trials. Eur Heart J. 2011 Oct 31.
McAlister FA. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in **normotensive** atherosclerotic patients: a collaborative meta-analysis of randomized trials. Eur Heart J. 2012 Feb;33(4):505-514.
McCall KL, Craddock D, Edwards K. Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Type 1 Receptor Blockers on the Rate of **New-Onset Diabetes Mellitus**: A Review and Pooled Analysis. Pharmacotherapy. 2006 Sep;26(9):1297-306.
McDonald MA, Simpson SH, Ezekowitz JA, et al. Angiotensin receptor blockers and risk of **myocardial infarction**: systematic review. BMJ. 2005Oct 15;331(7521):873. Epub 2005 Sep 23. CONCLUSIONS: Treatment with angiotensin receptor blockers was not associated with a significantly increased risk of myocardial infarction. The 95% confidence intervals do, however, not exclude an increase of up to 16% in the risk of myocardial infarction or a reduction in risk of up to 25%. Until further information specifically dealing with this issue is available from large prospective trials, our findings may alleviate recent concerns over the safety of this class of medications.
McDowell SE, et al. Systematic review and meta-analysis of **ethnic differences** in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ. 2006 May 20;332(7551):1177-81. Epub 2006 May 5.
McMurray JJ, Young JB, Dunlap ME, et al. Relationship of dose of background angiotensin-converting enzyme inhibitor to the benefits of candesartan in Candesartan in Heart failure: Assessment of reduction in Mortality and morbidity (**CHARM**)-added trial. American Heart Journal 2006;151: 992-998
Medical Letter. **Aliskiren (Tekturna)** for Hypertension. April 9,2007.
Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol. 2009 Dec;20(12):2641-50. Epub 2009 Nov 19.
Mitchell AA. Fetal risk from **ACE inhibitors in the first trimester**. BMJ 2011; DOI:10.1136/bmj.d5931.
Mogensen CE, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (**CALM**) study. BMJ. 2000 Dec 9;321(7274):1440-4.
Musini VM, Fortin PM, Bassett K, et al. Blood pressure lowering efficacy of **renin inhibitors** for primary hypertension: a Cochrane systematic review. J Hum Hypertens. 2009 Jan 22. We concluded that aliskiren has a dose-related blood pressure lowering effect better than placebo and magnitude of effect is similar to that determined for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.
Nakamae H, et al. Notable effects of angiotensin II receptor blocker, **valsartan, on acute cardiotoxic changes** after cyclophosphamide, doxorubicin, vincristine, & prednisolone. Cancer. 2005 Dec 1;104(11):2492-8.
NAVIGATOR Study Group, Effect of **Valsartan** on the Incidence of Diabetes and Cardiovascular Events. N Engl J Med 2010 0: NEJMoa1001121.
NICE: National Institute for Health and Clinical Excellence. **Hypertension Guidelines**. Aug 2011. http://www.nice.org.uk/nicemedia/live/13561/56015/56015.pdf
Nissen SE, Tuzcu EM, Libby P, et al. **CAMELOT** Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004 Nov 10;292(18):2217-25.
Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. **Hyperkalaemia**. BMJ. 2009 Oct 23;339:b4114. doi: 10.1136/bmj.b4114.
O'Hare AM, Kaufman JS, Covinsky KE, et al. Current guidelines for using angiotensin-converting enzyme inhibitors and angiotensin II-receptor antagonists in **chronic kidney disease**: is the evidence base relevant to **older** adults? Ann Intern Med. 2009 May 19;150(10):717-24.
Oertelt-Prigione Sabine, Crosignani Andrea, Gallieni Maurizio et al. Severe **hepatic encephalopathy** in a patient with liver cirrhosis after administration of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker combination therapy: a case report. Journal of Medical Case Reports 2010, 4:141doi:10.1186/1752-1947-4-141.
Opelz G and Döhler B. Treatment of kidney transplant recipients with ACE inhibitor/ARB and risk of **respiratory tract cancer**: a collaborative transplant study report. Am J Transplant 2011; DOI: 10.1111/j.1600-6143.2011.03681.x. (Higher cancers in subgroup: ACEi/ARB & if smokers)
Owan TE, et al. Trends in prevalence and outcome of **heart failure with preserved ejection fraction**. N Engl J Med. 2006 Jul 20;355(3):251-9.
Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. **ATLAS** Study Group. Circulation. 1999;100:2312-8.
Papademetriou V, Farsang C, Elmfeldt D, et al.; Study on Cognition and Prognosis in the Elderly study group. Stroke prevention with the angiotensin II type 1-receptor blocker candesartan in elderly patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (**SCOPE**). J Am Coll Cardiol. 2004 Sep 15;44(6):1175-80. (Zanchetti A, Elmfeldt D. Findings and implications of the Study on COgnition and Prognosis in the Elderly (SCOPE) - A review. Blood Press. 2006;15(2):71-9.)
Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; **AVOID** Study Investigators. **Aliskiren** 150→300mg od combined with losartan 100mg od in type 2 diabetes and nephropathy. N Engl J Med. 2008 Jun 5;358(23): 2433-46. (n=599 6months) Aliskiren may have renoprotective effects that are independent of its blood-pressure-lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended renoprotective treatment.
Pasternak B, Svanström H, Callréus T, et al. Use of angiotensin receptor blockers and the risk of **cancer**. Circulation 2011; 123:1729-1736.
Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the **ADVANCE** trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy. (InfoPOEMs: Perindopril (Aceon) plus indapamide (Lozol) is better than placebo in decreasing clinically relevant events in patients with type 2 diabetes who are at high risk of cardiovascular complications. Whether the combination is better than other medications -- like aspirin -- isn't addressed by this study. (LOE = 1b))
Persson F, Lewis JB, Lewis EJ, Rossing P, Hollenberg NK, Parving HH; for the **AVOID** study investigators. Impact of Baseline Renal Function on the Efficacy and Safety of Aliskiren Added To Losartan in Patients with Type 2 Diabetes and Nephropathy. Diabetes Care. 2010 Aug 6.
Petrella R, Michailidis P. Retrospective Analysis of Real-World Efficacy of **Angiotensin Receptor Blockers Versus Other Classes** of Antihypertensive Agents in Blood Pressure Management. Clin Ther. 2011 Aug 31.
Pharmacist's Letter. Angiotensin Receptor Blockers (ARBS) and **Cancer Risk.** Aug 2010.
Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse Effects of **Combination Angiotensin II Receptor Blockers Plus Angiotensin-Converting Enzyme Inhibitors** for Left Ventricular Dysfunction: A Quantitative Review of Data From Randomized Clinical Trials. Arch Intern Med. 2007 Oct 8;167(18):1930-6. Four studies (N = 17 337; mean follow-up, 25 months [range, 11-41 months]) were selected. Combination ARB plus

TOP

control treatment that included ACE inhibitors was associated with significant increases in medication discontinuations because of adverse effects in patients with chronic heart failure (RR, 1.38 [95% CI, 1.22-1.55]) or in patients with acute myocardial infarction with symptomatic left ventricular dysfunction (RR, 1.17 [95% CI, 1.03-1.34]), and for both conditions there were significant increases in worsening renal function (RR, 2.17 [95% CI, 1.59-2.97] and RR, 1.61 [95% CI, 1.31-1.98], respectively), hyperkalemia (RR, 4.87 [95% CI, 2.39-9.94] and RR, 1.33 [95% CI, 0.90-1.98], respectively; the latter was not significant), and symptomatic hypotension (RR, 1.50 [95% CI, 1.09-2.07], and RR, 1.48 [95% CI, 1.33-3.18], respectively).Combination ARB plus ACE inhibitor therapy in subjects with symptomatic left ventricular dysfunction was accompanied by marked increases in adverse effects.

Pilote L, Abrahamowicz M, Eisenberg M, et al. Effect of **different angiotensin-converting-enzyme inhibitors** on mortality among elderly patients with congestive **heart failure**. CMAJ. 2008 May 6;178(10):1303-11. When prescribing ACE inhibitors to patients, physicians should consider a possible 10%-15% increase in mortality with captopril and enalapril compared with ramipril among patients with congestive heart failure.

Pitt B, et al.; QUIET Study Group. The QUinapril Ischemic Event Trial (**QUIET**): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. Am J Cardiol. 2001 May 1;87(9):1058-63.

Pohl MA, Blumenthal S, Cordonnier DJ, et al. Independent and Additive Impact of Blood Pressure Control and Angiotensin II Receptor Blockade on Renal Outcomes in the Irbesartan Diabetic Nephropathy Trial: Clinical Implications and Limitations. J Am Soc Nephrol. 2005 Oct;16(10):3027-37. Epub 2005 Aug 24.

Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs. a diuretic. A report from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (**ALLHAT**). Arch Intern Med 2005; 165:936-46. (InfoPOEMs: It's blood pressure reduction, not the choice of drug, that prevents renal function decline in patients with hypertension, with or without diabetes. Neither the calcium channel blocker amlodipine (Norvasc) nor the angiotensin-converting enzyme inhibitor lisinopril (Prinivil) prevents the combined outcome of end-stage renal disease or a 50% decrease in renal function any better than the diuretic chlorthalidone (Hygroton). Results were the same in patients with already compromised renal function, as well as in patients with type 2 diabetes. (LOE = 1b))

Reboldi G, Angeli F, Cavallini C, Gentile G, Mancia G, Verdecchia P. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. J Hypertens. 2008 Jul;26(7):1282-9. This overview suggests that angiotensin II receptor blockers are as effective as angiotensin-converting enzyme inhibitors on the risk of myocardial infarction, cardiovascular mortality and total mortality. Angiotensin II receptor blockers may be slightly more protective than angiotensin-converting enzyme inhibitors on the risk of stroke.

REIN-Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia)Lancet. 1997 Jun 28;349(9069):1857-63.

Ridker PM, et al. Valsartan, Blood Pressure Reduction, and **C-Reactive Protein**. Primary Report of the Val-MARC Trial. Hypertension. 2006 May 19; [Epub ahead of print]

Ritter J M. Therapeutics: **Angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension**. BMJ 2011;342:doi:10.1136/bmj.d1673 (Published 7 April 2011)

Rouleau JL, Warnica WJ, Baillot R, et al.; IMAGINE (Ischemia Management with Accupril post-bypass Graft via Inhibition of the converting Enzyme) Investigators. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. Circulation. 2008 Jan 1;117(1):24-31. Epub 2007 Dec 10. In patients at low risk of cardiovascular events after CABG, routine early initiation of angiotensin-converting enzyme inhibitor therapy does not appear to improve clinical outcome up to 3 years after CABG; however, it increases the incidence of adverse events, particularly early after CABG. Thus, early after CABG, initiation of angiotensin-converting enzyme inhibitor therapy should be individualized and continually reassessed over time according to risk.

Ripamonti V, et al. Angiotensin-converting enzyme inhibitors slow recovery from **anemia** following cardiac surgery. Chest. 2006 Jul;130(1):79-84.

Robins GW, Scott LJ. **Eprosartan**: a review of its use in the management of hypertension. Drugs. 2005;65(16):2355-77.

Rossing K, Schjoedt KJ, Jensen BR, et al. Enhanced renoprotective effects of **ultrahigh doses of irbesartan** in patients with type 2 diabetes and microalbuminuria. Kidney Int. 2005 Sep;68(3):1190-8.

Ruggenenti P, Perna A, Loriga G, et al.; **REIN-2** Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease: multicentre, randomised controlled trial. Lancet. 2005 Mar 12;365(9463):939-46. (Interpretation: In pts with non-diabetic proteinuric nephropathies receiving background ACE-inhibitor therapy, no additional benefit from further blood-pressure reduction by felodipine could be shown.)

Ruggenenti P, Fassi A, Ilieva AP, ET AL. Preventing Microalbuminuria in Type 2 Diabetes (**BENEDICT**). N Engl J Med. 2004 Oct 31 (Ruggenenti P, et al. Impact of Blood Pressure Control and Angiotensin-Converting Enzyme Inhibitor Therapy on New-Onset **Microalbuminuria** in Type 2 Diabetes: A Post Hoc Analysis of the **BENEDICT** Trial. J Am Soc Nephrol. 2006 Nov 2; [Epub ahead of print]) Ruggenenti P, Iliev I, Costa GM, Parvanova A, Perna A, Giuliano GA, Motterlini N, Ene-Iordache B, Remuzzi G; Bergamo Nephrologic Diabetes Complications Trial Study Group. Preventing left ventricular hypertrophy by ACE inhibition in hypertensive patients with type 2 diabetes: a prespecified analysis of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). Diabetes Care. 2008 Aug;31(8):1629-34. Epub 2008 Apr 28.

Sandset EC, Bath PMW, Boysen G et al. The angiotensin-receptor blocker **candesartan for treatment of acute stroke (SCAST):** A randomised, placebo-controlled, double-blind trial. *Lancet* 2011.

Schaer BA, Schneider C, Jick SS, et al. Risk for incident **AF** in patients who receive antihypertensive drugs. Ann Intern Med 2010; 152:78-84.

Schrader J, Luders S, Kulschewski A, et al.; Acute Candesartan Cilexetil Therapy in Stroke Survivors Study Group. The **ACCESS** Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke. 2003 Jul;34(7):1699-703. Epub 2003 Jun 19.

Schellenbaum GD, et al. **Weight loss, muscle strength**, and angiotensin-converting enzyme inhibitors in older adults with congestive heart failure or hypertension. J Am Geriatr Soc. 2005 Nov;53(11):1996-2000.

Schrader J, Luders S, Kulschewski A, et al. **MOSES** Study Group. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005 Jun;36(6):1218-26. Epub 2005 May 5.

Schmieder RE, Philipp T, Gueredíaga J, et al. Long-term antihypertensive efficacy and safety of the oral direct renin inhibitor **aliskiren**: a 12-month randomized, double-blind comparator trial with **hydrochlorothiazide**. Circulation. 2009;119:417– 445.

Sciarretta Sebastiano; Palano Francesca; Tocci Giuliano; et al. Antihypertensive Treatment and Development of Heart Failure in Hypertension: A Bayesian Network Meta-analysis of Studies in Patients With Hypertension and High Cardiovascular Risk. Arch Intern Med. 2010;0(2010):archinternmed.2010.427.

Shahinfar S, Simpson RL, Carides AD, et al. Safety of **losartan** in hypertensive patients with **thiazide-induced hyperuricemia**. Kidney Int 1999;56:1879-1885.

Shiraishi J, Sawada T, Koide M, et al; Kyoto Heart Study Group. Cardio-Cerebrovascular Protective Effects of **Valsartan** in High-Risk Hypertensive Patients With Coronary Artery Disease (from the Kyoto Heart Study). Am J Cardiol. 2012 May 1;109(9):1308-14.

Sipahi I, Debanne SM, Rowland DT et al. **Angiotensin-receptor blockade and risk of cancer**: Meta-analysis of randomised controlled trials. Lancet Oncol 2010; DOI:10.1016/S1470-2045(10)70106-6.

Sink KM, Leng X, et al. Angiotensin-converting enzyme inhibitors and **cognitive decline** in older adults with hypertension: results from the cardiovascular health study. Arch Intern Med. 2009 Jul 13;169(13):1195-202. Centrally active ACE inhibitors included **captopril** (Capoten, Bristol-Myers Squibb), **fosinopril** (Monopril, Bristol-Myers Squibb), **lisinopril**, **perindopril**, **ramipril** (Altace, King Pharmaceuticals), and **trandolapril** (Mavik, Abbott Laboratories). Non-centrally-active ACE inhibitors included **benazepril** (Lotensin, Novartis Pharmaceuticals), **enalapril** (Vasotec, Merck), **moexipril** (Univasc, Schwarz Pharma), and **quinapril** (Accupril, Pfizer).

Sjølie AK, Klein R, Porta M, et al. for the **DIRECT** Programme Study Group. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (**DIRECT-Protect 2**): a randomised placebo-controlled trial. Lancet. 2008 Sep 25. [Epub ahead of print]

Slagman Maartje C J, Waanders Femke, Hemmelder Marc H, et al. for the HONEST (HOlland NEphrology STudy) Group. Moderate dietary **sodium restriction added to angiotensin converting enzyme inhibition** compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. BMJ 2011;343:doi:10.1136/bmj.d4366 (26 July 2011)

Solomon SD, Appelbaum E, Manning WJ, et al.; for the Aliskiren in Left Ventricular Hypertrophy (**ALLAY**) Trial Investigators. Effect of the Direct Renin Inhibitor Aliskiren, the Angiotensin Receptor Blocker Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy. Circulation. 2009 Jan 19. [Epub ahead of print] Aliskiren was as effective as losartan in promoting LV mass regression. Reduction in LV mass with the combination of aliskiren plus losartan was not significantly different from that with losartan monotherapy, independent of blood pressure lowering. These findings suggest that aliskiren was as effective as an angiotensin receptor blocker in attenuating this measure of myocardial end-organ damage in hypertensive patients with LV hypertrophy.

Solomon SD, Hee Shin S, Shah A, et al. Effect of the direct rennin inhibitor aliskiren on left ventricular remodelling following myocardial infarction *with systolic dysfunction.(**ASPIRE**) Eur Heart J 2011; 32: 1227–34.*

Strippoli GF, Craig MC, Schena FP, Craig JC. Role of blood pressure targets and specific antihypertensive agents used to prevent **diabetic nephropathy** and delay its progression. J Am Soc Nephrol. 2006 Apr;17 Suppl 2:S153-5. On the basis of available RCT evidence, ACEi are the only agents with proven renal benefit in patients who have diabetes with no nephropathy and the only agents with proven survival benefit in patients who have diabetes with nephropathy.

TOP

Sumukadas D, Witham MD, Struthers AD, McMurdo ME. Effect of **perindopril on physical function** in elderly people with functional impairment: a randomized controlled trial. CMAJ. 2007 Oct 9;177(8):867-74. Use of the ACE inhibitor perindopril improved exercise capacity in functionally impaired elderly people who had no heart failure and maintained health-related quality of life. The degree of improvement was equivalent to that reported after 6 months of exercise training.

Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-Selective Benefits of Medications in Treatment of **Acute Aortic Dissection** (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol. 2011 Sep 23.

Takahashi A, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on **chronic haemodialysis**--a randomized study. Nephrol Dial Transplant. 2006 Sep;21(9):2507-12. Epub 2006 Jun 9.

Tapaninen T, Backman JT, et al. **Itraconazole**, a P-glycoprotein and CYP3A4 inhibitor, markedly raises the plasma concentrations and enhances the renin-inhibiting effect of **aliskiren**. Clin Pharmacol. 2011Mar;51(3):359-67.

Teo KK, Yusuf S, Pfeffer M, et al.; ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of **aspirin**: a systematic review. Lancet. 2002 Oct 5;360(9339):1037-43. Review. Erratum in: Lancet 2003 Jan 4;361(9351):90.

Thind GS, Mahapatra RK, Johnson A, et al. **Low-dose captopril** titration in patients with moderate-to-severe hypertension treated with diuretics. *Circulation* 1983;67: 1340-6.

Thomas L. Managing **hypertensive emergencies** in the ED. Can Fam Physician. 2011 Oct;57(10):1137-97.

Thornley-Brown D, et al. Differing effects of antihypertensive drugs on the incidence of diabetes mellitus among patients with hypertensive kidney disease. (**AASK**) Arch Intern Med. 2006 Apr 10;166(7):797-805.

Tocci G, Paneni F, Palano F, et al. Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers and **Diabetes**: A Meta-Analysis of Placebo-Controlled Clinical Trials. Am J Hypertens. 2011 May;24(5):582-90.

Tofts RPH, Ferrer G, Oliveira E. How should one investigate a **chronic cough**? *Cleveland Clinic Journal of Medicine 2011; 78(2):84-85, 89; doi:10.3949/ccjm.77a.10033.*

TRANSCEND: The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (**TRANSCEND**) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008 Aug 29. [Epub ahead of print] (Mann JF, Schmieder RE, Dyal L, McQueen MJ, Schumacher H, et al.; TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) Investigators. Effect of telmisartan on renal outcomes: a randomized trial. Ann Intern Med. 2009 Jul 7;151(1):1-10, W1-2. Epub 2009 May 18.)

Tu K, Gunraj N, Mamdani M. Is **ramipril** really better than other angiotensin-converting enzyme inhibitors after acute myocardial infarction? Am J Cardiol. 2006 Jul 1;98(1):6-9. Epub 2006 Apr 27.

Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003 Nov 8;362(9395):1527-35.

Turner ST, Schwartz GL, Chapman AB, et al. **Plasma renin activity** predicts blood pressure responses to beta-blocker and thiazide diuretics as monotherapy and add-on for hypertension. Am J Hypertens 2010.

van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors **reduce mortality in hypertension**: A meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. Eur Heart J2012.

Verdecchia P, et al. Do angiotensin II receptor blockers increase the risk of myocardial infarction? Eur Heart J. 2005 Nov;26(22):2381-6. Epub 2005 Aug 4.

Viollet L, Thrush PT, Flanigan KM, et al. Effects of Angiotensin-Converting Enzyme Inhibitors and/or Beta Blockers on the **Cardiomyopathy in Duchenne Muscular Dystrophy**. Am J Cardiol. 2012 Mar 29.

Weir MR, Hollenberg NK, Zappe DH, et al. Antihypertensive effects of double the maximum dose of **valsartan in African-American's** with type 2 diabetes mellitus and albuminuria. J Hypertens. 2010 Jan;28(1):186-93.

Winkelmayer WC, et al. Efficacy & Safety of Angiotensin II Receptor Blockade in **Elderly** Patients With Diabetes. Diabetes Care. 2006 Oct;29(10):2210-2217. Of 1,513 people, 421 (27.8%) were aged >65 yrs (max 74 yrs).

Wright JT Jr, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the **AASK** trial.; African American Study of Kidney Disease and Hypertension Study Group. JAMA 2002 Nov 20;288(19):2421-31.

Wright JM, Musini VM. First-line drugs for hypertension. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD001841. First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

Yoon C, Yang HS, Jeon I, et al. Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and **cancer risk**: a meta-analysis of observational studies. CMAJ. 2011 Oct 4;183(14):E1073-84.

Yusuf S, Teo KK, Pogue J, et al for the **ONTARGET** investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008: 358:1547-1559. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit.
Mann JF, Schmieder RE, McQueen M, et al. ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008 Aug 16;372(9638):547-53. In people at high vascular risk, telmisartan's effects on major renal outcomes are similar to ramipril. Although **combination** therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes.

Yusuf S, Diener HC, Sacco RL, et al. **PRoFESS** Study Group. **Telmisartan** to Prevent Recurrent Stroke and Cardiovascular Events. N Engl J Med. 2008 Aug 27. [Epub ahead of print] Therapy with telmisartan initiated soon after an ischemic stroke and continued for 2.5 years did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes.

Zanchetti A, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the **VALUE** trial. J Hypertens. 2006 Nov;24(11):2163-2168.

Zhang Y, Zhang P, Mu Y, et al. The role of renin-angiotensin system blockade therapy in the prevention of **atrial fibrillation**: a meta-analysis of randomized controlled trials. Clin Pharmacol Ther. 2010 Oct;88(4):521-31.

Zhang Y, Fonarow GC, Sanders PW, et al. A Propensity-Matched Study of the Comparative Effectiveness of **Angiotensin Receptor Blockers Versus Angiotensin-Converting Enzyme Inhibitors** in Heart Failure Patients Age ≥65 Years. Am J Cardiol. 2011 Sep 3.

TOP

BETA-BLOCKER (BB): Comparison Chart

[1] Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.

[2] 2001 Canadian Hypertension Recommendations: What's New & What's Not so New but is Still Important. CJHP 2002;55:4651.

[3] FA McAlister, M Levine, KB Zarnke, et al. The 2000 recommendations for the management of hypertension. Can J Cardiol 2001; 17(5):543-559.

[4] 1999 Canadian recommendations for the management of hypertension. CMAJ 1999;161(Suppl):S1-S16.

[5] **1999 World Health Organization**–International Society of Hypertension Guidelines:Management of Hypertension. J Hypertens 1999;17:151-183.

[6] 6th Report-Joint National Committee on Prevention,Detection,Evaluation & Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413-46.

[7] Drugs for hypertension. Med Lett Drugs Ther 2001;43:17-22.
Webb AJS, Fischer U, Rothwell PM. Effects of **beta-blocker selectivity** on **blood pressure variability and stroke**: a systematic review. Neurology 2011;77:731–737.

[8] Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD. 2011.

[9] Micromedex 2010 online

[10] Hansten & Horn's Drug Interactions: Analysis & Management-Facts & Comparisons 2008.

[11] Treatment Guidelines: Drugs for Hypertension from The Medical Letter Feb 2003, repeated June 2005, January 2009, and updated January 2012.

[12] The **2012** Canadian Hypertension Education Program **Recommendations** www.hypertension.ca
Canadian Hypertension Education Program. **2011 CHEP recommendations** for the management of **hypertension**. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf .

[13] ALLHAT Working Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (**ALLHAT**). JAMA 2000;283:1967-75.

[14] Liu P, Arnold JM, Belenkie I, et al. The 2002/3 Canadian Cardiovascular Society consensus guideline update for the diagnosis and management of **heart failure**. Can J Cardiol. **2003** Mar 31;19(4):347-56.

[15] **Treatment Guidelines**: Drugs for Treatment of **Heart Failure** from The Medical Letter April **003**& Jan **2006.**

[16] Jessup M, Brozena S. Heart Failure. N Engl J Med 2003;348:2007-18.

[17] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (The **JNC 7**); JAMA. **2003** May;289(19):2560-72.

[18] ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction **2004**. http://www.acc.org/clinical/guidelines/stemi/index.pdf

[19] Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003 Nov 8;362(9395):1527-35.

[20] van der Woude HJ, Zaagsma J, Postma DS, Winter TH, van Hulst M, Aalbers R. Detrimental Effects of {beta}-Blockers in COPD: A Concern for Nonselective {beta}-Blockers. Chest. 2005 Mar;127(3):818-24.

[21] Dulin BR, Haas SJ, Abraham WT, Krum H. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. Am J Cardiol 2005; 95:896-898.

[22] Snow V, Barry P, Fihn SD, et al; American College of Physicians; American College of Cardiology Chronic Stable Angina Panel. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2004 Oct 5;141(7):562-7. Erratum in: Ann Intern Med. 2005 Jan 4;142(1):79.

[23] Diagnosis and Management of Chronic **Heart Failure** in the Adult: **ACC/AHA 2005 Guideline Update** for the (J Am Coll Cardiol 2005) http://www.acc.org/clinical/guidelines/failure/index.pdf
(**European 2005** Chronic Heart failure guidelines http://www.escardio.org/NR/rdonlyres/8A2848B4-5DEB-41B9-9A0A-5B5A90494B64/0/CHFFullTextehi205FVFW170505.pdf)

[24] Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet. 2004 Nov 6;364(9446):1684-9.

[25] Cissoko H, Jonville-Bera AP, Swortfiguer D, Giraudeau B, Autret-Leca E. [Neonatal outcome after exposure to beta adrenergic blockers late in pregnancy.] Arch Pediatr. 2005 May;12(5):543-7.
Seely EW, Ecker J. Clinical practice. **Chronic hypertension in pregnancy**. N Engl J Med. 2011 Aug 4;365(5):439-46.

[26] Chen ZM, Pan HC, Chen YP, et al.; **COMMIT** (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5;366(9497):1622-32. Second Chinese Cardiac Study COMMIT/CCS-2. Metoprolol 5mg IV over 2-3mins x 3 if HR & BP ok, then 15mins later 50mg po q6h Day 0-1, then 200mg controlled release od vs placebo x ~15days. ↓Reinfarction 2 vs 2.5%, ↓Ventricular fibrilation 2.5 vs 3 %, BUT ↑Cardiogenic shock 5 vs 3.9% (risk more with heart failure, systolic BP <120 & in the first 24hrs). INTERPRETATION: The use of early beta-blocker therapy in acute MI reduces the risks of reinfarction & ventricular fibrillation, but increases the risk of cardiogenic shock, esp. during the first day or so after admission. Consequently, it might generally be prudent to consider starting **beta-blocker therapy in hospital only when the haemodynamic condition after MI has stabilised**.

[27] Merkel C, Marin R, Angeli P, et al.. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. Gastroenterology. 2004 Aug;127(2):476-84.

[28] Jutabha R, Jensen DM, et al. Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. Gastroenterology. 2005 Apr;128(4):870-81.
Chalasani N, Boyer TD. Primary prophylaxis against variceal bleeding: beta-blockers, endoscopic ligation, or both? Am J Gastroenterol. 2005 Apr;100(4):805-7.

[29] Singh BN, Singh SN, Reda DJ, et al.; Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005 May 5;352(18):1861-72. Conclusion: Amiodarone and sotalol are equally efficacious in converting atrial fibrillation to sinus rhythm. Amiodarone is superior for maintaining sinus rhythm, but both drugs have similar efficacy in patients with ischemic heart disease. Sustained sinus rhythm is associated with an improved quality of life and improved exercise performance. (InfoPOEMs: Amiodarone was more effective than sotalol at maintaining normal sinus rhythm in patients with chronic atrial fibrillation. However, there was a worrisome trend toward increased mortality in the active treatment groups, and other studies have not found a benefit of rhythm therapy over rate control with anticoagulation. (LOE = 1b))

[30] Groszmann RJ. Beta-blockers to Prevent **Gastroesophageal Varices** in Patients with Cirrhosis. N Engl J Med 2005;353:2254-61. (Timolol is ineffective in preventing varices in unselected patients with cirrhosis & portal hypertension & are associated with an increased number of adverse events.) (InfoPOEMs: Beta-blockers do not prevent the development of varices in patients with cirrhosis and they increase the likelihood of serious adverse events. They are still appropriate for patients with established varices to prevent gastrointestinal hemorrhage. (LOE = 1b))

[31] Fleisher LA, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology. **ACC/AHA 2006** guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative **beta-blocker** therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology. Circulation. 2006 Jun 6;113(22):2662-74.
http://www.americanheart.org/downloadable/heart/1142081026765PeriopFinal.pdf
Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF. ACC/AHA 2007 Guidelines on **Perioperative Cardiovascular** Evaluation and Care for **Noncardiac Surgery**. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation. 2007 Sep 27; [Epub ahead of print]

[32] Devereaux PJ, Beattie WS, et al.. How strong is the evidence for the use of perioperative {beta} blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. BMJ. 2005 Jul 4; CONCLUSION: The evidence that perioperative beta blockers reduce major cardiovascular events is encouraging but too unreliable to allow definitive conclusions to be drawn.

[33] Perioperative Beta-Blockers. Pharmacist's Letter Aug, 2006.
POISE Study Group. Effects of extended-release metoprolol succinate (100mg SR x1 preop, then ~200mg SR od x 30 days if HR>45 & SBP>100) in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008 May 12. [Epub ahead of print] Our results highlight the risk in assuming a perioperative beta-blocker regimen has benefit without substantial harm, and the importance and need for large randomised trials in the perioperative setting. N=8,351.

TOP

Dunkelgrun M et al. Bisoprolol (Starting dose 2.5 mg daily, titrated to a perioperative heart rate of 50 to 70 beats per minute) and fluvastatin (fixed dose of 80 mg) for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery (before surgery, median: 34 days): A randomized controlled trial (**DECREASE-IV**). Ann Surg 2009 Jun; 249:921. (n=1066)
Patients randomized to bisoprolol (N = 533) had a lower incidence of perioperative cardiac death and nonfatal MI than those randomized to bisoprolol-control (2.1% vs. 6.0% events; hazard ratios: 0.34; 95% confidence intervals: 0.17-0.67; P = 0.002). Patients randomized to fluvastatin experienced a lower incidence of the end point than those randomized to fluvastatin-control therapy (3.2% vs. 4.9% events; hazard ratios: 0.65; 95% confidence intervals: 0.35-1.10), but statistical significance was not reached (P = 0.17). Bisoprolol was associated with a significant reduction of 30-day cardiac death and nonfatal MI, while fluvastatin showed a trend for improved outcome.

Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (**ESC**) and endorsed by the European Society of Anaesthesiology (ESA). Eur Heart J. 2009 Aug 27. [Epub ahead of print]

Fleischmann KE, Beckman JA, Buller CE, et al. **2009 ACCF/AHA** focused update on **perioperative beta blockade**. A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2009; DOI:10.1016/j.jacc.2009.07.004. Available at: http://content.onlinejacc.org. *Circulation* 2009: DOI: 10.1161/CIRCULATIONAHA.109.192690. Available at: http://circ.ahajournals.org.. http://content.onlinejacc.org/cgi/reprint/j.jacc.2009.07.004v1.pdf

Additional sources:

Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate **hypertension during pregnancy**. Cochrane Database Syst Rev 2007;(1):CD002252.

ACCF/AHA 2011 Focused Update of the Guidelines for the Management of Patients With **Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011 0: j.jacc.2011.02.009. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.02.009v1.pdf

ACCF- AHA-HRS Atrial Fibrillation 2011 Focused Update. Circulation 2011. http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181fa3cf4v1 (Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010; DOI: 10.1161/CIR.0b013e3181fa3cf4.)
Wann L. Samuel, Curtis Anne B., Ellenbogen Kenneth A., et al. **2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Circulation published February 14, 2011, doi:10.1161/CIR.0b013e31820f14c0 http://circ.ahajournals.org/cgi/reprint/CIR.0b013e31820f14c0v1

American College of Cardiology Foundation, , American Heart Association Task Force on Practice Guidelines, , American Association for Thoracic Surgery, , Society of Cardiovascular Anesthesiologists, , Society of Thoracic Surgeons, Hillis, L. David, Smith, Peter K., Anderson, Jeffrey L., et al. **2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery**: Executive Summary. J Am Coll Cardiol 2011 0: j.jacc.2011.08.008. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.08.008v1.pdf

Arnold JM, et al.; Canadian Cardiovascular Society. **Canadian** Cardiovascular Society consensus conference recommendations on **heart failure 2006**: diagnosis and management. Can J Cardiol. 2006 Jan;22(1):23-45. Erratum in: Can J Cardiol. 2006 Mar 1;22(3):271. http://www.ccs.ca/download/consensus_conference/consensus_conference_archives/Arnold_CCS_final.pdf (Arnold JM, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure **update 2007**: Prevention, management during intercurrent illness or acute decompensation, & use of biomarkers. Can J Cardiol. 2007 Jan;23(1):21-45.)

Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. **Perioperative** beta blockers in patients having non-cardiac surgery: a meta-analysis. Lancet. 2008 Dec 6;372(9654):1962-76. Epub 2008 Nov 13.
Noncardiac surgical patients given perioperative beta-blockers had the same rate of death from all causes, cardiovascular deaths, and congestive heart failure as patients given placebo. The rate of nonfatal myocardial infarctions was lower (number needed to treat [NNT] = 63) at the expense of a higher rate of nonfatal strokes (number needed to treat to harm [NNTH] = 275). In other words, for every 4 heart attacks averted, we would cause 1 stroke. (LOE = 1a-)

Bangalore S, Parkar S, Grossman E, Messerli FH. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of **new-onset diabetes** mellitus. Am J Cardiol. 2007 Oct 15;100(8):1254-62. Epub 2007 Aug 10. In conclusion, beta blockers are associated with an increased risk for new-onset DM, with no benefit for the end point of death or myocardial infarction and with a 15% increased risk for stroke compared with other agents. This risk was greater in patients with higher baseline body mass indexes and higher baseline fasting glucose levels and in studies in which beta blockers were less efficacious antihypertensive agents compared with other treatments.

Bangalore S, et al. Relation of Beta-Blocker–Induced Heart Rate Lowering and Cardioprotection in Hypertension. J Am Coll Cardiol. 2008 October;52:1482–9. In contrast to patients with myocardial infarction and heart failure, beta-blocker–associated reduction in heart rate increased the risk of cardiovascular events and death for hypertensive patients.

Barron TI et al. Beta blockers and **breast cancer mortality**: a population-based study. J Clin Oncol 2011; 29:2635.

Barsheshet A, Goldenberg I, O-Uchi J, et al. Mutations in cytoplasmic loops of the **KCNQ1 channel** and the risk of life-threatening events: implications for mutation-specific response to Beta-blocker therapy in type 1 **long-QT syndrome**. Circulation. 2012;125:1988 –1996.

Beta-Blocker Evaluation of Survival Trial Investigators. (**BEST** trial)A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001 May 31;344(22):1659-67. In a demographically diverse group of patients with NYHA class III and IV heart failure, bucindolol resulted in no significant overall survival benefit.

Bradley D, et al.; American College of Chest Physicians. Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005 Aug;128(2 Suppl):39S-47S.

Brodine WN, Tung RT, Lee JK, et al. MADIT-II Research Group. Effects of beta-blockers on implantable cardioverter defibrillator therapy and survival in the patients with ischemic cardiomyopathy (from the Multicenter Automatic Defibrillator Implantation Trial-II). Am J Cardiol. 2005 Sep 1;96(5):691-5.

Buckmiller L, Dyamenahalli U, Richter GT. Propranolol for airway **hemangiomas**: Case report of novel treatment. Laryngoscope. 2009 Jul 31. [Epub ahead of print]

Chen ZM, Pan HC, Chen YP, et al.; **COMMIT** (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5;366(9497):1622-32. Second Chinese Cardiac Study COMMIT/CCS-2. Metoprolol 5mg IV over 2-3mins x 3 if HR & BP ok, then 15mins later 50mg po q6h Day 0-1, then 200mg controlled release od vs placebo x ~16days. ↓Reinfarction 2 vs 2.5%, ↓Ventricular fibrilation 2.5 vs 3 %, BUT ↑Cardiogenic shock 5 vs 3.9%. INTERPRETATION: The use of early beta-blocker therapy in acute MI reduces the risks of reinfarction & ventricular fibrillation, but increases the risk of cardiogenic shock, esp. during the first day or so after admission. Consequently, it might generally be prudent to consider starting **beta-blocker therapy in hospital only when the haemodynamic condition after MI has stabilised**.(InfoPOEMs: The early use of metoprolol in patients with acute myocardial infarction who are also receiving thrombolytics and aspirin provides no short-term benefit compared with placebo. Since the early use, however, increases the risk of cardiogenic shock, it may be wise to delay starting metoprolol until the patient is hemodynamically stable. (LOE = 1b))

Chen JM, Heran BS, Perez MI, Wright JM. Blood pressure lowering efficacy of **beta-blockers** as second-line therapy for primary hypertension. **Cochrane** Database Syst Rev. **2010** Jan 20;(1):CD007185. Addition of a beta-blocker to diuretics or calcium-channel blockers reduces BP by 6/4mmHg at 1 times the starting dose and by 8/6 mmHg at 2 times the starting dose. When the blood pressure lowering effect of beta-blockers from this review was compared to that of thiazide diuretics from our previous review (Chen 2009), second-line beta-blockers reduce systolic BP to the same extent as second-line thiazide diuretics, but reduce diastolic BP to a greater degree. The different effect on diastolic BP means that beta-blockers have little or no effect on pulse pressure whereas thiazides cause a significant dose-related decrease in pulse pressure. This difference in the pattern of BP lowering with beta-blockers as compared to thiazides might be the explanation for the fact that beta-blockers appear to be less effective at reducing adverse cardiovascular outcomes than thiazide diuretics, particularly in older individuals.

Cleland JG, et al. COMET Investigators. A comparison of the effects of carvedilol and metoprolol on well-being, morbidity, and mortality (the "patient journey") in patients with heart failure: a report from the Carvedilol Or Metoprolol European Trial (**COMET**). J Am Coll Cardiol. 2006 Apr 18;47(8):1603-11. Epub 2006 Mar 29. (InfoPOEMs: Carvedilol (Coreg) treatment of patients with New York Heart Association (NYHA) functional class II-IV heart failure decreases mortality over 4 years more than metoprolol (number needed to treat = 18). Hospitalization rates, length of stay, and patient reports of symptoms are not different between the 2 drugs. (LOE = 1b))

Connolly SJ, et al. Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) Investigators. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA. 2006 Jan 11;295(2):165-71. Despite use of advanced ICD technology and treatment with a beta-blocker, shocks occur commonly in the first year after ICD implant. Amiodarone plus beta-blocker is effective for preventing these shocks and is more effective than sotalol but has an increased risk of drug-related adverse effects.

Cresci S, Kelly RJ, Cappola TP, et al. Clinical and **genetic** modifiers of long-term survival in heart failure. J Am Coll Cardiol 2009; 54:432-444). DOI:10.1016/j.jacc.2009.05.009.

Dahlof B, Devereux RB, Kjeldsen SE, et al.; **LIFE** Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002 Mar 23;359(9311):995-1003.

Dahlof B, Sever PS, Poulter NR, Wedel H, et al. **ASCOT** Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre RCT. Lancet. 2005 Sep 10;366(9489):895-906.

De Giorgi Vincenzo; Grazzini Marta; Gandini Sara; et al. Treatment With {beta}-Blockers and Reduced Disease Progression in Patients With **Thick Melanoma**. Arch Intern Med. 2011;171(8):779-781.

TOP

Devereaux PJ, Beattie WS, Choi PT, et al.. How strong is the evidence for the use of perioperative {beta} blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. BMJ. 2005 Jul 4; CONCLUSION: The evidence that perioperative beta blockers reduce major cardiovascular events is encouraging but too unreliable to allow definitive conclusions to be drawn.

Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of **COPD**. Thorax. 2008 Apr;63(4):301-5. Epub 2007 Oct 19. The use of beta blockers by inpatients with exacerbations of COPD is well tolerated and may be associated with reduced mortality. The potential protective effect of beta blockers in this population warrants further study.

Dib N, Oberti F, Cales P. Current management of the complications of **portal hypertension**: variceal bleeding and ascites. CMAJ. 2006 May 9;174(10):1433-43.

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (**MERIT-HF**) Lancet. 1999 Jun 12;353(9169):2001-7.

Ellenberger C, Tait G, Beattie WS. **Chronic beta Blockade** Is Associated with a Better Outcome after **Elective Noncardiac Surgery** than Acute beta Blockade: A Single-center Propensity-matched Cohort Study. Anesthesiology. 2011 Apr;114(4):817-23.

Espinola-Klein C, Weisser G, Jagodzinski A, et al. {beta}-Blockers in Patients With Intermittent Claudication and Arterial Hypertension: Results From the **Nebivolol or Metoprolol in Arterial Occlusive Disease** Trial. Hypertension. 2011 Aug;58(2):148-54.

EXPERT PANEL ON INTEGRATED GUIDELINES FOR CARDIOVASCULAR HEALTH AND RISK REDUCTION IN CHILDREN AND ADOLESCENTS. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011 Nov 14. [Epub ahead of print]

Fleisher LA, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology. **ACC/AHA 2006** guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative **beta-blocker** therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology. Circulation. 2006 Jun 6;113(22):2662-74. http://www.americanheart.org/downloadable/heart/1142081026765PeriopFinal.pdf

Flynn NO, Timmis A, Henderson R, Rajesh S, Fenu E; on behalf of the Guideline Development Group. Management of **stable angina**: summary of **NICE** guidance. BMJ. 2011 Aug 5;343:d4147. doi: 10.1136/bmj.d4147.

Fonarow GC, Abraham WT, Albert NM, et al. OPTIMIZE-HF Investigators and Coordinators. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the **OPTIMIZE-HF** program. J Am Coll Cardiol. 2008 Jul 15;52(3):190-9. The continuation of beta-blocker therapy in patients hospitalized with decompensated HF is associated with lower post-discharge mortality risk & improved treatment rates. In contrast, withdrawal of beta-blocker therapy is associated with worse risk and propensity-adjusted mortality.

Fontana RJ, Sanyal AJ, Ghany MG, et al. HALT-C Trial Group. Factors that Determine the Development and Progression of **Gastroesophageal Varices** in Patients with Chronic **Hepatitis C**. Gastroenterology. 2010 Mar 5.

Frithsen IL, Simpson WM Jr. Recognition and management of acute medication poisoning. Am Fam Physician. 2010 Feb 1;81(3):316-23.

Garcia-Pagan JC, Villanueva C, Albillos A, et al. Nadolol plus isosorbide mononitrate alone or associated with band ligation in the prevention of **recurrent bleeding**: a multicentre randomised controlled trial. Gut. 2009 Aug;58(8):1144-50. Epub 2009 Feb 12. Adding EBL (endoscopic band ligation) to pharmacological treatment did not reduce recurrent bleeding, the need for rescue therapy, or mortality, and was associated with more adverse events. Furthermore, associating EBL to drug therapy did not reduce the high rebleeding risk of HVPG (hepatic venous pressure gradient) non-responders.

Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver Diseases, Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of **gastroesophageal varices and variceal hemorrhage in cirrhosis**. Hepatology 2007;46(3):922-38. https://www.aasld.org/eweb/docs/practiceguidelines/VariesinGuidelinesSept2007FT.pdf

Garcia-Tsao, Guadalupe, Bosch, Jaime. Management of **Varices and Variceal Hemorrhage** in Cirrhosis. N Engl J Med 2010 362: 823-832.

Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of **hypertrophic cardiomyopathy**: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.Circulation 2011; DOI:10.1161/CIR.0b013e318223e2bd. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.06.011v1.pdf

Gillis AM, Verma A, Talajic M, et al. **CCS** Atrial Fibrillation Guidelines. **Canadian cardiovascular society atrial fibrillation guidelines 2010: rate and rhythm management**. Can J Cardiol. 2011 Jan-Feb;27(1):47-59.

Gluud LL, Klingenberg S, Nikolova D, Gluud C. **Banding ligation versus beta-blockers** as primary prophylaxis in **esophageal varices**: systematic review of randomized trials. Am J Gastroenterol. 2007 Dec;102(12):2842-8; quiz 2841, 2849. Banding ligation and beta-blockers may be used as primary prophylaxis in high-risk esophageal varices. The estimated effect of banding ligation in some trials may be biased and was associated with the duration of follow-up. Further high-quality trials are still needed.

Goldberger JJ, Bonow RO, Cuffe M, Dyer A, et al. PACE-MI Investigators. beta-Blocker use following myocardial infarction: **Low prevalence of evidence-based dosing**. Am Heart J. 2010 Sep;160(3):435-442.e1.

Go AS, et al. Atherosclerotic Disease, Vascular Function & Genetic Epidemiology (ADVANCE) Study. Statin & beta-blockers & the initial presentation of coronary heart disease. Ann Intern Med. 2006 Feb 21;144(4):229-38.

Go AS, Yang J, Gurwitz JH, Hsu J, Lane K, Platt R. Comparative effectiveness of different beta-adrenergic antagonists on mortality among adults with **heart failure** in clinical practice. Arch Intern Med. 2008 Dec 8;168(22):2415-21. Compared with atenolol, the adjusted risks of death were slightly higher with shorter-acting metoprolol tartrate but did not significantly differ for carvedilol in adults with heart failure. Our results should be interpreted cautiously and they suggest the need for randomized trials within real-world settings comparing a broader spectrum of beta-blockers for heart failure.

Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of **Raynaud's phenomenon**. BMJ. 2012 Feb 7;344:e289.

Halonen J, et al. **Intravenous** administration of **metoprolol** is more effective than oral administration in the prevention of **atrial fibrillation** after cardiac surgery. Circulation. 2006 Jul 4;114(1 Suppl):I1-4. The dosage was 1 to 3 mg/h in the intravenous group and from 25 mg twice per day to 50 mg 3 times per day in the oral group. The incidence of postoperative AF was significantly lower in the intravenous group than in the oral group (16.8% versus 28.1%, P=0.036). No serious adverse effects were associated with intravenous metoprolol therapy. CONCLUSIONS: Our study suggests that intravenous metoprolol is well-tolerated and more effective than oral metoprolol in the prevention of AF after cardiac surgery.

Halonen Jari, Loponen Pertti, Järvinen Otso, et al. **Metoprolol Versus Amiodarone** in the Prevention of **Atrial Fibrillation** After Cardiac Surgery: A Randomized Trial. *Ann Intern Med* Dec 7, 2010 153:703-709.

Hamm CW, Bassand JP, Agewall S, et al. **ESC** Guidelines for the management of **acute coronary syndromes** in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Sep 21.

Hawkins NM, Petrie MC, MacDonald MR, et al. **Heart failure and chronic obstructive pulmonary disease**. The quandary of beta-blockers and beta-agonists. J Am Coll Cardiol 2011; 57:2127-2138.

Heart Failure Society Of America. **HFSA 2006** Comprehensive Heart Failure Practice Guideline. J Card Fail. 2006 Feb;12(1):e1-2.

Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: Main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). Circulation. 2001 Apr 3;103(13):1721-6.

Hernandez AF, Hammill BG, O'Connor CM, et al. Clinical effectiveness of beta-blockers in **heart failure**. Findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry. J Am Coll Cardiol 2009; 53:184-192. In elderly patients hospitalized with heart failure and LVSD, incident beta-blocker use was clinically effective and independently associated with lower risks of death and rehospitalization. Patients with preserved systolic function had poor outcomes, and beta-blockers did not significantly influence the mortality and rehospitalization risks for these patients.

Hogeling M, Adams S, Wargon O. A randomized controlled trial of **propranolol for infantile hemangiomas**. Pediatrics. 2011 Aug;128(2):e259-66.

Huynh BC, Rovner A, Rich MW. Long-term survival in elderly patients hospitalized for **heart failure**: 14-year follow-up from a prospective randomized trial. Arch Intern Med. 2006 Sep 25;166(17):1892-8.

ICSI: Institute for Clinical Systems Improvement (ICSI). **Preoperative evaluation**. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 Jun.

Jabbour A, Macdonald PS, Keogh AM, et al. **Differences between beta-blockers** in patients with chronic **heart failure and chronic obstructive pulmonary disease**: a randomized crossover trial. J Am Coll Cardiol. 2010 Apr 27;55(17):1780-7.

TOP

Jansen L, Below J, Chang-Claude J, et al. Beta blocker use and **colorectal cancer risk**: Population-based case-control study. Cancer. 2012 May 14.
Jeon H, Jang IJ, Lee S, Ohashi K, Kotegawa T, Ieiri I, Cho JY, Yoon SH, Shin SG, Yu KS, Lim KS. **Apple Juice** Greatly Reduces Systemic Exposure to **Atenolol**. Br J Clin Pharmacol. 2012 May 11.
Jondeau Guillaume, Neuder Yannick, Eicher Jean-Christophe, et al. , and for the **B-CONVINCED** Investigators. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. European Heart Journal Advance Access published on August 30, 2009, DOI 10.1093/eurheartj/ehp323.
Juul AB, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. BMJ. 2006 Jun 24;332(7556):1482. Perioperative metoprolol did not significantly affect mortality and cardiac morbidity in these patients with diabetes.
Kanthan GL, Wang JJ, Rochtchina E, Mitchell P. Use of antihypertensive medications and topical beta-blockers and the long-term incidence of **cataract** and cataract surgery. Br J Ophthalmol. 2009 Jul 23. [Epub ahead of print]
Khan N, McAlister FA. Re-examining the efficacy of **beta-blockers** for the treatment of hypertension: a **meta-analysis**. CMAJ. 2006 Jun 6;174(12):1737-42. Beta-blockers should not be considered first-line therapy for older hypertensive patients without another indication for these agents; however, in younger patients beta-blockers are associated with a significant reduction in cardiovascular morbidity and mortality.
Komajda M, Lutiger B, Madeira H, et al.; CARMEN investigators and co-ordinators. Tolerability of carvedilol and ACE-Inhibition in mild heart failure. Results of CARMEN (Carvedilol ACE-Inhibitor Remodelling Mild CHF EvaluatioN). Eur J Heart Fail. 2004 Jun;6(4):467-75.
Kramer JM, Curtis LH, Dupree CS, Pelter D, Hernandez A, Massing M, Anstrom KJ. Comparative effectiveness of beta-blockers in **elderly patients with heart failure**. Arch Intern Med. 2008 Dec 8;168(22):2422-8; discussion 2428-32. this elderly population, the comparative effectiveness of EBBBs vs non-EBBBs was similar for 1-year survival, whereas the rehospitalization rate was higher for patients receiving EBBBs.
Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; on behalf of the Guideline Development Group. **Management of hypertension**: summary of **NICE** guidance. BMJ. 2011 Aug 25;343:d4891.
Kwon S, Thompson R, Florence M, et al. **β-Blocker Continuation After Noncardiac Surgery**: A Report From the Surgical Care and Outcomes Assessment Program. Arch Surg. 2012 Jan 16.
Lafuente-Lafuente C, et al. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of **atrial fibrillation**: a systematic review of randomized controlled trials. Arch Intern Med. 2006 Apr 10;166(7):719-28.
Lafuente-Lafuente Carmelo, Isabelle Mahé, Fabrice Extramiana. Management of **atrial fibrillation**. BMJ 2009;339:b5216, doi: 10.1136/bmj.b5216
Lanfear DE, Jones PG, Marsh S, et al. Beta2-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. JAMA. 2005 Sep 28;294(12):1526-33.
Lanfear DE, Hrobowski T, Peterson EL, et al. Association of **Beta Blocker Exposure** with Outcomes in Heart Failure Differs Between **African American** and White Patients. Circ Heart Fail. 2012 Jan 19.
Lawless CE, Tamlyn T, Shah R, Karim FM, Khan E, Creech S. **Titration of carvedilol in elderly** heart failure patients. Am J Geriatr Cardiol. 2005 Sep-Oct;14(5):230-5.
Lindholt JS, Vammen S, Juul S, Henneberg EW, Fasting H. The validity of ultrasonographic scanning as screening method for **abdominal aortic aneurysm**. Eur J Vasc Endovasc Surg. 1999;17:472– 475.
Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005 Oct 29-Nov 4;366(9496):1545-53. (InfoPOEMs: If these authors have identified all the relevant research, it appears that in comparison with placebo, beta-blockers do not reduce cardiovascular morbidity or mortality but decrease the risk of strokes. However, in comparison with other antihypertensive medications, beta-blockers are associated with a significantly higher risk of stroke. Most of the included studies used atenolol and the data on other beta-blockers are inconclusive. Before throwing the baby out with the bathwater, remember that some patients with hypertension will need beta-blockers to treat their comorbid coronary artery disease, congestive heart failure, and so forth. (LOE = 1a-))
Lo GH, Chen WC, Wang HM, Lee CC. Controlled trial of ligation plus nadolol versus **nadolol alone** for the prevention of first **variceal bleeding**. Hepatology. 2010 Jul;52(1):230-7.
McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: **beta-blocker dose, heart rate** reduction, and death in patients with heart failure. Ann Intern Med. 2009 Jun 2;150(11):784-94. The magnitude of heart rate reduction is statistically significantly associated with the survival benefit of beta-blockers in heart failure, whereas the dose of beta-blocker is not.
Medical Letter- Treatment Guidelines. **Treatment of Atrial Fibrillation**. Sept 2010.
Melhem-Bertrandt A et al. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative **breast cancer**. J Clin Oncol 2011; 29:2645.
Messerli FH, Bell DS, Fonseca V, et al. GEMINI Investigators. Body weight changes with beta-blocker use: results from GEMINI. Am J Med. 2007 Jul;120(7):610-5. (n=1106 over 5months) Patients taking metoprolol had a significant mean (+/-SE) weight gain of 1.19 (+/-0.16) kg (P <.001); patients taking carvedilol did not (0.17 [+/-0.19] kg; P =.36). Metoprolol tartrate was associated with increased weight gain compared to carvedilol; weight gain was most pronounced in subjects with hypertension and diabetes who were not taking insulin therapy.
Mitchell LB; **CCS** Atrial Fibrillation Guidelines Committee. Canadian cardiovascular society atrial fibrillation guidelines 2010: prevention and treatment of **atrial fibrillation following cardiac surgery**. Can J Cardiol. 2011 Jan-Feb;27(1):91-7.
NICE: National Institute for Health and Clinical Excellence. **Hypertension Guidelines**. Aug 2011. http://www.nice.org.uk/nicemedia/live/13561/56015/56015.pdf
Norberto L, Polese L, Cillo U, et al. A randomized study comparing ligation with propranolol for primary prophylaxis of **variceal bleeding** in candidates for liver transplantation. Liver Transpl. 2007 Sep;13(9):1272-8. In conclusion, propranolol and banding are similarly effective in reducing the incidence of variceal bleeding in candidates for LT, but ligation can be complicated by fatal bleeding and is more expensive. Our results suggest that banding should not be utilized as primary prophylaxis in transplant candidates who can be treated with BB.
October 28, 2010 (Chicago, Illinois) — Propranolol, an old drug being used off label, is an effective way to reduce vision-threatening **periocular infantile hemangiomas**, according to a study presented here at the American Academy of Ophthalmology and Middle East Africa Council of Ophthalmology 2010 Joint Meeting."[Oral] propranolol is not a common treatment used by ophthalmologists, but it may be now," said David Plager, MD, who presented the findings. "It gives impressive results." Dr. Plager is professor of ophthalmology and director of the Section of Pediatric Ophthalmology at Indiana University in Indianapolis. Propranolol, an oral beta blocker, "looks to be a very promising addition to our treatment armamentarium," Dr. Plager told Medscape Medical News. J AAPOS. 2010;14:251-256. Abstract
Ong HT. **Beta blockers in hypertension and cardiovascular disease**. BMJ. 2007 May 5;334(7600):946-9.
Oregon's Drug Effectiveness Review Project (DERP) **Beta Adrenergic Blockers: Comparative Drug Class Review** July 2009. **http://derp.ohsu.edu/final/BB_Final_Report_Update%204_09_JUL1.pdf**
Packer M, et al. Carvedilol Prospective Randomized Cumulative Survival Study Group. (**COPERNICUS**) Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001 May 31;344(22):1651-8. The previously reported benefits of carvedilol with regard to morbidity and mortality in patients with mild-to-moderate heart failure were also apparent in the patients with severe heart failure who were evaluated in this trial.
Paravastu SC, Mendonca D, Da Silva A. Beta blockers for **peripheral arterial disease**. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD005508. There is currently no evidence that beta blockers adversely affect walking distance in people with intermittent claudication. However, due to the lack of large published trials beta blockers should be used with caution if clinically indicated.
Pasker-de Jong PC, Zielhuis GA, van Gelder MM, et al. Antihypertensive treatment during pregnancy and functional development at primary school age in a historical cohort study. BJOG. 2010 May 12. Conclusions In this hypothesis-generating study, **labetalol exposure** in utero seemed to increase the risk of **ADHD** among children of primary school age, whereas prenatal methyldopa exposure might influence sleep.
Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. **INVEST** Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003 Dec 3;290(21):2805-16.
Perioperative Beta-Blockers. Pharmacist's Letter Aug,2006.
Peter K. Lindenauer, M.D., Penelope Pekow, Ph.D., Kaijun Wang et al. **Perioperative Beta-Blocker** Therapy and Mortality after Major Noncardiac Surgery. NEJM 2005; 353:349-361. *Conclusions:* Perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk, patients undergoing major noncardiac surgery. Patient safety may be enhanced by increasing the use of beta-blockers in high-risk patients (InfoPOEMs: Patients undergoing major surgery who are at high risk of complications -- those with heart disease, cerebrovascular disease, diabetes, or renal insufficiency -- benefit from perioperative beta-blockade. Low-risk patients (except perhaps those with hypertension and those undergoing high-risk surgery) do not. However, given the possible harms of suddenly discontinuing beta-blockers, those who are already taking them should continue doing so, even if they are at low-risk. (LOE = 2b))
Poldermans D, et al. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study Group. Should major vascular surgery be delayed because of **preoperative cardiac testing** in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? J Am Coll Cardiol. 2006 Sep 5;48(5):964-9. Epub 2006 Aug 17.
Poulter NR, Dobson JE, et al. **Baseline heart rate**, antihypertensive treatment, and prevention of cardiovascular outcomes in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial). J Am Coll Cardiol 2009; 54:1154-1161.
Powe DG et al. Beta-blocker drug therapy reduces **secondary cancer formation in breast cancer** and improves cancer specific survival. Oncotarget 2010; 1:628.
Price C et al. Propranolol vs corticosteroids for infantile hemangiomas. Arch Dermatol Dec 2011; 147(12):1371-76.
Propranolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002;35:72–79.

TOP

Raheem IA, Saaid R, Omar SZ, et al. **Oral nifedipine versus intravenous labetalol** for acute blood pressure control in **hypertensive emergencies of pregnancy**: a randomised trial. BJOG. 2012 Jan;119(1):78-85.
Rangel Carlos; Shu Richard G.; Lazar Lawrence D. et al; {beta}-Blockers for Chest Pain Associated With Recent **Cocaine Use** Arch Intern Med. 2010;170(10):874-879.
Redelmeier D, Scales D, Kopp A. {beta} blockers for **elective surgery** in elderly patients: population based, retrospective cohort study. BMJ. 2005 Oct 6; [Epub ahead of print] CONCLUSIONS: Patients receiving metoprolol do not have as low a perioperative cardiac risk as patients receiving atenolol, in accord with possible acute withdrawal after missed doses.
Roden DM. Clinical practice. **Long-QT syndrome**. N Engl J Med. 2008 Jan 10;358(2):169-76.
Roy D, Talajic M, Nattel S, Wyse DG, et al. Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus **rate control** for atrial fibrillation and heart failure. (**AF-CHF**) N Engl J Med. 2008 Jun 19;358(25):2667-77. In patients with atrial fibrillation and congestive heart failure, a routine strategy of rhythm control does not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy.
Rutten Frans H.; Zuithoff Nicolaas P. A.; et al; {beta}-Blockers May Reduce Mortality and Risk of Exacerbations in Patients With **Chronic Obstructive Pulmonary Disease**. Arch Intern Med. 2010;170(10):880-887.
Salpeter S, Ormiston T, Salpeter E, Salpeter S Md. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005 Oct 19;4:CD003566. AUTHORS' CONCLUSIONS: Cardioselective beta-blockers, given to patients with COPD in the identified studies did not produce adverse respiratory effects. Given their demonstrated benefit in conditions such as heart failure, coronary artery disease and hypertension, cardioselective beta-blockers should not be routinely withheld from patients with COPD.
Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for reversible airway disease. Cochrane Database Syst Rev. 2002;(1):CD002992. CONCLUSIONS: Cardioselective beta1-blockers, given to patients with mild-moderate reversible airway disease, do not produce clinically significant adverse respiratory effects in the short term. It is not possible to comment on their effects in patient with more severe or less reversible disease, or on their effect on the frequency or severity of acute exacerbations. Given their demonstrated benefit in conditions such as heart failure, coronary artery disease and hypertension, cardioselective beta1-blockers should not be withheld from patients with mild-moderate reversible airway disease.
Sampat U, Varadarajan P, Turk R, et al. Effect of beta-blocker therapy on survival in patients with **severe aortic regurgitation**. Results from a cohort of 756 patients. J Am Coll Cardiol 2009; 54:452-457.
Sarafidis P, Bogojevic Z, Basta E, Kirstner E, Bakris GL. Comparative efficacy of two different beta-blockers on 24-hour blood pressure control. J Clin Hypertens (Greenwich). 2008 Feb;10(2):112-8. In conclusion, metoprolol succinate was more effective in sustaining 24-hour and early morning BP reductions compared with atenolol in a small group of hypertensive patients also treated with once-daily low-dose hydrochlorothiazide.
Schaer BA, Schneider C, Jick SS, et al. Risk for **incident AF** in patients who receive antihypertensive drugs. Ann Intern Med 2010; 152:78-84.
Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of **cocaine**. Circulation. 2010 Dec 14;122(24):2558-69.
Seely EW, Ecker J. Clinical practice. **Chronic hypertension in pregnancy**. N Engl J Med. 2011 Aug 4;365(5):439-46.
Senzolo M, Cholongitas E, Burra P, et al. beta-Blockers protect against **spontaneous bacterial peritonitis** in cirrhotic patients: a meta-analysis. Liver Int. 2009 Apr 28. [Epub ahead of print] This analysis suggests a role of beta-blockers in preventing SBP in ascitic cirrhotics, independent of haemodynamic response. Further formal RCTs are needed to confirm this finding.
Sersté T, Melot C, Francoz C, et al. **Deleterious effects of beta-blockers** on survival in patients with cirrhosis and **refractory ascites**. Hepatology. 2010 May 25.
Shaddy RE, Boucek MM, Hsu DT, et al. Pediatric Carvedilol Study Group. **Carvedilol for children** and adolescents with heart failure: a randomized controlled trial. JAMA. 2007 Sep 12;298(10):1171-9. These preliminary results suggest that carvedilol does not significantly improve clinical heart failure outcomes in children and adolescents with symptomatic systolic heart failure. However, given the lower than expected event rates, the trial may have been underpowered. There may be a differential effect of carvedilol in children and adolescents based on ventricular morphology.
Shah A, Moon-Grady A, Bhogal N, et al. Effectiveness of **sotalol as first-line therapy for fetal supraventricular tachyarrhythmias**. Am J Cardiol. 2012 Jun 1;109(11):1614-8.
Shayan, Yasaman R., Prendiville, Julie S., Goldman, Ran D. Use of **propranolol in treating hemangiomas**. Can Fam Physician 2011 57: 302-303.
Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade (**propranolol**) in **Marfan's syndrome**. N Engl J Med. 1994;330:1335–1341
Short Philip M, Lipworth Samuel I W, Elder Douglas H J, et al. Effect of **β blockers in treatment of chronic obstructive pulmonary disease**: a retrospective cohort study. BMJ 2011;342:doi:10.1136/bmj.d2549 (10 May 2011)
Sipahi I, Tuzcu EM, Wolski KE, Nicholls SJ, Schoenhagen P, Hu B, Balog C, Shishehbor M, Magyar WA, Crowe TD, Kapadia S, Nissen SE. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. Ann Intern Med. 2007 Jul 3;147(1):10-8. The analysis demonstrates that beta-blockers can slow progression of coronary atherosclerosis.
Stecker EC, et al. Prophylactic **pacemaker** use to allow beta-blocker therapy in patients with chronic heart failure with bradycardia. Am Heart J. 2006 Apr;151(4):820-8.
Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-Selective Benefits of Medications in Treatment of **Acute Aortic Dissection** (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol. 2011 Sep 23.
Talwalkar JA, Kamath PS. An evidence-based medicine approach to beta-blocker therapy in patients with **cirrhosis**. Am J Med. 2004 Jun 1;116(11):759-66.
Tan ST, Itinteang T, Leadbitter P. Low-dose propranolol for multiple **hepatic and cutaneous hemangiomas** with deranged liver function. Pediatrics. 2011 Mar;127(3):e772-6.
Tess AV, Smetana GW. Medical evaluation of patients undergoing **electroconvulsive** therapy. N Engl J Med. 2009 Apr 2;360(14):1437-44.
The Cardiac Insufficiency Bisoprolol Study II (**CIBIS-II**): a randomised trial. Lancet. 1999 Jan 2;353(9146):9-13.
Thomas L. Managing **hypertensive emergencies** in the ED. Can Fam Physician. 2011 Oct;57(10):1137-97.
Tripathi D, Ferguson JW, Kochar N, et al.. Randomized controlled trial of **carvedilol** versus variceal band ligation for the prevention of the first **variceal bleed**. Hepatology. 2009 Apr 24. [Epub ahead of print] Carvedilol is effective in preventing the first variceal bleed. Carvedilol is an option for primary prophylaxis in patients with high-risk esophageal varices.
Treatment Guidelines from the Medical Letter. Pharmaceutical Drug **Overdose**. Sept 2006. (Beta blockers/Calcium-channel blockers: Treatment glucagon, calcium chloride, calcium gluconate)
Turnes J, et al. Pharmacological reduction of portal pressure and long-term risk of first **variceal bleeding** in patients with cirrhosis. Am J Gastroenterol. 2006 Mar;101(3):506-12.
UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713-9.
van Gelder IC, Groenveld HF, Crijns HJ, et al. **Lenient** versus strict **rate control** in patients with atrial fibrillation. (**RACE 2**) N Engl J Med 2010; DOI:10.1056/NEJMoa1001337.
van Gestel YR, Hoeks SE, Sin DD, et al. The Impact of **Cardioselective Beta-Blockers** on Mortality in Patients with **COPD and Atherosclerosis**. Am J Respir Crit Care Med. 2008 Jun 19. [Epub ahead of print] Cardioselective beta-blockers were associated with reduced mortality in COPD patients undergoing vascular surgery. In carefully selected patients with **COPD**, the use of cardioselective beta-blockers appears to be safe and associated with reduced mortality.
Viollet L, Thrush PT, Flanigan KM, et al. Effects of Angiotensin-Converting Enzyme Inhibitors and/or Beta Blockers on the **Cardiomyopathy in Duchenne Muscular Dystrophy**. Am J Cardiol. 2012 Mar 29.
Waqar S, Sarkar PK. **Exacerbation of psoriasis** with beta-blocker therapy. CMAJ. 2009 Jul 7;181(1-2):60.
Wann L. Samuel, Curtis Anne B., Ellenbogen Kenneth A., et al. **2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Circulation published February 14, 2011, doi:10.1161/CIR.0b013e31820f14c0 http://circ.ahajournals.org/cgi/reprint/CIR.0b013e31820f14c0v1
Warmack TS, Estes MA, Heldenbrand S, Franks AM. {beta}-Adrenergic Antagonists in **Hypertension**: A Review of the Evidence (December). Ann Pharmacother. 2009 Nov 24.
Wax PM, et al. **Beta-blocker ingestion**: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila). 2005;43(3):131-46. http://www.aapcc.org/FinalizedPMGdlns/beta-blocker%20guideline%20for%20AAPCC%202005-3-30.pdf
Webb AJS, Fischer U, Rothwell PM. Effects of **beta-blocker selectivity** on **blood pressure variability and stroke**: a systematic review. Neurology 2011;77:731–737.
Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G. Primary prevention with metoprolol in patients with hypertension. Mortalityresults from the **MAPHY** study. JAMA. 1988 Apr 1;259(13):1976-82.
Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence. Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005 Sep 4; [Epub ahead of print] CONCLUSIONS: Although noninferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, our results indicate that it may be as safe and efficacious to initiate treatment for CHF with bisoprolol as with enalapril. n=1010.
Willenheimer R. Effect on mode and cause of death of initiation of treatment for chronic heart failure with bisoprolol followed by additional enalapril compared to the opposite sequence: results of the randomized **CIBIS III** trial. World Congress of Cardiology 2006; September 6, 2006; Barcelona, Spain.
Wiysonge C, et al. **Beta-blockers for hypertension**. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD002003. The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension. This conclusion is based on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo or no treatment. More importantly, it is based on the trend towards worse outcomes in comparison with calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics. Most of the evidence for these conclusions comes from trials where atenolol was the beta-blocker used (75% of beta-blocker participants in this review). However, it is not known at present whether beta-blockers have differential effects on younger and elderly patients or whether there are differences between the diffe

beta-blockers.
World Gastroenterology Organisation (WGO). **Esophageal varices**. Munich (Germany): WGO; 2008 Jun. 17 p. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/18_treatment_e_varices_en.pdf
Wright JM, Musini VM. First-line drugs for hypertension. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD001841. First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.
Wyse DG, Waldo AL, DiMarco JP, et al. Atrial Fibrillation Follow-up Investigation of Rhythm Management (**AFFIRM**) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 Dec 5;347(23):1825-33. Management of atrial fibrillation with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy. Anticoagulation should be continued in this group of high-risk patients.
Zimetbaum Peter. **In the Clinic: Atrial Fibrillation**. *Ann Intern Med* December 7, 2010 153:ITC6-1; doi:10.1059/0003-4819-153-11-201012070-01006

TOP

CALCIUM CHANNEL BLOCKER (CCB): Comparison Chart

[1] Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.

[2] 2001 Canadian Hypertension Recommendations: What's New & What's Not so New but is Still Important. CJHP 2002;55:4651.

[3] FA McAlister, M Levine, KB Zarnke, et al. The 2000 recommendations for the management of hypertension. Can J Cardiol 2001; 17(5):543-559.

[4] 1999 Canadian recommendations for the management of hypertension. CMAJ 1999;161(Suppl):S1-S16.

[5] **1999 World Health Organization**–International Society of Hypertension Guidelines:Management of Hypertension. J Hypertens 1999;17:151-183.

[6] 6th Report-Joint National Committee on Prevention,Detection,Evaluation & Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413-46.

[7] Drugs for hypertension. Med Lett Drugs Ther 2001;43:17-22.

[8] Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD.2011.

[9] Micromedex 2010 online

[10] Hansten & Horn's Drug Interactions: Analysis & Management-Facts & Comparisons 2008.

[11] Treatment Guidelines: Drugs for Hypertension from The Medical Letter Feb 2003, repeated June 2005, January 2009, updated 2012.

[12] The **2012 Canadian** Hypertension Education Program **Recommendations** www.hypertension.ca
Canadian Hypertension Education Program. **2011 CHEP recommendations** for the management of **hypertension**. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf .

[13] ALLHAT Working Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (**ALLHAT**). JAMA 2000;283:1967-75.

[14] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (The **JNC 7**); JAMA. **2003** May;289(19):2560-72.

[15] Black HR, Elliott WJ, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (**CONVINCE**) trial. JAMA. 2003 Apr 23-30;289(16):2073-82. The CONVINCE trial did not demonstrate equivalence of a COER verapamil-based antihypertensive regimen compared with a regimen beginning with a diuretic or beta-blocker. When considered in the context of other trials of calcium antagonists, these data indicate that the effectiveness of calcium-channel therapy in reducing cardiovascular disease is similar but not better than diuretic or beta-blocker treatment.

[16] Ruggenenti P, Fassi A, Ilieva AP, ET AL. Preventing Microalbuminuria in Type 2 Diabetes (**BENEDICT**). N Engl J Med. 2004 Oct 31
Ruggenenti P, Fassi A, Ilieva AP, et al. BENEDICT-B Study Investigators. Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial. J Hypertens. 2011 Feb;29(2):207-16.

[17] Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003 Nov 8;362(9395):1527-35.

[18] Wassertheil-Smoller S, Psaty B, Greenland P, et al. Association between cardiovascular outcomes and antihypertensive drug treatment in older women. JAMA 2004; 292:2849-59.

[19] Ruggenenti P, Perna A, Loriga G, et al.; **REIN-2** Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease: multicentre, randomised controlled trial. Lancet. 2005 Mar 12;365(9463):939-46. (Interpretation: In pts with non-diabetic proteinuric nephropathies receiving background ACE-inhibitor therapy, no additional benefit from further blood-pressure reduction by felodipine could be shown.)

Additional articles:

ACCF- AHA-HRS Atrial Fibrillation 2011 Focused Update. Circulation 2011. http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181fa3cf4v1 (Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010; DOI: 10.1161/CIR.0b013e3181fa3cf4.)

Allan GM, Ivers N, Kolber M. **Medical management of renal stones**: More than analgesia? Can Fam Physician. 2011 Feb;57(2):198.

Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (**ACCOMPLISH**): a prespecified secondary analysis of a randomised controlled trial. Lancet. 2010 Feb 17.

Chen N, Zhou M, Yang M, et al. Calcium channel blockers versus other classes of drugs for hypertension. Cochrane Database Syst Rev. 2010 Aug 4;8:CD003654. Diuretics are preferred first-line over CCBs to optimize reduction of cardiovascular events. The review does not distinguish between CCBs, ACE inhibitors or ARBs, but does provide evidence supporting the use of CCBs over beta-blockers.

Choi HK, Soriano LC, Zhang Y, Rodríguez LAG. **Calcium channel blockers, losartan**, and the risk of **incident gout** among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.

Conde-Agudelo A, Romero R, Kusanovic JP. **Nifedipine in the management of preterm labor**: a systematic review and metaanalysis. Am J Obstet Gynecol. 2011 Feb;204(2):134.e1-20.

Dahlof B, Sever PS, Poulter NR, Wedel H, et al. ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre RCT. Lancet. 2005 Sep 10;366(9489):895-906. (InfoPOEMs: In this study, patients with hypertension and at least 3 additional cardiac risk factors have slightly fewer deaths from all causes, slightly fewer strokes, and were slightly less likely to develop diabetes if they were treated with amlodipine plus perindopril than if they were treated with atenolol and bendroflumethiazide. One would need to treat between 60 and 1000 high-risk patients for a median of 5.5 years with amlodipine instead of atenolol to prevent one additional death. (LOE = 2b))

Evangelista A, Tornos P, Sambola A, et al.. Long-term vasodilator therapy in patients with severe aortic regurgitation. N Engl J Med. 2005 Sep 29;353(13):1342-9. (InfoPOEMs: This small study does not find that vasodilators such as nifedipine (Procardia) or enalapril (Vasotec) delay the need for aortic valve replacement (AVR) in patients with asymptomatic but severe aortic regurgitation. The study was quite small, and although it is possible that a small but clinically important benefit was not detected, this seems unlikely since the trends actually run against active treatment. (LOE = 1b-))

EXPERT PANEL ON INTEGRATED GUIDELINES FOR CARDIOVASCULAR HEALTH AND RISK REDUCTION IN CHILDREN AND ADOLESCENTS. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011 Nov 14. [Epub ahead of print]

Flynn NO, Timmis A, Henderson R, Rajesh S, Fenu E; on behalf of the Guideline Development Group. Management of **stable angina**: summary of **NICE** guidance. BMJ. 2011 Aug 5;343:d4147. doi: 10.1136/bmj.d4147.

Frithsen IL, Simpson WM Jr. Recognition and management of acute medication **poisoning**. Am Fam Physician. 2010 Feb 1;81(3):316-23.

Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of **hypertrophic cardiomyopathy**: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.Circulation 2011; DOI:10.1161/CIR.0b013e318223e2bd. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.06.011v1.pdf

Gillis AM, Verma A, Talajic M, et al. CCS Atrial Fibrillation Guidelines. **Canadian cardiovascular society atrial fibrillation guidelines 2010: rate and rhythm management**. Can J Cardiol. 2011 Jan-Feb;27(1):47-59.

Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of **Raynaud's phenomenon**. BMJ. 2012 Feb 7;344:e289.

Hamm CW, Bassand JP, Agewall S, et al. **ESC** Guidelines for the management of **acute coronary syndromes** in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Sep 21.

Hollingsworth JM, et al. Medical therapy to **facilitate urinary stone passage**: a meta-analysis. Lancet. 2006 Sep 30;368(9542):1171-9. Patients given calcium-channel blockers or alpha blockers had a 65% (absolute risk reduction=0.31 95% CI 0.25-0.38) greater likelihood of stone passage than those not given such treatment (pooled risk ratio 1.65; 95% CI 1.45-1.88). The pooled risk ratio for alpha blockers was 1.54 (1.29-1.85) and for calcium-channel blockers with steroids was 1.90 (1.51-2.40). (InfoPOEMs: The limited amount of available data suggest that alpha blockers and calcium channel blockers appear to speed the passage of kidney stones. Furthermore, it appears that combining these medications with steroids provides additional benefit. (LOE = 1a-))

Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. (**ACCOMPLISH**) N Engl J Med. 2008 Dec 4;359(23):2417-2428.
The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such event

TOP

(Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized, controlled trial. Lancet 2010; DOI:10.1016/S0140-6736(09)62100-0.)

Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the **VALUE** randomised trial. Lancet. 2004 Jun 19;363(9426):2022-31.

Jung S-Y, Choi N-K, Kim J-Y, et al. **Short-acting nifedipine and risk of stroke** in elderly hypertensive patients. Neurology 2011;77:1229 –1234.

Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; on behalf of the Guideline Development Group. **Management of hypertension**: summary of **NICE** guidance. BMJ. 2011 Aug 25;343:d4891.

Lafuente-Lafuente Carmelo, Isabelle Mahé, Fabrice Extramiana. Management of **atrial fibrillation**. BMJ 2009;339:b5216, doi: 10.1136/bmj.b5216

Leenen FH, et al. Clinical Events in High-Risk Hypertensive Patients Randomly Assigned to **Calcium Channel Blocker Versus Angiotensin-Converting Enzyme Inhibitor** in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Hypertension. 2006 Jul 24; [Epub ahead of print]

López-Pintor RM, et al. Amlodipine and **nifedipine** used with cyclosporine induce different effects on **gingival enlargement**. Transplant Proc. 2009 Jul-Aug;41(6):2351-3.

Lyell DJ, Pullen KM, Mannan J, et al. Maintenance **nifedipine tocolysis** compared with placebo: a randomized controlled trial. Obstet Gynecol. 2008 Dec;112(6):1221-6. When compared with placebo, maintenance nifedipine tocolysis did not confer a large reduction in preterm birth or improvement in neonatal outcomes.

Makani H, Bangalore S, Romero J, et al. Effect of Renin-Angiotensin system blockade (ACEI/ARB) on calcium channel blocker-associated **peripheral edema**. Am J Med. 2011 Feb;124(2):128-35.

Medical Letter- Treatment Guidelines. **Treatment of Atrial Fibrillation**. Sept 2010.

Melmed S, Casanueva FF, Hoffman AR, et al. **Diagnosis and treatment of hyperprolactinemia**: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88.

NICE: National Institute for Health and Clinical Excellence. **Hypertension Guidelines**. Aug 2011. http://www.nice.org.uk/nicemedia/live/13561/56015/56015.pdf

O'Connor CM, et al. Effect of amlodipine on mode of death among patients with advanced heart failure in the **PRAISE** trial. Prospective Randomized Amlodipine Survival Evaluation. Am J Cardiol. 1998 Oct 1;82(7):881-7.

Olson KR, et al. **Calcium channel blocker ingestion**: an evidence-based consensus guideline for out-of-hospital management. Washington (DC): American Association of Poison Control Centers; 2005. http://www.aapcc.org/DiscGuidelines/CCB%20guidelinefinal.pdf

Pepine CJ, et al.; **INVEST** Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003 Dec 3;290(21):2805-16.

Raheem IA, Saaid R, Omar SZ, et al. **Oral nifedipine versus intravenous labetalol** for acute blood pressure control in **hypertensive emergencies of pregnancy**: a randomised trial. BJOG. 2012 Jan;119(1):78-85.

Rothwell PM, Howard SC, Dolan E, et al. on behalf of the ASCOT-BPLA and MRC Trial Investigators. Effects of **beta blockers and calcium-channel blockers** on within-**individual variability** in blood pressure and risk of stroke. Lancet Neurol. 2010 Mar 11.

Sanaee F, Clements JD, Waugh AW, et al. Drug-disease interaction: **Crohn's disease elevates verapamil** plasma concentrations but reduces response to the drug proportional to disease activity. Br J Clin Pharmacol. 2011 Nov;72(5):787-97. doi: 10.1111/j.1365-2125.2011.04019.x.

Saseen JJ, et al. Comparison of **nifedipine alone and with diltiazem or verapamil** in hypertension. Hypertension. 1996 Jul;28(1):109-14.

Shibata MC, Leon H, Chatterley T, et al. Do calcium channel blockers increase the diagnosis of **heart failure** in patients with hypertension? Am J Cardiol. 2010 Jul 15;106(2):228-35.

Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of **ureteral calculi**. Ann Emerg Med. 2007 Nov;50(5):552-63. Epub 2007 Aug 3. Our results suggest that "medical expulsive therapy," using either alpha-antagonists or calcium channel blockers, augments the stone expulsion rate compared to standard therapy for moderately sized distal ureteral stones. This meta-analysis of low-quality studies shows that ureteral stone passage can be enhanced by treating patients with an alpha-blocker such as tamsulosin (Flomax) or the calcium channel blocker nifedipine (Procardia). Better studies may refute these findings, but for now either approach is an option. (LOE = 1a-)

Stone PH, et al.; Antianginal efficacy of **ranolazine** when added to treatment with amlodipine: the **ERICA** (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol. 2006 Aug 1;48(3):566-75. Epub 2006 Jun 15.

Sucu Murat, Yuce Murat, Davutoglu Vedat. **Amlodipine-induced massive gingival** hypertrophy *Can Fam Physician* April 2011 57: 436-437.

Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-Selective Benefits of Medications in Treatment of **Acute Aortic Dissection** (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol. 2011Sep 23.

Thomas L. Managing **hypertensive emergencies** in the ED. Can Fam Physician. 2011 Oct;57(10):1137-97.

Treatment Guidelines from the Medical Letter. Pharmaceutical Drug **Overdose**. Sept 2006. (Beta blockers/Calcium-channel blockers: Treatment glucagon, calcium chloride, calcium gluconate)

van Gelder IC, Groenveld HF, Crijns HJ, et al. **Lenient** versus strict **rate control** in patients with atrial fibrillation. (**RACE 2**) N Engl J Med 2010; DOI:10.1056/NEJMoa1001337.

Wang L, Li YM, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. Dig Dis Sci. 2009 Nov;54(11):2303-11. Epub 2008 Dec 24. Sublingual nifedipine results in excellent or good clinical results in approximately 75% of adults with mild to moderate achalasia. For those patients not responding to pharmacotherapy, laparoscopic or thoracic myotomy is more effective than either botulinum toxin injection or pneumatic dilation. (LOE = 1a-)

Webb AJ, Rothwell PM. Effect of **dose and combination of antihypertensives on interindividual blood pressure variability**: a systematic review. Stroke. 2011 Oct;42(10):2860-5.

Wilcox CB, Nassar N, Roberts CL. Effectiveness of **nifedipine tocolysis** to facilitate external cephalic version: a systematic review. BJOG. 2011 Mar;118(4):423-8. doi: 10.1111/j.1471-0528.2010.02824.x.

Worcester EM, Coe FL. Clinical practice. **Calcium kidney stones**. N Engl J Med. 2010 Sep 2;363(10):954-63.

Wright JM, Musini VM. First-line drugs for hypertension. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD001841. First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

Wright AJ, Gomes T, Mamdani MM, et al. The risk of **hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers**. CMAJ. 2011 Feb 22;183(3):303-7.

Zimetbaum Peter. In the Clinic: **Atrial Fibrillation**. *Ann Intern Med* December 7, 2010 153:ITC6-1; doi:10.1059/0003-4819-153-11-201012070-01006

TOP

Thiazide Like Diuretics and Miscellaneous Antihypertensives

[1] Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). The ALLHAT Officers and Coordinators for the **ALLHAT** Collaborative Research Group. JAMA. 2002;288:2981-2997.

Veterans Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. **1967**;202(11):1028-1034.

Hypertension Detection and Follow-up Program Cooperative Group (**HDFP**). Five-year findings of the Hypertension Detection and Follow-up Program, I: reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA. 1979;242(23):2562-2571.

Multiple Risk Factor Intervention Trial Research Group (**MRFIT**) . Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. JAMA. 1982;248(12):1465-1477.

[2] 2001 Canadian Hypertension Recommendations: What's New & What's Not so New but is Still Important. CJHP 2002;55:4651.

[3] FA McAlister, M Levine, KB Zarnke, et al. The 2000 recommendations for the management of hypertension. Can J Cardiol 2001; 17(5):543-559.

[4] 1999 Canadian recommendations for the management of hypertension. CMAJ 1999;161(Suppl):S1-S16.

[5] **1999 World Health Organization**–International Society of Hypertension Guidelines:Management of Hypertension. J Hypertens 1999;17:151-183.

[6] **6th Report-Joint National Committee** on Prevention,Detection,Evaluation & Treatment of High Blood Pressure. Arch Intern Med **1997**;157:2413-46.

[7] Drugs for hypertension. Med Lett Drugs Ther 2001;43:17-22.

[8] Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD.2011.

[9] Micromedex 2010 online

[10] Hansten & Horn's Drug Interactions: Analysis & Management-Facts & Comparisons 2008.

[11] Treatment Guidelines: Drugs for Hypertension from The Medical Letter Feb 2003, repeated June 2005, January 2009, updated 2012.

[12] The **2012** Canadian Hypertension Education Program **Recommendations** www.hypertension.ca
Canadian Hypertension Education Program. **2011 CHEP recommendations** for the management of **hypertension**. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf .

[13] ALLHAT Working Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (**ALLHAT**). JAMA 2000;283:1967-75.

[14] Liu P, Arnold JM, et al. The 2002/3 Canadian Cardiovascular Society consensus guideline update for the diagnosis and management of **heart failure**. Can J Cardiol. **2003** Mar 31;19(4):347-56. [Arnold JM, et al.; Canadian Cardiovascular Society. **Canadian** Cardiovascular Society consensus conference recommendations on **heart failure 2006**: diagnosis and management. Can J Cardiol. 2006 Jan;22(1):23-45. Erratum in: Can J Cardiol. 2006 Mar 1;22(3):271. (Arnold JM, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure **update 2007**: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol. 2007 Jan;23(1):21-45.)

[15] **Treatment Guidelines**: Drugs for Treatment of **Heart Failure** from The Medical Letter April **2003**

[16] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (The **JNC 7**); JAMA. **2003** May;289(19):2560-72.

[17] Messerli FH, Grossman E, Lever AF. Do thiazide diuretics confer specific protection against strokes? Arch Intern Med. 2003 Nov 24;163(21):2557-60.

[18] Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension. 2004 Jan;43(1):4-9. Epub 2003 Nov 24.

[19] Davis BR, Furberg CD, Wright JT Jr, Cutler JA, Whelton P; ALLHAT Collaborative Research Group. Setting the record straight. Ann Intern Med. 2004 Jul 6;141(1):39-46.

[20] Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003 Nov 8;362(9395):1527-35.

[21] Davis BR, Furberg CD, Wright JT Jr, Cutler JA, Whelton P; ALLHAT Collaborative Research Group. ALLHAT: setting the record straight. Ann Intern Med. 2004 Jul 6;141(1):39-46.

[22] Dickerson LM, Gibson MV. Management of hypertension in older persons. Am Fam Physician. 2005 Feb 1;71(3):469-76.

[23] Jackson T. Wright, Jr, MD, PhD; J. Kay Dunn, PhD; et al.; for the ALLHAT Collaborative Research Group. Outcomes in Hypertensive Black and Nonblack Patients Treated With Chlorthalidone, Amlodipine, and Lisinopril. JAMA. 2005;293:1595-1608.

[24] Mahboob Rahman, MD, MS; Sara Pressel, MS; Barry R. Davis, MD, PhD; et al.; for the ALLHAT Collaborative Research Group **Renal Outcomes** in High-Risk Hypertensive Patients Treated With an Angiotensin-Converting Enzyme Inhibitor or a Calcium Channel Blocker vs a Diuretic. A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**)
Arch Intern Med. 2005;165:936-946.

[25] Diagnosis and Management of Chronic Heart Failure in the Adult: **ACC/AHA 2005 Guideline Update** for the (J Am Coll Cardiol 2005) http://www.acc.org/clinical/guidelines/failure/index.pdf

[26] Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of 3 different a1-adrenergic blockers for distal ureteral stones. J Urology 2005; 173:2010-12. (InfoPOEMs: Alpha1-adrenergic blockers
increase the frequency of spontaneous passage of distal ureteral renal stones. All 3 agents -- tamsulosin (Flomax), terazosin (Hytrin), and doxazosin (Cardura) -- were equally effective. (LOE = 2b))

[27] McConnell JD, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. N Engl J Med. 2003 Dec 18;349(25):2387-2398.
Anothaisintawee T, Attia J, Nickel JC, et al.. Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. JAMA. 2011 Jan 5;305(1):78-86.

[28] Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate (20-40mg tid) and hydralazine (37.5-75mg tid) in blacks with heart failure (**A-HeFT**). N Engl J Med. 2004 Nov 11;351(20):2049-57.

29. Wright JT, JA, et al, for the **ALLHAT** Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. JAMA 2005;293:1595- 608 & ACP Journal Club . (InfoPOEMs: Thiazide-type diuretics are the best initial agents for the treatment of hypertension for most patients, including both blacks and nonblacks. (LOE = 1b-))

30. Whelton PK, Barzilay J, Cushman WC, et al.; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). Arch Intern Med. 2005 Jun 27;165(12):1401-9.

31. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs. a diuretic. A report from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (**ALLHAT**). Arch Intern Med 2005; 165:936-46. (InfoPOEMs: It's blood pressure reduction, not the choice of drug, that prevents renal function decline in patients with hypertension, with or without diabetes. Neither the calcium channel blocker amlodipine (Norvasc) nor the angiotensin-converting enzyme inhibitor lisinopril (Prinivil) prevents the combined outcome of end-stage renal disease or a 50% decrease in renal function any better than the diuretic chlorthalidone (Hygroton). Results were the same in patients with already compromised renal function, as well as in patients with type 2 diabetes. (LOE = 1b))

32. Turnbull F, Neal B, Algert C, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005 Jun 27;165(12):1410-9.

33. Kaplan SA, et al; Medical Therapy of Prostatic Symptoms (**MTOPS**) Research Group. Combination therapy with **doxazosin & finasteride** for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater. J Urol. 2006 Jan;175(1):217-20; discussion 220-1.

34. Rahman M, et al.; ALLHAT Collaborative Research Group. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline **glomerular filtration rate**. Ann Intern Med. 2006 Feb 7;144(3):

TOP

35. Khachaturian et al. Antihypertensive Medication Use and Incident **Alzheimer** Disease: The Cache County Study. Arch Neurol. 2006 Mar 13; [Epub ahead of print] CONCLUSIONS: These data suggest that AH medications, and specifically potassium-sparing diuretics, are associated with reduced incidence of AD. Because the latter association is a new finding, it requires confirmation in further study.
36. Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol. 2005;46:425-31.
37. Chrysostomou A, Pedagogos E, MacGregor L.. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist spironolactone in patients who have persistednt proteinuria and are on long-term angiotension-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. Clin J Am Soc Nephrol. 2006 Jan 3;1:256-62.
38. Davis BR, et al.; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation. 2006 May 9;113(18):2201-10. Epub 2006 May 1. HF risk decreased with chlorthalidone versus amlodipine or lisinopril use during year 1. Subsequently, risk for those individuals taking chlorthalidone versus amlodipine remained decreased but less so, whereas it was equivalent to those given lisinopril. Prior medication use, follow-up blood pressures, and concomitant medications are unlikely to explain most of the HF differences. Diuretics are superior to calcium channel blockers and, at least in the short term, angiotensin-converting enzyme inhibitors in preventing HF in hypertensive individuals.
39. Ahmed A, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. Eur Heart J. 2006 Jun;27(12):1431-1439. Epub 2006 May 18.
40. Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y. Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. J Rheumatol. 2006 Jul;33(7):1341-5. Epub 2006 Jun 1.
41. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol. 2006 Jun 15;97(12):1759-64. Epub 2006 Apr 27.
42. Verhamme K, Mosis et al. Spironolactone and risk of upper gastrointestinal events: population based case-control study. BMJ. 2006 Aug 12;333(7563):330. Epub 2006 Jul 13.
43. Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ. 2006 Jul 21; [Epub ahead of print] (InfoPOEMs: In-hospital mortality is not affected by the use of high-dose furosemide to treat or prevent acute renal failure, and furosemide increases the hospital length of stay. (LOE = 1a))
44. Zhang W, et al. EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006 Oct;65(10):1301-11. Epub 2006 May 17.
45. Esptein M, et al. Selective Aldosterone Blockade with Eplerenone Reduces Albuminuria in Patients with Type 2 Diabetes. Clin J Am Soc Nephrol. 2006 Sep;1(5):940-51.
46. Janssens HJ, et al. Gout, not induced by diuretics? A case-control study from primary care. Ann Rheum Dis. 2006 Aug;65(8):1080-3. Epub 2005 Nov 16.
47. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol. 2006 Jun 15;97(12):1759-64. Epub 2006 Apr 27.
48. Barzilay JI, Davis BR, Cutler JA, et al. Fasting Glucose Levels and Incident Diabetes Mellitus in Older NondiabeticAdults Randomized to Receive 3 Different Classes of Antihypertensive Treatment: A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2006 Nov 13;166(20):2191-201. Fasting glucose levels increase in older adults with hypertension regardless of treatment type. For those taking chlorthalidone vs other medications, the risk of developing FG levels higher than 125 mg/dL (6.9 mmol/L) is modestly greater, but there is no conclusive or consistent evidence that this diuretic-associated increase in DM risk increases the risk of clinical events.
49. Hollingsworth JM, et al. Medical therapy to **facilitate urinary stone passage**: a meta-analysis. Lancet. 2006 Sep 30;368(9542):1171-9. Patients given calcium-channel blockers or alpha blockers had a 65% (absolute risk reduction=0.31 95% CI 0.25-0.38) greater likelihood of stone passage than those not given such treatment (pooled risk ratio 1.65; 95% CI 1.45-1.88). The pooled risk ratio for alpha blockers was 1.54 (1.29-1.85) and for calcium-channel blockers with steroids was 1.90 (1.51-2.40). (InfoPOEMs: The limited amount of available data suggest that alpha blockers and calcium channel blockers appear to speed the passage of kidney stones. Furthermore, it appears that combining these medications with steroids provides additional benefit. (LOE = 1a-))
50. Chobanian AV. Clinical practice. **Isolated systolic hypertension in the elderly**. N Engl J Med. 2007 Aug 23;357(8):789-96.
51. Black HR, Davis B, Barzilay J, Nwachuku C, et al. Metabolic and Clinical Outcomes in Non-Diabetic Individuals with the Metabolic Syndrome Assigned to Chlorthalidone, Amlodipine, or Lisinopril as Initial Treatment for Hypertension: A Report from the **ALLHAT** Study. Diabetes Care. 2007 Nov 13; [Epub ahead of print] Despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, CV disease outcomes in older hypertensive adults with MetS, as compared to treatment with CCBs and ACEI.
52. Wright JT, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the **metabolic syndrome**. ALLHAT. Arch Intern Med 2008; 168:207-217. The ALLHAT findings fail to support the preference for calcium channel blockers, alpha-blockers, or angiotensin-converting enzyme inhibitors compared with thiazide-type diuretics in patients with the MetS, despite their more favorable metabolic profiles.
53. Bomback AS, et al. Change in proteinuria after adding **aldosterone blockers** to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis. 2008 Feb;51(2):199-211. Although data suggest that adding MRBs to ACE-inhibitor and/or ARB therapy yields significant decreases in proteinuria without adverse effects of hyperkalemia and impaired renal function, routine use of MRBs as additive therapy in patients with chronic kidney disease cannot be recommended yet.
54. Lim LS, Fink HA, Kuskowski MA, Taylor BC, Schousboe JT, Ensrud KE; for the Osteoporotic Fractures in Men (MrOS) Study Group. Loop Diuretic Use and Increased Rates of Hip Bone Loss in Older Men: The Osteoporotic Fractures in Men Study. Arch Intern Med. 2008 Apr 14;168(7):735-740. We conclude that loop diuretic use in older men is associated with increased rates of hip **bone loss**. These results suggest that the potential for bone loss should be considered when loop diuretics are prescribed to older patients in clinical practice.
55. Arroll B, Kenealy T, Elley CR. Should we prescribe diuretics for patients with **prediabetes** and hypertension? BMJ. 2008 Aug 21;337:a679. doi: 10.1136/bmj.a679.
56. Davis BR, Kostis JB, Simpson LM, et al. for the ALLHAT Collaborative Research Group. **Heart Failure** With Preserved and Reduced Left Ventricular Ejection Fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation. 2008 Nov 10. [Epub ahead of print] In **ALLHAT**, with adjudicated outcomes, **chlorthalidone** significantly reduced the occurrence of new-onset hospitalized HFPEF and HFREF compared with amlodipine and doxazosin. Chlorthalidone also reduced the incidence of new-onset HFPEF compared with lisinopril. Among high-risk hypertensive men and women, HFPEF has a better prognosis than HFREF.
57. FDA Nov/08 Balanced Health Products, Inc. announced a recall of **STARCAPS** due to the presence of an undeclared drug ingredient, Bumetanide. Bumetanide is a diuretic indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease including nephrotic syndrome.
58. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. (**ACCOMPLISH**)N Engl J Med. 2008 Dec 4;359(23):2417-2428.
The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.
59. Escribano J, Balaguer A, Pagone F, Feliu A, Roqué I Figuls M. Pharmacological interventions for preventing complications in idiopathic hypercalciuria. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD004754. There is some evidence that in patients with idiopathic hypercalciuria and recurrent stones, the addition of thiazides to a normal or modified diet for short to long periods (five months to three years) reduced the number of stone recurrences and decreased the stone formation rate. Thiazides and neutral potassium phosphate decreased calciuria in symptomatic patients with idiopathic hypercalciuria. There were no studies investigating the effect of pharmacological treatment on other clinical complications or asymptomatic idiopathic **hypercalciuria**.
60. Carbone LD, Johnson KC, Bush AJ, Robbins J, Larson JC, Thomas A, LaCroix AZ. **Loop diuretic use and fracture** in postmenopausal women: findings from the Women's Health Initiative. Arch Intern Med. 2009 Jan 26;169(2):132-40. After adjustment for confounding variables, no significant association was found between ever use of loop diuretics and changes in BMD, falls, and fractures. Loop diuretics were used by women in poor health who were already at risk for fractures. However, prolonged use of loop diuretics was associated with higher fracture risk in postmenopausal women.
61. Al-Balas M, Bozzo P, Einarson A. Use of diuretics **during pregnancy**. Can Fam Physician. 2009 Jan;55(1):44-5. Many studies--including a meta-analysis of almost 7000 neonates exposed to diuretics during pregnancy—did not find an increased risk of adverse effects, such as birth defects, fetal growth restriction, thrombocytopenia, or diabetes, among neonates exposed to diuretics in utero.
62. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM, Endocrine Society. Case detection, diagnosis, and treatment of patients with **primary aldosteronism**: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008 Sep;93(9):3266-81.
63. Pitt B, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. (RALES) N Engl J Med. 1999 Sep 2;341(10):709-17.
64. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004 Aug 5;351(6):543-51.
65. Krum H, Skiba M, Gilbert RE. Comparative metabolic effects of **hydrochlorothiazide and indapamide** in hypertensive diabetic patients receiving ACE inhibitor therapy. Diabet Med. 2003 Sep;20(9):708-12
Hydrochlorothiazide 12.5 mg/day, when added to background ACE inhibitor therapy with fosinopril in hypertensive diabetic patients, resulted in a metabolic profile that was similar, if not superior on certain

TOP

comparison with indapamide 2.5 mg/day.
66. Spence JD, Huff M, Barnett PA. Effects of **indapamide versus hydrochlorothiazide** on plasma lipids and lipoproteins in hypertensive patients: a direct comparison. Can J Clin Pharmacol. 2000 Spring;7(1):32-7. Triglyceride levels increased significantly more with indapamide than with HCTZ (P=0.02). The two drugs had similar effects on blood pressure and serum potassium; neither drug affected plasma glucose. Claims that indapamide is superior to HCTZ appear unwarranted; in view of the substantial cost difference, this finding, if confirmed in larger studies, has important policy implications.
67. Shafi T, Appel LJ, Miller ER 3rd, Klag MJ, Parekh RS. Changes in serum potassium mediate thiazide-induced **diabetes**. Hypertension. 2008 Dec;52(6):1022-9. Epub 2008 Nov 3. Erratum in: Hypertension. 2009 Feb;53(2):e19. After year 1, chlorthalidone use was not associated with increased diabetes risk. In conclusion, thiazide-induced diabetes occurs early after initiating treatment and appears to be mediated by changes in serum potassium. Potassium supplementation might prevent thiazide-induced diabetes. This hypothesis can and should be tested in a randomized trial.
68. Grimm RH Jr, Grandits GA, Prineas RJ, et al. Long-term effects on **sexual** function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS) Hypertension. 1997 Jan;29(1 Pt 1):8-14. In conclusion, long-term incidence of erection problems in treated hypertensive men is relatively low but is higher with chlorthalidone treatment. Effects of erection dysfunction with chlorthalidone appear relatively early and are often tolerable, and new occurrences after 2 years are unlikely. The rate of reported sexual problems in hypertensive women is low and does not appear to differ by type of drug. Similar incidence rates of erection dysfunction in placebo and most active drug groups caution against routine attribution of erection problems to antihypertensive medication.
69. Jackson T. Wright, Jr; Jeffrey L. et al; **ALLHAT** Collaborative Research Group ALLHAT Findings Revisited in the Context of Subsequent Analyses, Other Trials, & Meta-analyses *Arch Intern Med*. 2009;169(9):832-842.
70. Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of **aldosterone** in the metabolic syndrome and resistant hypertension. Ann Intern Med. 2009 Jun 2;150(11):776-83.
71. Guerrera M. et al. Therapeutic Uses of **Magnesium**. Am Fam Physician. 2009; 80(1):157-162.
72. Wright JM, Musini VM. First-line drugs for hypertension. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD001841. **First-line** low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.
73. Chen JM, Heran BS, Wright JM. Blood pressure lowering efficacy of diuretics as **second-line** therapy for primary hypertension. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007187.
74. Moser Marvin; Feig Peter U. **Fifty Years of Thiazide Diuretic Therapy** for Hypertension. Arch Intern Med. 2009;169(20):1851-1856.
75. Ernst ME, Moser M. Use of **diuretics** in patients with hypertension. N Engl J Med. 2009 Nov 26;361(22):2153-64.
76. Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. **Hyperkalaemia**. BMJ. 2009 Oct 23;339:b4114. doi: 10.1136/bmj.b4114.
77. Boger-Megiddo I, Heckbert SR, Weiss NS, et al. **Myocardial infarction and stroke** associated with diuretic based two drug antihypertensive regimens: population based case-control study. BMJ 2010;340: 25 Jan 2010.
78. Pharmacist's Letter. **Clonidine abuse**. Mar, 2010.
79. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. **Continuous versus intermittent** infusion of **furosemide** in acute decompensated heart failure. J Card Fail. 2010 Mar;16(3):188-93.
80. Wei Li, Struthers Allan D, Fahey Tom, et al. **Spironolactone** use and renal toxicity: population based longitudinal analysis. BMJ 2010;340:c1768
81. Stafford RS.; Bartholomew L. Kay; et al; the **ALLHAT** Collaborative Research Group Impact of the **ALLHAT/JNC7 Dissemination Project** on Thiazide-Type Diuretic Use. Arch Intern Med. 2010;170(10):851-858.
82. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of **ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis**. J Hepatol. 2010 Jun 1.
83. Abdel-Qadir HM, Tu JV, Yun L, Austin PC, Newton GE, Lee DS. Diuretic dose and long-term outcomes in elderly patients with **heart failure** after hospitalization. Am Heart J. 2010 Aug;160(2):264-271.e1.
84. Worcester EM, Coe FL. Clinical practice. **Calcium kidney stones**. N Engl J Med. 2010 Sep 2;363(10):954-63.
85. Lacourcière Y, Poirier L, Lefebvre J, et al. Increasing the doses of both **diuretics and angiotensin receptor blockers** is beneficial in subjects with uncontrolled systolic hypertension. Can J Cardiol. 2010 Oct;26(8):313-9.
86. Sciarretta Sebastiano; Palano Francesca; Tocci Giuliano; et al. Antihypertensive Treatment and Development of Heart Failure in Hypertension: A Bayesian Network Meta-analysis of Studies in Patients With Hypertension and High Cardiovascular Risk. Arch Intern Med. 2010;0(2010):archinternmed.2010.427.
87. Health Canada Nov/10: **Beijing 101 Hair Consultants: Hair Growth Formula D-2653-Band Hair Growth Tonic E-0583-D**: The Singapore Health Sciences Authority advised consumers to stop using one batch of these products (Beijing 101 Hair Consultants Hair Growth Formula D-2653-B batch# 20091201, and Hair Growth Tonic E-0583-D batch# 20091201) after testing of these batches revealed the presence of undeclared minoxidil. **101 Zhangguang: Gold 101 Super Effective Hair Growth Agentand Fabao 101D Doctor Zhao's Chinese Traditional Herbal Hair Care Formula**: The Hong Kong Department of Health warned consumers not to buy or use these two products after they were found to contain undeclared minoxidil.
88. Medical Letter. **Drugs for Kidney Stones**. Nov 29, 2010. (Tamsulosin or long aciting nifedipine +/- corticosteroid) Medical Letter. **Drugs for Kidney Stones**. Nov 29, 2010. (Tamsulosin or nifedipine +/- ocrticosteroid)
89. CAU (**Canadian Urological Association**) 2010 Update: Guidelines for the management of **benign prostatic hyperplasia** http://www.cua.org/guidelines/bph_2009_en__v2a.pdf
Nickel JC, Méndez-Probst CE, Whelan TF, Paterson RF, Razvi H. 2010 Update: Guidelines for the management of benign prostatic hyperplasia. Can Urol Assoc J. 2010 Oct;4(5):310-6.
90. Rossitto G, Kamath G, Messerli FH. Should **alpha-blockers ever be used** as antihypertensive drugs? *Cleveland Clinic Journal of Medicine* 2010; 77(12):884-888; doi:10.3949/ccjm.77a.10058
91. Kurlan R. Clinical practice. **Tourette's Syndrome**. N Engl J Med. 2010 Dec 9;363(24):2332-8.
92. Messerli F, Makani H, Benjo A, et al. Antihypertensive efficacy of **HCTZ (hydrochlorothiazide) as evaluated by ABPM**. A meta-analysis of randomized trials. J Am Coll Cardiol 2011; 57:590-600.
93. Anothaisintawee T, Attia J, Nickel JC, et al.. Management of **chronic prostatitis/chronic pelvic pain syndrome**: a systematic review and network meta-analysis. JAMA. 2011 Jan 5;305(1):78-86.
94. **Benign prostatic hyperplasia** (BPH): **American** Urological Association (**AUA**) Guidelines **2011**. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chap_1_GuidelineManagementof(BPH).pdf
95. Allan GM, Ivers N, Kolber M. **Medical management of renal stones**: More than analgesia? Can Fam Physician. 2011 Feb;57(2):198.
96. Aurora RN, Zak RS, Auerbach SH, et al. Standards of Practice Committee, American Academy of Sleep Medicine. Best practice guide for the treatment of **nightmare disorder in adults**. J Clin Sleep Med 2010 Aug 15;6(4):389-401. (prazosin, ? clonidine etc)
97. FDA Mar/11 **:** USA Far Ocean Group, Inc. issues voluntary nationwide recall of **U-Prosta**, a product marketed as a dietary supplement that contains undeclared terazosin.
98. Psaty BM, Lumley T, Furberg CD. Meta-analysis of health outcomes of chlorthalidone-based vs nonchlorthalidone-based low-dose diuretic therapies. JAMA 2004;292:43-44.
99. Shahinfar S, Simpson RL, Carides AD, et al. Safety of **losartan** in hypertensive patients with **thiazide-induced hyperuricemia**. Kidney Int 1999;56:1879-1885.
100. Dorsch MP, Gillespie BW, Erickson SR, et al. **Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide**: a retrospective cohort analysis. Hypertension. 2011 Apr;57(4):689-94.
101. Pacak K. Preoperative management of the **pheochromocytoma** patient. J Clin Endocrinol Metab 2007;92:4069-4079.
102. Václavík Jan, Sedlák Richard, Plachy Martin, et al. Addition of **Spironolactone** in Patients With **Resistant Arterial Hypertension (ASPIRANT)**: A Randomized, Double-Blind, Placebo-Controlled Trial. Hypertension 57: 1069-1075;.
103. **NICE**: National Institute for Health and Clinical Excellence. **Hypertension Guidelines**. Aug 2011. http://www.nice.org.uk/nicemedia/live/13561/56015/56015.pdf
104. Falk RH. **Cardiac amyloidosis**: a treatable disease, often overlooked. Circulation. 2011 Aug 30;124(9):1079-85.
105. Cockburn J, Moar VA, et al. Final report of study on **hypertension during pregnancy**: the effects of specific treatment on the growth (eg. **methyldopa**) and development of the children. Lancet 1982;1:647-9.
106. Collins R, Yusuf S, Peto R. Overview of randomised trials of **diuretics in pregnancy**. Br Med J (Clin Res Ed) 1985;290:17-23.
107. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; on behalf of the Guideline Development Group. **Management of hypertension**: summary of **NICE** guidance. BMJ. 2011 Aug 25;343:d4891.
108. Antoniou T, Gomes T, Mamdani MM, et al. **Trimethoprim-sulfamethoxazole induced hyperkalaemia** in elderly patients receiving **spironolactone**: nested case-control study. BMJ. 2011 Sep 12;343:d5228.
109. Sica DA, Carter B, Cushman W, Hamm L. **Thiazide and Loop Diuretics**. J Clin Hypertens (Greenwich). 2011 Sep;13(9):639-643. doi:10.1111/j.1751-7176.2011.00512.x.
110. Health Canada Oct/11: **Huo Li Bao and Ren Sem Tu Chon Chin Kuo Pill** - The Singapore Health Sciences Authority warned that these Chinese pain-relief products contain prescription and/or over-the-counter drugs (furosemide, piroxicam, chlorpheniramine, and/or dexamethasone).
111. Thomas L. Managing **hypertensive emergencies** in the ED. Can Fam Physician. 2011 Oct;57(10):1137-97.
112. Ho JM, Juurlink DN. Considerations when prescribing **trimethoprim-sulfamethoxazole**. CMAJ. 2011 Oct 11.
113. Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with **heart failure** in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). Circulati

TOP

2011;124:1811–1818.
114. Health Canada Nov/11 **Slimming Kapsul** The Hong Kong Department of Health warned that this weight-loss product contains an unauthorized drug (sibutramine) and a prescription drug (**spironolactone**).
115. EXPERT PANEL ON INTEGRATED GUIDELINES FOR CARDIOVASCULAR HEALTH AND RISK REDUCTION IN CHILDREN AND ADOLESCENTS. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011 Nov 14. [Epub ahead of print]
116. Leung AA, Wright A, Pazo V, et al. Risk of **thiazide-induced hyponatremia** in patients with hypertension. Am J Med. 2011 Nov;124(11):1064-72.
117. Kostis JB, Cabrera J, Cheng JQ, et al. Association between **chlorthalidone** treatment of systolic hypertension and long-term survival (**SHEP**). JAMA. 2011 Dec 21;306(23):2588-93. In the SHEP trial, treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up.
118. Choi HK, Soriano LC, Zhang Y, Rodríguez LAG. **Calcium channel blockers, losartan**, and the risk of **incident gout** among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.
119. Garrison SR, Dormuth CR, Morrow RL, et al. **Nocturnal leg cramps** and prescription use that precedes them: a sequence symmetry analysis. Arch Intern Med. 2012 Jan 23;172(2):120-6. (common with LABA's, diuretics)
120. Jones AG, Evans PH, Vaidya B. **Phaeochromocytoma**. BMJ. 2012 Feb 20;344:e1042.
121. Worster AS, Bhanich Supapol W. Fluids and diuretics for acute **ureteric colic**. Cochrane Database Syst Rev. 2012 Feb 15;2:CD004926. We found no reliable evidence in the literature to support the use of diuretics and high volume fluid therapy for people with acute ureteric colic.
122. Ernst ME, Neaton JD, Grimm RH Jr, et al. Multiple Risk Factor Intervention Trial Research Group. Long-term effects of **chlorthalidone versus hydrochlorothiazide** on electrocardiographic left ventricular hypertrophy in the multiple risk factor intervention trial. (**MRFIT**) Hypertension. 2011 Dec;58(6):1001-7.
123. Frassetto L, Kohlstadt I. Treatment and prevention of **kidney stones**: an update. Am Fam Physician. 2011 Dec 1;84(11):1234-42.
124. Dickson *G.* **Gynescomastia**. Am Fam Physician. 2012 Apr 1;85(7):716-722. (spironolactone SE)

TOP

ORAL ANTIHYPERTENSIVES Summary/Guidelines Comparison Chart

[1] Palmer, B. Managing Hyperkalemia Caused by Inhibitors of the Renin-Angiotensin-Aldosterone System. N Engl J Med 2004;351:585-92.

[2] Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.

[3] 2001 Canadian Hypertension Recommendations: What's New & What's Not so New but is Still Important. CJHP 2002;55:4651.

[4] FA McAlister, M Levine, KB Zarnke, et al. The 2000 recommendations for the management of hypertension. Can J Cardiol 2001; 17(5):543-559.

[5] 1999 Canadian recommendations for the management of hypertension. CMAJ 1999;161(Suppl):S1-S16.

[6] **1999 World Health Organization**–International Society of Hypertension Guidelines:Management of Hypertension. J Hypertens 1999;17:151-183.

[7] 6th Report-Joint National Committee on Prevention,Detection,Evaluation & Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413-46.

[8] Drugs for hypertension. Med Lett Drugs Ther 2001;43:17-22. & Initial Therapy of Hypertension Med Lett Drugs Ther **2004**;46:53-55.

[9] Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD. 2011.

[10] Micromedex 2010 online

[11] Hansten & Horn's Drug Interactions: Analysis & Management-Facts & Comparisons 2008.

[12] Treatment Guidelines: Drugs for Hypertension from The Medical Letter Feb 2003, repeated June 2005, January 2009, updated 2012.

[13] The **2012 Canadian** Hypertension Education Program **Recommendations** www.hypertension.ca
(Patient instructions for purchasing & using home blood pressure measurements can be found at www.hypertension.ca/tools & at www.heartandstroke.ca/bp)
Hackam DG, Khan NA, Hemmelgarn BR, et al. Canadian Hypertension Education Program. The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part 2 - **therapy**. Can J Cardiol. 2010 May;26(5):249-58.
Quinn RR, Hemmelgarn BR, Padwal RS, et al. Canadian Hypertension Education Program. The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part I - blood pressure measurement, **diagnosis and assessment of risk**. Can J Cardiol. 2010 May;26(5):241-8.
Canadian Hypertension Education Program. **2011 CHEP recommendations** for the management of **hypertension**. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf .

[14] ALLHAT Working Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (**ALLHAT**). JAMA 2000;283:1967-75.

[15] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, & Treatment of High Blood Pressure (The **JNC 7**); JAMA. **2003** May;289(19):2560-72. (Complete report in Hypertension 2003;42:1206-1252)

[16] Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm RH Jr, Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, Williams G, Wittes J, Zanchetti A, Anders RJ. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (**CONVINCE**) trial. JAMA. 2003 Apr 23-30;289(16):2073-82.

[17] August P. Initial treatment of hypertension. N Engl J Med. 2003 Feb 13;348(7):610-7.

[18] Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003; 362: 1527-35

[19] McConnell JD, Roehrborn CG, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. N Engl J Med. 2003 Dec 18;349(25):2387-2398.

[20] NICE Guidelines Aug,2004 Management of Hypertension in Adults in Primary Care http://www.nice.org.uk/pdf/CG018fullguideline.pdf

[21] Davis BR, Furberg CD, Wright JT Jr, Cutler JA, Whelton P; ALLHAT Collaborative Research Group. ALLHAT: setting the record straight. Ann Intern Med. 2004 Jul 6;141(1):39-46.

[22] Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate (20-40mg tid) and hydralazine (37.5-75mg tid) in blacks with heart failure (**A-HeFT**). N Engl J Med. 2004 Nov 11;351(20):2049-57.

[23] Diagnosis and Management of Chronic **Heart Failure** in the Adult: **ACC/AHA 2005 Guideline Update** for the (J Am Coll Cardiol 2005) http://www.acc.org/clinical/guidelines/failure/index.pdf
(**European 2005** Chronic Heart failure guidelines http://www.escardio.org/NR/rdonlyres/8A2848B4-5DEB-41B9-9A0A-5B5A90494B64/0/CHFFullTextehi205FVFW170505.pdf)

[24] Yusuf S., Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004 (online version published Sept 3,2004) Yusuf S, et al. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52.

Additional sources:

AACE Hypertension Task Force. American Association of Clinical **Endocrinologists** Medical Guidelines for Clinical Practice for the diagnosis and treatment of hypertension. Endocr Pract. **2006** Mar-Apr;12(2):193-222.

Abalos E, et al. Antihypertensive drug therapy for mild to moderate **hypertension during pregnancy**. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD002252. It remains unclear whether antihypertensive drug therapy for mild to moderate hypertension during pregnancy is worthwhile.

Abidov A, Rozanski A, Hachamovitch R, et al. Prognostic significance of **dyspnea** in patients referred for cardiac stress testing. N Engl J Med. 2005 Nov 3;353(18):1889-98.

ACCF/AHA 2011 Focused Update of the Guidelines for the Management of Patients With **Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines**.** J Am Coll Cardiol 2011 0: j.jacc.2011.02.009. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.02.009v1.pdf

ACCF/AHA 2011 American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents, , American Academy of Neurology, , American Geriatrics Society, , American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, , Association ofBlack Cardiologists, , European Society of Hypertension, , Aronow, Wilbert S., Fleg, Jerome L., Pepine, Carl J., et al. **ACCF/AHA 2011 Expert Consensus** Document on **Hypertension in the Elderly.** J Am Coll Cardiol 2011 0: j.jacc.2011.01.008. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.01.008v1.pdf

ACCORD Study Group, Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001286

Acosta AA et al. Prevalence of Persistent **Prehypertension in Adolescents**. J Pediatr. 2011 Dec 6.

ACTIVE I Investigators. Irbesartan in Patients with Atrial Fibrillation. N Engl J Med 2011; 364:928-938. (Not reduce CV events)

AHA Writing Group Members, Roger VL, Go AS, Lloyd-Jones DM, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Roger VL, Turner MB; On behalf of the American Heart Association Heart Disease and Stroke Statistics Writing Group. Executive Summary: **Heart Disease and Stroke Statistics—2011 Update**: A Report From the American Heart Association. Circulation. 2011 Feb 1;123(4):459-463.

Allan, G. Michael, Mallery, Laurie, Ivers, Noah. Treating hypertension in the **very elderly**. Can Fam Physician 2010 56: 1141.

Allen N, Berry J, Ning H, et al. Impact of blood pressure and **blood pressure change during middle age** on the remaining lifetime risk for cardiovascular disease the cardiovascular lifetime risk pooling project. Circulation 2012;

Al-Mallah MH, et al. Angiotensin-converting enzyme inhibitors in coronary artery disease and **preserved left ventricular** systolic function: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2006 Apr 18;47(8):1576-83. Epub 2006 Mar 29. Treatment of 100 patients for an average duration of 4.4 years prevents either of the adverse outcomes (one death, or one nonfatal myocardial infarction, or one cardiovascular death or one coronary revascularization procedure). CONCLUSIONS: The cumulative evidence provided by this meta-analysis shows a modest favorable effect of ACEIs on the outcome of patients with CAD and preserved LV systolic function.

American College of Physicians. **In the clinic. Hypertension**. Ann Intern Med. Dec 2,2008;149:ITC6(1-15; quiz 16).

American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, et al. **Diet and lifestyle recommendations revision 2006**: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006 Jul 4;114(1):82-96.

Anderson JL, Adams CD, Antman EM, et al. **ACC/AHA 2007** guidelines for the management of patients with **unstable angina/non-ST-elevation myocardial infarction**. A report of the American College of Cardiolo Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2007; DOI:10.1016/j.jacc.2007.02.028. Available at: http://content.onlinejacc.org/cgi/content/full/50/7/e1. *Circulation* 2007;

TOP

DOI:10.1161/CIRCULATIONAHA.107.185752. Available at: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.185752. (**2011 ACCF/AHA Focused Update** of the Guidelines for the Management of Patients With **Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011 0: j.jacc.2011.02.009. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.02.009v1.pdf)

Anderson RJ, Bahn GD, Moritz TE, et al.; for the **VADT** Study Group. Blood Pressure and Cardiovascular Disease risk in the Veterans Affairs Diabetes Trial (VADT) Diabetes Care. 2010 Nov 8. DBP <70 mmHg elevated CVD risk.

Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, for the Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality. A randomized clinical trial. Ann Intern Med 2005; 142:233-39. (InfoPOEMs: A smoking cessation program resulted in fewer deaths over the next 15 years than usual care, even though only 1 in 5 (21.7%) of the participants actually quit smoking. More important, though, is the good evidence that smoking cessation decreases the risk of dying by heart disease, cardiovascular disease, or lung cancer. Yes, it's what we expected, but it's good to know for sure. (LOE = 1b-))

Antonia Trichopoulou, Philippos Orfanos, Teresa Norat, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ, Apr 2005; 10.1136/bmj.38415.644155.8F.

Appel LJ, et al. American Heart Association. **Dietary approaches** to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension. 2006 Feb;47(2):296-308.

Appel LJ, Wright JT Jr, Greene T, et al. Intensive bloodpressure control in hypertensive chronic kidney disease. (**AASK**) N Engl J Med 2010;363:918-29.

Archbold KH, Vasquez MM, Goodwin J et al. Effects of **Sleep Patterns** and Obesity on Increases in **Blood Pressure** in a 5-Year Period: Report from the Tucson Children's Assessment of Sleep Apnea Study. J Pediatr. 2012 Jan 25.

Arguedas JA, Perez MI, Wright JM. **Treatment blood pressure targets** for hypertension. Cochrane Database Syst Rev 2009; 3:CD004349. Treating patients to lower than standard BP targets, </=140-160/90-100 mmHg, does not reduce mortality or morbidity.

Arima H, Anderson C, Omae T, et al; for the Perindopril Protection Against Recurrent Stroke Study (**PROGRESS**) Collaborative Group. Effects of Blood Pressure Lowering on Intracranial and Extracranial Bleeding in Patients on Antithrombotic Therapy: The PROGRESS Trial. Stroke. 2012 Jun;43(6):1675-1677.

Arnlov J, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation. 2005 Aug 16;112(7):969-75.

Arnold JM, et al.; Canadian Cardiovascular Society. **Canadian** Cardiovascular Society consensus conference recommendations on **heart failure 2006**: diagnosis and management. Can J Cardiol. 2006 Jan;22(1):23-45. Erratum in: Can J Cardiol. 2006 Mar 1;22(3):271. (Arnold JM, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure **update 2007**: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol. 2007 Jan;23(1):21-45.)

Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. **Antiplatelet agents for prevention of pre-eclampsia**: a meta-analysis of individual patient data. Lancet 2007;369:1791-8.

Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP; for the PROVE IT-TIMI 22 Trial Investigators. What Is the **Optimal Blood Pressure in Patients After Acute Coronary Syndromes**?: Relationship of Blood Pressure and Cardiovascular Events in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 Trial. Circulation. 2010 Nov 8.

Bangalore Sripal, Kumar Sunil, Kjeldsen Sverre E et al. Antihypertensive drugs and **risk of cancer**: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. *The Lancet Oncology* - 30 November 2010 DOI: 10.1016/S1470-2045(10)70260-6. (Combo of ACEI & ARB possible higher risk)

Bangalore Sripal, Kumar Sunil, Wetterslev Jørn, et al. **Angiotensin receptor blockers and risk of myocardial infarction**: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ 2011;342:doi:10.1136/bmj.d2234 (Published 26 April 2011). –no increase in MI.

Bangalore S, Kumar S, Lobach I, et al. **Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose**: Observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011. DOI: 10.1161/CIRCULATIONAHA.110.016337.

Barbe´ F, Dura´ n-Cantolla J, Sa´ nchez-de-la-Torre M, et al. Effect of **continuous positive airway pressure on the incidence of hypertension** and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307(20):2161-2168.

Barzilay JI, Davis BR, Cutler JA, et al. Fasting Glucose Levels and Incident **Diabetes Mellitus** in Older NondiabeticAdults Randomized to Receive 3 Different Classes of Antihypertensive Treatment: A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). Arch Intern Med. 2006 Nov 13;166(20):2191-201. Fasting glucose levels increase in older adults with hypertension regardless of treatment type. For those taking chlorthalidone vs other medications, the risk of developing FG levels higher than 125 mg/dL (6.9 mmol/L) is modestly greater, but there is no conclusive or consistent evidence that this diuretic-associated increase in DM risk increases the risk of clinical events.

Batool-Anwar S, Malhotra A, Forman J, Winkelman J, Li Y, Gao X. **Restless legs syndrome and hypertension** in middle-aged women. Hypertension. 2011;58:791–796.

Beardmore KS, Morris JM, Gallery ED. Excretion of **antihypertensive medication into human breast milk**: a systematic review. Hypertens Pregnancy 2002;21:85-95.

Beckett NS, Peters R, Fletcher AE, et al. the **HYVET** Study Group. Treatment of Hypertension in Patients 80 Years of Age or Older. N Engl J Med. 2008 Mar 31; [Epub ahead of print] The results provide evidence that antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older is beneficial.

Beckett N, Peters R, Tuomilehto J, et al. for the **HYVET** Study Group. **Immediate and late benefits** of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial. BMJ. 2011 Jan 4;344:d7541. doi: 10.1136/bmj.d7541.

Bergersen BM. Cardiovascular Risk in Patients with **HIV Infection** : Impact of Antiretroviral Therapy. Drugs. 2006;66(15):1971-87.

Beyer F, Dickinson H, Nicolson Dj, Ford G, Mason J. Combined **calcium, magnesium and potassium** supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev. 2006 Jul 19;3:CD004805.

Bhaskaran K, Douglas I, Evans S, et al. Angiotensin receptor blockers and **risk of cancer**: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. BMJ. 2012 Apr 24;344:e2697.

Bhatt DL, et al. **REACH** Registry Investigators. International prevalence, recognition, and treatment of **cardiovascular risk factors** in outpatients with atherothrombosis. JAMA. 2006 Jan 11;295(2):180-9.

Bhatia RS, et al. Outcome of **heart failure** with **preserved ejection fraction** in a population-based study. N Engl J Med. 2006 Jul 20;355(3):260-9.

Bibbins-Domingo, Kirsten, Chertow, Glenn M., Coxson, Pamela G., et al. Projected Effect of Dietary **Salt Reductions** on Future Cardiovascular Disease. N Engl J Med 2010 0: NEJMoa0907355.

Birks EJ, et al. **Left ventricular assist device** and drug therapy for the reversal of heart failure. N Engl J Med. 2006 Nov 2;355(18):1873-84.

Bisognano JD, Bakris G, Nadim MK, et al. **Baroreflex activation therapy** lowers blood pressure in patients with resistant hypertension. Results from the double-blind, randomized, placebo-controlled **Rheos Pivotal Trial**. J Am Coll Cardiol 2011; DOI:10.1016/j.jacc.2011.06.008.

Blood Pressure Lowering Treatment Trialists' Collaboration. (BPLTTC) Effects of different regimens to lower blood pressure on major cardiovascular events in **older & younger adults**: meta-analysis of randomised trials. BMJ. 2008 May 17;336(7653):1121-1123. Epub 2008 May 14. Reduction of blood pressure produces benefits in younger (<65 years) and older (>/=65 years) adults, with no strong evidence that protection against major vascular events afforded by different drug classes varies substantially with age.

Blumenthal James A.; Babyak Michael A.; Hinderliter Alan; et al. Effects of the **DASH Diet** Alone and in Combination With Exercise and Weight Loss on Blood Pressure and Cardiovascular Biomarkers in Men and Women With High Blood Pressure: The **ENCORE** Study. *Arch Intern Med*. 2010;170(2):126-135.

Bobrie G, et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure **self-measurement** in elderly treated hypertensive patients. JAMA. 2004 Mar 17;291(11):1342-9. (Bobrie G, et al. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? Arch Intern Med. 2001 Oct 8;161(18):2205-11.) (Fagard RH, et al.Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. J Hum Hypertens. 2005 Oct;19(10):801-7.) (Hozawa A, et al. Prognostic value of **home heart rate** for cardiovascular mortality in the general population: the Ohasama study. Am J Hypertens. 2004 Nov;17(11 Pt 1):1005-10.)

Boden WE, O'rourke RA, Teo KK, Hartigan PM, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. **COURAGE** Trial Research Group. N Engl J Med. 2007 Mar 26; [Epub ahead of print] As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy. PCI does not lower the rates of myocardial infarction or death in patients with stable coronary artery disease who receive optimal medical treatment, a large trial concluded. The study, released early online by NEJM, randomized nearly 2300 patients either to PCI with optimal medical therapy (intensive pharmacologic treatment plus lifestyle intervention) or to optimal medical therapy alone. After a median follow-up of almost 5 years, 19% in the PCI group died or had MIs, compared with 18.5% who received medical therapy alone. PCI patients were more likely to be free of angina after 1 and 3 years, but there was no significant difference after 5 years. One-third of patients in the medical therapy group ultimately required revascularization, while 21% in the PCI group needed additional revascularization. An editorialist concludes: "Patients whose condition is clinically unstable, who have left main coronary artery disease, or in whom medical therapy has failed to control symptoms remain candidates for revascularization, but PCI should not play a major role as part of a secondary prevention strategy."
Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C, Zhang W,et al.; COURAGE Trial Research Group, Mancini GB. Effect of PCI on quality of life in patients with stable coronary disease. N Aug 14;359(7):677-87. Among patients with stable angina, both those treated with PCI and those treated with optimal medical therapy alone had marked improvements in health status during follow-up. The PCI

TOP

but significant, incremental benefits that disappeared by 36 months.
Borden WB, Redberg RF, Mushlin AI, et al. **Patterns and intensity of medical therapy** in patients undergoing percutaneous coronary intervention. JAMA 2011; 305:1882-1889. (after Courage study publication)
Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction (**STICH**). N Engl J Med 2011. DOI: 10.1056/NEJMoa1100358. (CABG vs medical therapy)
Bosworth, HB. Olsen, Maren K. et al. Two **Self-management** Interventions to Improve Hypertension Control: A Randomized Trial. Ann Intern Med November 17, 2009 151:687-695; doi:10.1059/0003-4819-151-10-200911170-00148.
Bosworth HB, Powers BJ, Olsen MK, et al. **Home blood pressure management** and improved blood pressure control: results from a randomized controlled trial. Arch Intern Med. 2011;171(13):1173-1180.
Bradley TD, Logan AG, Kimoff RJ, et al.; CANPAP Investigators. **Continuous positive airway pressure** for central sleep apnea & heart failure. N Engl J Med. 2005 Nov 10;353(19):2025-33. (InfoPOEMs: There is no evidence that continuous positive airway pressure (CPAP) improves mortality or reduces the need for transplantation in patients with heart failure and central sleep apnea. (LOE = 1b))
Brandt MC, Mahfoud F, Reda S, et al. **Renal sympathetic denervation** reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension J Am Coll Cardiol 2012; 59:901-909.
Braunwald E, et al. Rosenberg YD, Rouleau JL; **PEACE** Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004 Nov 11;351(20):2058-68. Epub 2004 Nov 7.
Brindle P, et al. Accuracy and impact of **risk assessment in the primary prevention** of cardiovascular disease: a systematic review. Heart. 2006 Dec;92(12):1752-9. Epub 2006 Apr 18.
Brouwer IA, et al. SOFA Study Group. Effect of **fish oil on ventricular tachyarrhythmia** and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA. 2006 Jun 14;295(22):2613-9. Our findings do not indicate evidence of a strong protective effect of intake of omega-3 PUFAs from fish oil against ventricular arrhythmia in patients with ICDs.
Brown MJ, McInnes GT, Papst CC, et al. **Aliskiren** and the calcium channel blocker **amlodipine combination** as an initial treatment strategy for hypertension control (**ACCELERATE**): a randomised, parallel-group trial. Lancet. 2011 Jan 12.
Brown IJ, Stamler J, Van Horn L, et al. **Sugar-sweetened beverage**, sugar intake of individuals and their blood pressure: INTERMAP study. Hypertension 2011.
Budoff MJ, et al. Assessment of Coronary Artery Disease by **Cardiac Computed Tomography**, A Scientific Statement From the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation. 2006 Oct 2; [Epub ahead of print]
Buijsse B, Feskens EJ, Kok FJ, Kromhout D. **Cocoa intake**, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study. Arch Intern Med. 2006 Feb 27;166(4):411-7.
Buijsse, B, Weikert C, Drogan D et al. **Chocolate consumption** in relation to blood pressure and risk of CV disease in German adults. Eur Heart J 2010: DOI:10.1093/eurheartj/ehq068.
Bursi F, et al. **Systolic and diastolic heart failure** in the community. JAMA. 2006 Nov 8;296(18):2209-16.
Calhoun DA, Jones D, Textor S, et al. **Resistant Hypertension**: Diagnosis, Evaluation, and Treatment. A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008 Apr 7; [Epub ahead of print] (Tobe SW, Lewanczuk R. Resistant hypertension. Can J Cardiol. 2009 May;25(5):315-7.)
Campbell NR, Brant R, Johansen H, et al.; Canadian Hypertension Education Program Outcomes Research Task Force. Increases in antihypertensive prescriptions and reductions in cardiovascular events in Canada. Hypertension. 2009 Feb;53(2):128-34. Epub 2008 Dec 29. This study demonstrates that the reduction in cardiovascular death and hospitalization rates is associated with an increase in antihypertensive prescriptions and that it coincides with the introduction of the Canadian Hypertension Education Program.
Campbell NR, Hemmelgarn BR. New recommendations for the use of **ambulatory blood pressure monitoring** in the diagnosis of hypertension. CMAJ. 2012 Apr 3;184(6):633-4.
Canadian Physical Activity Guidelines-Jan 2011. Clinical Practice Guideline Development Report. Canadian Society for Exercise Physiology. http://www.csep.ca/CMFiles/Guidelines/CPAGuideline_Report_JAN2011.pdf
Caton AR, Bell EM, Druschel CM, Werler MM, Lin AE, Browne ML, et al. **Antihypertensive medication use during pregnancy** and the risk of cardiovascular malformations. Hypertension 2009;54:63-70.
Caritis S, Sibai B, Hauth J, et al. Lowdose **aspirin to prevent preeclampsia** in women at high risk. N Engl J Med 1998; 338:701-5.
Carter Barry L.; Rogers Meaghan; Daly Jeanette; et al. The Potency of **Team-Based** Care Interventions for Hypertension: A Meta-analysis. *Arch Intern Med*. 2009;169(19):1748-1755.
Carter Barry L.; Ardery Gail; Dawson Jeffrey D.;et al. **Physician and Pharmacist Collaboration** to Improve Blood Pressure Control. Arch Intern Med. 2009;169(21):1996-2002.
Casas JP, et al. Effect of inhibitors of the **renin-angiotensin system** and other antihypertensive drugs on **renal outcomes**: systematic review and meta-analysis. Lancet. 2005 Dec 10;366(9502):2026-2033. INTERPRETATION: The benefits of ACE inhibitors or ARBs on renal outcomes in placebo-controlled trials probably result from a blood-pressure-lowering effect. In patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain unproven, and there is uncertainty about the greater renoprotection seen in non-diabetic renal disease.
CDC: Centers for Disease Control and Prevention. Vital signs: **Prevalence, treatment, and control of hypertension—United States**, 1999-2002 and 2005-2008. MMWR Morb Mortal Wkly Rep 2011; 60:1-6.
Chang CH, Lin JW, Wu LC, Lai MS. Angiotensin receptor blockade and risk of **cancer** in type 2 diabetes mellitus: A nationwide case-control study. J Clin Oncol 2011; DOI 10.1200/JCO.2011.35.1908. The results did not show an effect of ARBs as a class on increasing cancer incidence in patients with diabetes. However, there was a negative association of losartan but a positive one of candesartan and telmisartan with the overall occurrence of cancer.
Charpentier MM, Bundeff A. Treating hypertension in the **very elderly**. Ann Pharmacother. 2011 Sep;45(9):1138-43.
Chen JM, Heran BS, Perez MI, Wright JM. Blood pressure lowering efficacy of **beta-blockers** as second-line therapy for primary hypertension. **Cochrane** Database Syst Rev. 2010 Jan 20;(1):CD007185.
Chen ST, Maruthur NM, Appel LJ. The effect of **dietary patterns** on estimated coronary heart disease risk: results from the Dietary Approaches to Stop Hypertension (**DASH**) trial. Circ Cardiovasc Qual Outcomes. 2010;3:484 – 489.
Chen L, Caballero B, Mitchell DC, et al. Reducing consumption of **sugar-sweetened beverages** is associated with reduced blood pressure. A prospective study among United States adults. Circulation 2010.
Chen N, Zhou M, Yang M, et al. **Calcium channel blockers versus** other classes of drugs for hypertension. Cochrane Database Syst Rev. 2010 Aug 4;8:CD003654. Diuretics are preferred first-line over CCBs to optimize reduction of cardiovascular events. The review does not distinguish between CCBs, ACE inhibitors or ARBs, but does provide evidence supporting the use of CCBs over beta-blockers.
Chobanian AV. Clinical practice. **Isolated systolic hypertension in the elderly**. N Engl J Med. 2007 Aug 23;357(8):789-96.
Chobanian, Aram V.The **Hypertension Paradox** -- More Uncontrolled Disease despite Improved Therapy. N Engl J Med 2009 361: 878-887.
Choi HK, Soriano LC, Zhang Y, Rodríguez LAG. **Calcium channel blockers, losartan**, and the risk of **incident gout** among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.
Chow CK, Pell AC, Walker A, O'Dowd C, Dominiczak AF, Pell JP. **Families of patients with premature** coronary heart disease: an obvious but neglected target for primary prevention. BMJ. 2007 Sep 8;335(7618):481-5.
Cissoko H, Jonville-Bera AP, Swortfiguer D, Giraudeau B, Autret-Leca E. [Neonatal outcome after exposure to beta adrenergic blockers late in pregnancy.] Arch Pediatr. 2005 May;12(5):543-7.
Clark C. E., Smith L. F. P., Taylor R. S., Campbell J. L. **Nurse led interventions** to improve control of blood pressure in people with hypertension: systematic review and meta-analysis BMJ 2010;341:c3995
Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic **blood pressure between arms** with vascular disease and mortality: a systematic review and meta-analysis. Lancet 2012
Clark CE, Taylor RS, Shore AC, Campbell JL. The difference in blood pressure readings **between arms** and survival: primary care cohort study. BMJ 2012;344:e1327.
Clayton TC, Lubsen J, et al. **Risk score** for predicting death, myocardial infarction, and stroke in patients with stable angina, based on a large randomised trial cohort of patients. BMJ. 2005 Oct 15;331(7521):869. Epub 2005 Oct 6.
Cleland JG, et al.; Cardiac **Resynchronization**-Heart Failure (CARE-HF) Study. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005 Apr 14;352(15):1539-49. Epub 2005 Mar 7.
Cnossen JS, Vollebregt KC, Vrieze N, et al. Accuracy of mean arterial pressure and blood pressure measurements in predicting **pre-eclampsia**: systematic review and meta-analysis. BMJ. 2008 May 17;336(7653):1117-20. Epub 2008 May 14. When blood pressure is measured in the first or second trimester of pregnancy, the mean arterial pressure is a better predictor for pre-eclampsia than systolic blood pressure, diastolic blood pressure, or an increase of blood pressure.
Cohen HW, Hailpern SM, Fang J, Alderman MH. **Sodium intake** and mortality in the NHANES II follow-up study. Am J Med. 2006 Mar;119(3):275.e7-14.
Conen D, et al. Usefulness of B-type **natriuretic peptide and C-reactive protein** in predicting the presence or absence of left ventricular hypertrophy in patients with systemic hypertension. Am J Cardiol. 2006 Jan 15;97(2):249-52.
Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary **sodium reduction on cardiovascular disease** outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ. 2007 Apr 20; [Epub ahead of print] Sodium reduction, previously shown to lower blood pressure, may also reduce long term risk of cardiovascular events.
Cooper WO, et al. Major congenital malformations after **first-trimester exposure to ACE** inhibitors. N Engl J Med. 2006 Jun 8;354(23):2443-51. (see also Pharmacist's Letter July 2006)
Cooper-DeHoff RM, Gong Y, Handberg EM, et al. **Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease**. (**INVEST**) JAMA. 2010 Jul 7;304(1):61-8.
Cosselman KE, Krishnan RM, Oron AP, et al. Blood pressure response to controlled **diesel exhaust** exposure in human subjects. Hypertension. 2012 May;59(5):943-8.
Cragg J, Krassioukov A. **Autonomic dysreflexia**. CMAJ. 2011 Oct 11.
Dahlof B, Sever PS, Poulter NR, Wedel H, et al. ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (**ASCOT-BPLA**): a multicentre RCT. Lancet. 2005 Sep 10;366(9489):895-906. (InfoPOEMs: In t hypertension and at least 3 additional cardiac risk factors have slightly fewer deaths from all causes, slightly fewer strokes, and were slightly less likely to develop diabetes if they were treated with amlodipine plus perindopril than if they were treated with atenolol and b

TOP

would need to treat between 60 and 1000 high-risk patients for a median of 5.5 years with amlodipine instead of atenolol to prevent one additional death. (LOE = 2b)) (Sever P, Dahlof B, Poulter N, et al. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. Eur Heart J 2006; 27:2982-2988.)

Dahlof B, et al. LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (**LIFE**): a randomised trial against atenolol. Lancet. 2002 Mar 23;359(9311):995-1003. (Lindholm LH, et al.; LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002 Mar 23;359(9311):1004-10.)(Ibsen H, et al. Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. Diabetes Care. 2006 Mar;29(3):595-600.)

Danaei G, Finucane MM, Kin JK, et al. **National, regional, and global trends in systolic blood pressure since 1980**: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. Lancet 2011.

Dagenais GR, Lu J, Faxon DP, et al. Effects of Optimal Medical Treatment With or Without Coronary Revascularization on Angina and Subsequent Revascularizations in Patients With Type 2 Diabetes Mellitus and Stable Ischemic Heart Disease. Circulation. 2011 Mar 28. (**BARI 2D**)

Davis BR, et al.; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Role of diuretics in the prevention of **heart failure**: the ALLHAT. Circulation. 2006 May 9;113(18):2201-10. Epub 2006 May 1. HF risk decreased with chlorthalidone versus amlodipine or lisinopril use during year 1. Subsequently, risk for those individuals taking chlorthalidone versus amlodipine remained decreased but less so, whereas it was equivalent to those given lisinopril. Prior medication use, follow-up blood pressures, and concomitant medications are unlikely to explain most of the HF differences. Diuretics are superior to calcium channel blockers and, at least in the short term, angiotensin-converting enzyme inhibitors in preventing HF in hypertensive individuals.

de la Sierra A, Segura J, et al. Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of **ambulatory blood pressure monitoring**. Hypertension. 2011 May;57(5):898-902.

Desch S, Schmidt J, Kobler D, et al. Effect of **Cocoa Products** (chocolate) on Blood Pressure: Systematic Review and Meta-Analysis. Am J Hypertens. 2009 Nov 12.

Deshmukh A, Kumar G, Kumar N, et al. Effect of Joint National Committee VII Report on Hospitalizations for **Hypertensive Emergencies** in the United States. Am J Cardiol. 2011 Sep3

Dietary Guidelines for Americans (DGA) 2010. Full Guideline: http://www.health.gov/dietaryguidelines/dga2010/DietaryGuidelines2010.pdf, Summary: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/ExecSumm.pdf

Digoxin (Ahmed A, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the **DIG** trial. Eur Heart J. 2006 Jan;27(2):178-86. Epub 2005 Dec 8. & Adams KF Jr, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol. 2005 Aug 2;46(3):497-504).

Dickinson BD, Havas S for the Council on Science and Public Health. Reducing the population burden of cardiovascular disease by reducing **sodium intake**. Arch Intern Med 2007; 167:1460-1468.

Dicpinigaitis PV. **Angiotensin-converting enzyme inhibitor**-induced **cough**: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(suppl):169-73S.

Dobrosielski DA, Gibbs BB, Ouyang P, et al. Effect of **Exercise** on Blood Pressure in Type 2 Diabetes: A Randomized Controlled Trial. J Gen Intern Med. 2012 May 19.

Dorsch MP, Gillespie BW, Erickson SR, et al. **Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide**: a retrospective cohort analysis. Hypertension. 2011 Apr;57(4):689-94.

Douma S, Petidis K, Doumas M, et al. Prevalence of **primary hyperaldosteronism** in resistant hypertension: a retrospective observational study. Lancet. 2008 Jun 7;371(9628):1921-6. Although the prevalence of primary hyperaldosteronism in patients with resistant hypertension was high, it was substantially lower than previously reported.

Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does **B-type natriuretic peptide** predict death and cardiac events in patients with **heart failure**: systematic review. BMJ. 2005 Mar 19;330(7492):625.

Drozda J. Jr., Messer JV, Spertus J, et al. **ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension**: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. J Am Coll Cardiol 2011;58:xxx–xxx. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.05.002v1.pdf

Duggan ST, Chwieduk CM, Curran MP. **Aliskiren**: a review of its use as monotherapy and as combination therapy in the management of hypertension. Drugs. 2010 Oct 22;70(15):2011-49. Dusing R. Sexual dysfunction in male patients with hypertension: influence of antihypertensive drugs. Drugs. 2005;65(6):773-86.

Ebrahim S, Beswick A, Burke M, Davey Smith G. **Multiple risk factor interventions** for **primary** prevention of coronary heart disease. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD001561.

Egan Brent M.; Zhao Yumin; Axon R. Neal. **US Trends in Prevalence, Awareness, Treatment, and Control** of Hypertension, 1988-2008. JAMA. 2010;303(20):2043-2050.

Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and Apparent Treatment **Resistant Hypertension in the United States, 1988 to 2008**. Circulation. 2011 Aug 8.

Elmer PJ, et al. **PREMIER** Collaborative Research Group. Effects of comprehensive **lifestyle** modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. Ann Intern Med. 2006 Apr 4;144(7):485-95. Summary for patients in: Ann Intern Med. 2006 Apr 4;144(7):I27.

Ernst ME, Neaton JD, Grimm RH Jr, et al. Multiple Risk Factor Intervention Trial Research Group. Long-term effects of **chlorthalidone versus hydrochlorothiazide** on electrocardiographic left ventricular hypertrophy in the multiple risk factor intervention trial. (**MRFIT**) Hypertension. 2011 Dec;58(6):1001-7.

ESCAPE Trial Group. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009 Oct 22; 361:1639.

Espinola-Klein C, Weisser G, Jagodzinski A, et al. {beta}-Blockers in Patients With Intermittent Claudication and Arterial Hypertension: Results From the **Nebivolol or Metoprolol in Arterial Occlusive Disease** Trial. Hypertension. 2011 Aug;58(2):148-54.

Estruch R, Martinez-González MA, Corella D et al. Effects of a **Mediterranean-style diet** on cardiovascular risk factors. A randomized trial. Ann Intern Med 2006; 145:1-11.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on **Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents**: Summary Report. Pediatrics. 2011 Nov 14.

Fagard RH, Celis H, Thijs L, Wouters S. **Regression of left ventricular mass** by antihypertensive treatment: a meta-analysis of randomized comparative studies. Hypertension. 2009 Nov;54(5):1084-91.

FDA June/11 Food and Drug Administration drug safety: **No increase in risk of cancer** with certain blood pressure drugs—**angiotensin receptor blockers (ARBs).** June 2, 2011. http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm

Fernstrom JD, et al. Long-term Changes in Blood Pressure in Extremely Obese Patients Who Have Undergone **Bariatric** Surgery. Arch Surg. 2006 Mar;141(3):276-83.

Feringa HH, et al. Cardioprotective medication is associated with improved survival in patients with **peripheral arterial disease**. J Am Coll Cardiol. 2006 Mar 21;47(6):1182-7. Epub 2006 Feb 23.

Fitzharris P, Jordan A. Investigating **recurrent angio-oedema**. BMJ. 2011 Oct 24;343:d6607.

Flack JM, Sica DA, Bakris G, et al. **Management of high blood pressure in blacks**. An update of the International Society on Hypertension in Blacks consensus statement. *Hypertension* 2010; DOI: 10.1161/HYPERTENSIONAHA.110.152892. Available at: http://hyper.ahajournals.org

Fletcher RD, Amdur RL, et al. **Blood Pressure Control Among US Veterans**: A Large Multiyear Analysis of Blood Pressure Data From the Veterans Administration Health Data Repository. Circulation. 2012 May 22;125(20):2462-8.

Flynn NO, Timmis A, Henderson R, Rajesh S, Fenu E; on behalf of the Guideline Development Group. Management of **stable angina**: summary of **NICE** guidance. BMJ. 2011 Aug 5;343:d4147. doi: 10.1136/bmj.d4147.

Flynn JT, Pierce CB, Miller ER 3rd, Charleston J, et al. Reliability of **resting blood pressure measurement** and classification using an **oscillometric device** in **children** with chronic kidney disease. J Pediatr 2011.

Folsom AR, et al. An assessment of incremental coronary risk prediction using **C-reactive protein** and other novel risk markers: the atherosclerosis risk in communities study. Arch Intern Med. 2006 Jul 10;166(13):1368-73.

Ford ES. Trends in **mortality from all causes and cardiovascular disease among hypertensive and nonhypertensive adults** in the United States. Circulation. 2011 Apr 26;123(16):1737-44.

Forman JP, Stampfer MJ, Curhan GC. **Diet and lifestyle** risk factors associated with incident hypertension in women. JAMA. 2009 Jul 22;302(4):401-11.

Fouque D, Laville M, Boissel JP. **Low protein diets for chronic kidney disease** in non diabetic adults. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD001892.

Franco OH, de Laet C, Peeters A, Jonker J, Mackenbach J, Nusselder W. Effects of **physical activity** on life expectancy with cardiovascular disease. Arch Intern Med. 2005 Nov 14;165(20):2355-60.

Franklin SS, Thijs L, Hansen TW, et al. Significance of **White-Coat Hypertension in Older Persons** With Isolated Systolic Hypertension: A Meta-Analysis Using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes Population. Hypertension. 2012 Jan 17.

Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med. 2008 Apr 14;168(7):713-20. Adh

TOP

DASH-style diet is associated with a lower risk of CHD and stroke among middle-aged women during 24 years of follow-up.
Fung MM, Peters K, Redline S, et al. for the Osteoporotic Fractures in Men Research Group. **Decreased Slow Wave Sleep** Increases Risk of Developing Hypertension in Elderly Men. Hypertension. 2011 Aug 29.
Garcia MJ, Lessick J, Hoffmann MH; CATSCAN Study Investigators. Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis. JAMA. 2006 Jul 26;296(4):403-11. The results of this study indicate that MDCT coronary angiography performed with 16-row scanners is limited by a high number of nonevaluable cases and a high false-positive rate. Thus, its routine implementation in clinical practice is not justified. Nevertheless, given its high sensitivity & negative predictive value, 16-row MDCT may be useful in excluding coronary disease in selected patients in whom a false-positive or inconclusive stress test result is suspected.
Gee ME, et al. Outcomes Research Task Force of the Canadian Hypertension Education Program. **Antihypertensive Medication Use**, Adherence, Stops, & Starts in Canadians With Hypertension. Can J Cardiol. 2012Apr 20.
Gheorghiade M, et al. **OPTIMIZE-HF** Investigators and Coordinators. **Systolic blood pressure** at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006 Nov 8;296(18):2217-26.
Glynn LG, Murphy AW, Smith SM, Schroeder K, Fahey T. **Self-monitoring and other non-pharmacological interventions** to improve the management of hypertension in primary care: a systematic review. Br J Gen Pract. 2010 Dec;60(581):e476-88.
Godtfredsen NS, Prescott E, Osler M. Effect of **smoking** reduction on lung cancer risk. JAMA. 2005 Sep 28;294(12):1505-10.
Gray L, Lee I-M, Sesso HD, Batty GD. **Blood pressure in early adulthood**, hypertension in middle age, and future cardiovascular disease mortality: HAHS (Harvard Alumni Health Study). J Am Coll Cardiol 2011; 58:2396-2403.
Green BB, Cook AJ, Ralston JD, et al. Effectiveness of home blood pressure monitoring, **Web communication, and pharmacist** care on hypertension control: a randomized controlled trial. JAMA. 2008 Jun 25;299(24):2857-67. Pharmacist care management delivered through secure patient Web communications improved BP control in patients with hypertension.
Grundvold I, Skretteberg PT, Liestøl K, et al. **Upper normal blood pressures** predict **incident atrial fibrillation** in healthy middle-aged men: a 35-year follow-up study. Hypertension. 2012;59:198 –204.
Gueyffier F, et al. Antihypertensive drugs in **very old people**: a subgroup meta-analysis of randomised controlled trials. INDANA Group. Lancet. 1999 Mar 6;353(9155):793-6.
Guimont C, et al. Effects of **job strain** on blood pressure: a prospective study of male and female white-collar workers. Am J Public Health. 2006 Aug;96(8):1436-43. Epub 2006 Jun 29. (InfoPOEMs: Work stress has no meaningful effect on blood pressure. (LOE = 1b))
Gupta AK, Dahlof B, Dobson J, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. (**Ascot**) Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. Diabetes Care. 2008 May;31(5):982-8. Epub 2008 Jan 30. Baseline FPG >5 mmol/l, BMI, and use of an atenolol +/- diuretic regimen were among the major determinants of NOD in hypertensive patients. The model developed from these data allows accurate prediction of NOD among hypertensive subjects.
Hallan S, Astor B, Romundstad S, Aasarød K, Kvenild K, Coresh J. Association of Kidney Function and Albuminuria With Cardiovascular Mortality in Older vs Younger Individuals: The HUNT II Study. Arch Intern Med. 2007 Dec 10;167(22):2490-6. Reduced kidney function and microalbuminuria are risk factors for cardiovascular death, independent of each other and traditional risk factors. The combined variable improved cardiovascular risk stratification at all age levels, but particularly in elderly persons where the predictive power of traditional risk factors is attenuated.
Haller H, Ito S, Izzo JL Jr, et al. **Olmesartan** for the delay or prevention of microalbuminuria in type 2 diabetes. (**ROADMAP**) N Engl J Med 2011;364:907-17. (n=4447 over 3.2yr. Improved microalbuminuria, but increased fatal CV events)
Halton TL, Willett WC, Liu S et al. **Low-carbohydrate-diet** score and the risk of coronary heart disease in **women**. N Engl J Med 2006; 355:1991-2002.
Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of **peripheral arterial disease**. JAMA. 2006 Feb 1;295(5):547-53.
Hara A, Tanaka K, Ohkubo T, et al. **Ambulatory Versus Home Versus Clinic Blood Pressure**: The Association With Subclinical Cerebrovascular Diseases: The Ohasama Study. Hypertension. 2011 Nov 14.
Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, et al. **Omega-6 Fatty Acids** and Risk for Cardiovascular Disease. A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. Circulation. 2009 Jan 26. [Epub ahead of print] In summary, the AHA supports an omega-6 PUFA intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD.
Harel Z et al. The effect of combination treatment with **aliskiren and blockers of the renin-angiotensin system** on hyperkalaemia and acute kidney injury: systematic review and meta-analysis. BMJ. 2012 Jan 9;344:e42.
Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. **Physical Activity** and Public Health. Updated Recommendation for Adults From the American College of Sports Medicine and the American Heart Association. (**AHA**) Circulation. 2007 Aug 1; [Epub ahead of print] To promote and maintain health, all healthy adults aged 18 to 65 yr need moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic physical activity for a minimum of 20 min on three days each week. [I (A)] Combinations of moderate- and vigorous-intensity activity can be performed to meet this recommendation. [IIa (B)] For example, a person can meet the recommendation by walking briskly for 30 min twice during the week and then jogging for 20 min on two other days. Moderate-intensity aerobic activity, which is generally equivalent to a brisk walk and noticeably accelerates the heart rate, can be accumulated toward the 30-min minimum by performing bouts each lasting 10 or more minutes.
Havas S, Dickinson BD, Wilson M. The urgent need to **reduce sodium (salt) consumption**. JAMA. 2007 Sep 26;298(12):1439-41.
He FJ, Marciniak M, Visagie E, et al. Effect of Modest **Salt Reduction** on Blood Pressure, Urinary Albumin, and Pulse Wave Velocity in White, Black, and Asian Mild Hypertensives. Hypertension. 2009 Jul 20. [Epub ahead of print]
He J, Wofford MR, Reynolds K, et al. Effect of **dietary protein** (40g/day: soy & milk) supplementation on blood pressure. A randomized controlled trial. Circulation 2011; doi:10.1161/circulationaha.110.009159.
Head Geoffrey A, Mihailidou Anastasia S, Duggan Karen A, et al. **Ambulatory Blood Pressure** Working Group of the High Blood Pressure Research Council of Australia. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: prospective cohort study. BMJ 2010;340:c1104, doi: 10.1136/bmj.c1104
Health Canada Jan/12 **RASILEZ** (aliskiren) and RASILEZ HCT (aliskiren/hydrochlorothiazide) - Potential Risks of Cardiovascular and Renal Adverse Events in Patients with Type 2 Diabetes - Novartis Pharmaceuticals Canada Inc. The combination of **aliskiren with ACE inhibitors and ARBs is now contraindicated in patients with type 2 diabetes**. The Product Monograph will be updated accordingly.
Heart Failure Society Of America. **HFSA 2006** Comprehensive Heart Failure Practice Guideline. J Card Fail. 2006 Feb;12(1):e1-2.
Heisler M, Hofer TP, Schmittdiel JA, et al. Improving blood pressure control through a **clinical pharmacist outreach program** in patients with diabetes mellitus in 2 high-performing health systems: the adherence and intensification of medications cluster randomized, controlled pragmatic clinical trial. *Circulation.* 2012;125:2863–2872.
Hermida RC, Ayala DE, Mojón A, Fernández JR. **Bedtime Dosing of Antihypertensive Medications** Reduces Cardiovascular Risk in CKD. J Am Soc Nephrol. 2011 Oct 24.
Heran BS, Musini VM, Bassett K, et al. **Angiotensin receptor blockers for heart failure**. Cochrane Database Syst Rev. 2012 Apr 18;4:CD003040. In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity. ARBs are better tolerated than ACEIs but do not appear to be as safe and well tolerated as placebo in terms of withdrawals due to adverse effects. Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.
Hippisley-Cox J., Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. BMJ 2005;330:1059-1063 (7 May), doi:10.1136/bmj.330.7499.1059. Conclusions: Combo of statins, aspirins, & beta-blockers improve survival in high risk pts with cardiovascular dx, although the addition of an angiotensin converting enzyme inhibitor conferred no additional benefit despite the analysis being adjusted for congestive cardiac failure.
Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of **QRISK**, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ. 2007 Jul 5; [Epub ahead of print] Using QRISK 8.5% of patients aged 35-74 are at high risk (20% risk or higher over 10 years) compared with 13% when using the Framingham algorithm and 14% when using ASSIGN. Using QRISK 34% of women and 73% of men aged 64-75 would be at high risk compared with 24% and 86% according to the Framingham algorithm. UK estimates for 2005 based on QRISK give 3.2 million patients aged 35-74 at high risk, with the Framingham algorithm predicting 4.7 million and ASSIGN 5.1 million.
Hodgkinson J, Mant J, Martin U, et al. Relative effectiveness of **clinic and home blood pressure monitoring compared with ambulatory** blood pressure monitoring in diagnosis of hypertension: systematic review. BMJ 2011;342:doi:10.1136/bmj.d3621 (Published 24 June 2011).
Hodgson JM, Puddey IB, Woodman RJ, et al. Effects of **black tea** on blood pressure: A randomized controlled trial. Arch Intern Med2012; 172:186-188.
Hofmeyr GJ, Lawrie TA, Atallah AN, et al. **Calcium supplementation during pregnancy** for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2010 Aug 4;8:CD001059.
Hollingsworth JM, et al. Medical therapy to **facilitate urinary stone passage**: a meta-analysis. Lancet. 2006 Sep 30;368(9542):1171-9. Patients given calcium-channel blockers or alpha blockers had a 65% (absolute risk reduction=0.31 95% CI 0.25-0.38) greater likelihood of stone passage than those not given such treatment (pooled risk ratio 1.65; 95% CI 1.45-1.88). The pooled risk ratio for alpha blockers was 1.54 (1.29-1.85) and for calcium-channel blockers with steroids was 1.90 (1.51-2.40). (InfoPOEMs: The limited amount of available data suggest that alpha blockers and calcium channel blockers appear to speed the passage of kidney stones. Furthermore, it appears that combining these medications with steroids provides additional benefit. (LOE = 1a-))
Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes. N Engl J Med. 2008 Sep 10. [Epub ahead of print] (**UKPDS 81**) The benefits of previously improved blood-pressure control were not sustained when between-group differences in blood pressure were lost. Early improvement in blood-pressure control in patients with both type 2 diabetes and hypertensi associated with a reduced risk of complications, but it appears that good blood-pressure control must be continued if the benefits are to be maintained.

TOP

Hooper L, et al. Risks and benefits of **omega 3 fats** for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006 Mar 24; [Epub ahead of print] (Wang C, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006 Jul;84(1):5-17.)

Hooper L, Summerbell CD, Thompson R, et al. **Reduced or modified dietary fat** for preventing cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD002137. DOI: 10.1002/14651858.CD002137.pub2. The findings are suggestive of a small but potentially important reduction in cardiovascular risk on modification of dietary fat, but not reduction of total fat, in longer trials. Lifestyle advice to all those at risk of cardiovascular disease and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates. The ideal type of unsaturated fat is unclear.

Horne Rosemary S. C., Yang Joel S. C., Walter Lisa M., et al. **Elevated Blood Pressure During Sleep** and Wake in Children With Sleep-Disordered Breathing. Pediatrics 2011; 128:1 e85-e92; doi:10.1542/peds.2010-3431

Howard BV, et al. **Low-fat dietary pattern** and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006 Feb 8;295(6):655-66.

Hou FF, Zhang X, Zhang GH, et al. Efficacy & safety of **benazepril** for advanced chronic renal (CKD pts) insufficiency. N Engl J Med. 2006 Jan 12;354(2):131-40. (InfoPOEMs: In a group of nondiabetic patients with serum creatinine levels between 3.0 & 5.0 mg/dL, benazepril slows the progression of renal disease. These pts were carefully monitored for any changes in renal function during the first 8 weeks, and were carefully screened & monitored to detect any early adverse effects on renal function. (LOE = 1b))

Houston TK, Allison JJ, Sussman M, et al. Culturally appropriate **storytelling** to improve blood pressure. A randomized trial. *Ann Intern Med* 2011; 154:77-84.

Hueb Whady, Lopes Neuza, Gersh Bernard J., et al. Ten-Year Follow-Up Survival of the Medicine, Angioplasty, or Surgery Study (**MASS II**): A Randomized Controlled Clinical Trial of 3 Therapeutic Strategies for Multivessel Coronary Artery Disease. Circulation 122: 949-957.

ICSI Health Care Guideline: Hypertension Diagnosis and Treatment. Nov 2010.

Jackson R, Broad J, Connor J, Wells S. **Alcohol** and ischaemic heart disease: probably no free lunch. Lancet. 2005 Dec 3;366(9501):1911-2.

Jansen L, Below J, Chang-Claude J, et al. **Beta blocker use and colorectal cancer risk**: Population-based case-control study. Cancer. 2012 May 14.

Joaquín Durán-Cantolla, Felipe Aizpuru, Jose María Montserrat, et al. , Spanish Sleep and Breathing Group. **Continuous positive airway pressure (CPAP) as** treatment for systemic hypertension in people with obstructive **sleep apnoea**: randomised controlled trial. BMJ 341:doi:10.1136/bmj.c5991 (Published 24 Nov 2010).

Jones AG, Evans PH, Vaidya B. **Phaeochromocytoma**. BMJ. 2012 Feb 20;344:e1042.

Jung S-Y, Choi N-K, Kim J-Y, et al. **Short-acting nifedipine and risk of stroke** in elderly hypertensive patients. Neurology 2011;77:1229 –1234.

Juraschek SP, Guallar E, Appel LJ, Miller ER 3rd. Effects of **vitamin C supplementation** on blood pressure: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2012 May;95(5):1079-88.

Kaikkonen KS, et al. **Family history** and the risk of sudden cardiac death as a manifestation of an acute coronary event. Circulation. 2006 Oct 3;114(14):1462-7. Epub 2006 Sep 25.

Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. Circulation. 2005 Jun 7;111(22):2906-12. Epub 2005 May 31. (InfoPOEMs: There is no evidence from randomized trials that percutaneous coronary intervention (PCI) improves important clinical outcomes better than careful medical management for patients with chronic stable coronary artery disease (CAD). Although this is the largest study to date, it's still limited by a relatively small number of outcomes of interest. (LOE = 1a))

Kerr E, Lucatorto MA, Holleman R, et al. **Monitoring performance for blood pressure** management among patients with **diabetes** mellitus. Arch Intern Med 2012.

Kessler CS, Joudeh Y. Evaluation and treatment of **severe asymptomatic hypertension**. Am Fam Physician. 2010 Feb 15;81(4):470-6.

Khachaturian et al. Antihypertensive Medication Use and Incident **Alzheimer** Disease: The Cache County Study. Arch Neurol. 2006 Mar 13; [Epub ahead of print]

Khan NA, et al. Canadian Hypertension Education Program. The **2006 Canadian Hypertension Education Program** recommendations for the management of hypertension: Part II - Therapy. Can J Cardiol. 2006 May 15;22(7):583-93.

Kim JW, et al. How well do clinic-based **blood pressure measurements** agree with the mercury standard? J Gen Intern Med. 2005 Jul;20(7):647-9. (InfoPOEMs: In this study, usual blood pressure readings in an office were frequently higher a standardized measurement, leading to incorrect labeling of blood pressure control in 1 of 5 patients. Several conclusions can be drawn from this study, which replicates the findings in other studies: First, retrain yourself to take an accurate blood pressure reading (see: http://www.theberries.ns.ca/SPRING2005a/taking_BP_technique.html). Second, train your office nurses how to do it correctly. Third, retrain them often, since other research has shown high recidivism. Fourth, check any patients with high blood pressure readings yourself, using good technique. (LOE = 1b))

Kokkinos P, Myers J, Kokkinos JP, et al. **Exercise Capacity and Mortality** in Black and White Men. Circulation. 2008 Jan 22; [Epub ahead of print] Exercise capacity is a strong predictor of all-cause mortality in blacks and whites. The relationship was inverse and graded, with a similar impact on mortality outcomes for both blacks and whites.

Korniyenko A, Alviar CL, Cordova JP, Messerli FH. **Visceral angioedema** due to angiotensin-converting enzyme inhibitor therapy. Cleve Clin J Med. 2011 May;78(5):297-304.

Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; on behalf of the Guideline Development Group. **Management of hypertension**: summary of **NICE** guidance. BMJ. 2011 Aug 25;343:d4891.

Kronish IM, Woodward M, Sergie Z, et al. Meta-analysis: impact of drug class on **adherence to antihypertensives**. Circulation. 2011 Apr 19;123(15):1611-21.

Ku E, Park J, Vidhun J, Campese V. The **hazards of dual renin-angiotensin blockade** in chronic kidney disease. Arch Intern Med. 2009 Jun 8;169(11):1015-8.

Kurnik D, Vesterman-Landes J, Bialik M, et al. **Hyperkalemia and renal function during monotherapy and dual Renin-Angiotensin blockade** in the community setting. Clin Ther. 2011 Apr;33(4):456-64.

LactMed 2011. http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

Lakoski SG, Greenland P, Wong ND, et al. **Coronary Artery Calcium Scores** and Risk for Cardiovascular Events in Women Classified as "Low Risk" Based on Framingham Risk Score: The Multi-Ethnic Study of Atherosclerosis (MESA).Arch Intern Med. 2007 Dec 10;167(22):2437-42. The presence of CAC in women considered to be at low risk based on FRS was predictive of future CHD and CVD events. Advanced CAC identified a subset of low-risk women at higher risk based on current risk stratification strategies.

Lennestal R, Olausson PO, Kallen B. **Maternal use of antihypertensive drugs in early pregnancy** and delivery outcome, notably the presence of heart defects in the infants. Eur J Clin Pharmacol 2 009;65:615-25.

Law M R, Morris J K, Wald N J et al. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665, doi: 10.1136/bmj.b1665 (Published 19 May 2009) With the exception of the extra protective effect of β blockers given shortly after a myocardial infarction and the minor additional effect of calcium channel blockers in preventing stroke, all the classes of blood pressure lowering drugs have a similar effect in reducing CHD events and stroke for a given reduction in blood pressure so excluding material pleiotropic effects.

Leaf A, et al.; Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by **fish oil n-3** fatty acid intake. Circulation. 2005 Nov 1;112(18):2762-8.

Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on **medication adherence** and persistence, blood pressure, and low-density lipoprotein cholesterol. *JAMA* 2006; DOI:10.1001/jama.296.21.joc60162.

Lee M, Saver JL, Chang B, Chang K-H, Hao Q, Ovbiagele B. Presence of baseline **prehypertension and risk of incident stroke**: a meta-analysis. Neurology 2011;77:1330 –1337.

Leenen FH, et al. Clinical Events in High-Risk Hypertensive Patients Randomly Assigned to **Calcium Channel Blocker Versus Angiotensin-Converting Enzyme Inhibitor** in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Hypertension. 2006 Jul 24; [Epub ahead of print]

Levine RJ, Hauth JC, Curet LB, et al. Trial of **calcium to prevent preeclampsia**. N Engl J Med 1997;337:69-76.

Lewis JE, Boyle E, Magharious L, Myers MG. Evaluation of a **community-based automated blood pressure measuring device**. CMAJ. 2002 Apr 30;166(9):1145-8.

Li DK, Yang C, Andrade S, et al. Maternal exposure to **angiotensin converting enzyme inhibitors** in the **first trimester and risk of malformations** in offspring: A retrospective cohort study. BMJ 2011; DOI: 10.1136/bmj.d5931.

Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005 Oct 29-Nov 4;366(9496):1545-53. (InfoPOEMs: If these authors have identified all the relevant research, it appears that in comparison with placebo, beta-blockers do not reduce cardiovascular morbidity or mortality but decrease the risk of strokes. However, in comparison with other antihypertensive medications, beta-blockers are associated with a significantly higher risk of stroke. Most of the included studies used atenolol and the data on other beta-blockers are inconclusive. Before throwing the baby out with the bathwater, remember that some patients with hypertension will need beta-blockers to treat their comorbid coronary artery disease, congestive heart failure, and so forth. (LOE = 1a-))

Lip GY, Felmeden DC, Dwivedi G. **Antiplatelet agents and anticoagulants** for hypertension. Cochrane Database Syst Rev. 2011 Dec 7;12:CD003186. Antiplatelet therapy with ASA for primary prevention in patients with elevated blood pressure provides a benefit, reduction in myocardial infarction, which is negated by a harm of similar magnitude, increase in major haemorrhage.The benefit of antiplatelet therapy for secondary prevention in patients with elevated blood pressure is many times greater than the harm.Benefit has not been demonstrated for warfarin therapy alone or in combination with aspirin in patients with elevated blood pressure.

Lopez-Garcia E, et al. **Coffee** consumption and coronary heart disease in men and women: a prospective cohort study. Circulation. 2006 May 2;113(17):2045-53. Epub 2006 Apr 24. (InfoPOEMs: There is no evidence that coffee consumption increases the likelihood that someone will develop heart disease. (LOE = 2b))

Lovibond K, Jowett S, Barton P, et al. **Cost-effectiveness of options for the diagnosis** of high blood pressure in primary care: a modelling study. Lancet 2011; DOI:10.1016/S0140-6736(11)61184-7.

Magee LA, Helewa M, Moutquin JM, von Dadelszen P, Hypertension Guideline Committee, Society of Obstetricians and Gynaecologists of Canada. Diagnosis and classification. In: Diagnosis, evaluation, and manager **hypertensive disorders of pregnancy**. J Obstet Gynaecol Can 2008 Mar;30(3 Suppl 1):S9-15. http://www.sogc.org/guidelines/documents/gui206CPG0803_001.pdf

TOP

Maitland ML, Bakris GL, Black HR et al. Initial assessment, surveillance, and management of blood pressure in patients receiving **vascular endothelial growth factor signaling pathway inhibitors**. J Natl Cancer Inst 2010;102:596-604.
Makani H, Messerli FH, Romero J, et al. Meta-Analysis of Randomized Trials of **Angioedema** as an Adverse Event of Renin-Angiotensin System Inhibitors. Am J Cardiol. 2012 Apr 20.
Mancia G, De Backer G, Dominiczak A, et al. Management of Arterial Hypertension of the ESH; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (**ESH**) and of the European Society of Cardiology (ESC). J Hypertens. **2007** Jun;25(6):1105-87. Erratum: J Hypertens. 2007 Aug;25(8):1749.
Mancia G, De Backer G, Dominiczak A, et al. **2007** Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (**ESC**). Eur Heart J 2007 Jun;28(12):1462-536.
Mancia Giuseppe, Parati Gianfranco, Revera Miriam, et al. **Statins**, antihypertensive treatment, and blood pressure control in clinic and over 24 hours: evidence from PHYLLIS randomised double blind trial. BMJ 2010
Mancia G, Agabiti-Rosei E, Ambrosioni E, et al. **Hypertension and migraine** comorbidity: Prevalence and risk of **cerebrovascular** events. Evidence from a large, multicenter, cross-sectional survey in Italy (MIRACLES study). J Hypertens 2011; 29:309-318.
Mancia G. Antihypertensives in **octogenarians**. BMJ. 2012 Jan 4;344:d7293.
Martin U, Coleman JJ. Monitoring **renal function** in hypertension. BMJ. 2006 Oct 28;333(7574):896-9.
Marin JM, Agusti A, Villar I, et al. Association between treated and untreated **obstructive sleep apnea and risk of hypertension**. JAMA. 2012;307(20):2169-2176.
Mazzaglia G et al. **Adherence** to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009 Oct 20; 120:1598.
McAlister, Finlay A., Zhang, Jianguo, Tonelli, Marcello, et al. The safety of **combining angiotensin-converting-enzyme inhibitors with angiotensin-receptor blockers** in elderly patients: a population-based longitudinal analysis. CMAJ 2011 0: cmaj.101333.
McAlister FA, Wilkins K, Joffres M, et al. Changes in the rage of awareness, treatment and control of hypertension in **Canada over the past two decades.** CMAJ 2011; DOI:10.1503/cmaJ.101767.
McAlister FA; for the Renin Angiotension System Modulator Meta-Analysis Investigators. **Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers** are beneficial in **normotensive atherosclerotic** patients: a collaborative meta-analysis of randomized trials. Eur Heart J. 2011 Oct 31.
McAlister FA; for the Renin Angiotension System Modulator Meta-Analysis Investigators. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in **normotensive atherosclerotic** patients: a collaborative meta-analysis of randomized trials. Eur Heart J. 2011 Oct 31.
McCall DO, McGartland CP, McKinley MC, et al. **Dietary intake of fruits and vegetables** improves microvascular function in hypertensive subjects in a dose-dependent manner. Circulation. 2009;119:2153–2160.
McDonald MA, Simpson SH, Ezekowitz JA, et al. Angiotensin receptor blockers and risk of **myocardial infarction**: systematic review. BMJ. 2005Oct 15;331(7521):873. Epub 2005 Sep 23. CONCLUSIONS: Treatment with angiotensin receptor blockers was not associated with a significantly increased risk of myocardial infarction. The 95% confidence intervals do, however, not exclude an increase of up to 16% in the risk of myocardial infarction or a reduction in risk of up to 25%. Until further information specifically dealing with this issue is available from large prospective trials, our findings may alleviate recent concerns over the safety of this class of medications.
McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of **ethnic differences** in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ. 2006 May 20;332(7551):1177-81. Epub 2006 May 5.
McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment & **dementia** in patients without apparent prior cerebrovascular disease. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD004034. There was no convincing evidence from the trials identified that blood pressure lowering prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease. There were significant problems identified with analysing the data, however, due to the number of patients lost to follow-up and the number of placebo patients given active treatment. This introduced bias. More robust results may be obtained by analysing one year data to reduce differential drop-out or by conducting a meta-analysis using individual patient data.
McManus RJ, Glasziou P, Hayen A, Mant J, Padfield P, Potter J, Bray EP, Mant D. **Blood pressure self monitoring**: questions and answers from a national conference. BMJ. 2008 Dec 22;337:a2732. doi: 10.1136/bmj.a2732.
McManus RJ, Mant J, Bray EP, et al. Telemonitoring and **self-management in the control of hypertension (TASMINH2):** A randomised controlled trial. Lancet 2010; DOI:10.1016/S0140-6736(10)60964-6.
Medical Letter. **Aliskiren (Tekturna)** for Hypertension. April 9,2007.
Messerli FH, et al. Dogma disputed: can aggressively **lowering diastolic blood pressure** in hypertensive patients with coronary artery disease be **dangerous**? Ann Intern Med. 2006 Jun 20;144(12):884-93. (InfoPOEMs: Lower is not always better. Despite a push toward lower blood pressure in many populations, bad outcomes (mortality, myocardial infarction, and stroke) are increased in patients with coronary artery disease (CAD) if their blood pressure consistently remains lower than 70 mmHg diastolic. (LOE = 1b))
Messerli FH, Williams B, Ritz E. **Essential hypertension**. Lancet. 2007 Aug 18;370(9587):591-603.
Meyers RS, Siu A. Pharmacotherapy Review of Chronic **Pediatric Hypertension**. Clin Ther. 2011 Oct 7.
Minutolo R, Agarwal R, Borrelli S, et al. Prognostic role of **ambulatory blood pressure measurement** in patients with **nondialysis chronic kidney disease.** *Arch Intern Med*. 2011;171(12):1090-1098.
Mitchell AA. Fetal risk from **ACE inhibitors in the first trimester**. BMJ 2011; DOI:10.1136/bmj.d5931.
Moolchan ET, Robinson ML, Ernst M, et al. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics 2005;115:407-14. (InfoPOEMs: Approximately 1 in 5 adolescents (20%) given weekly therapy sessions and a nicotine patch will not be smoking 6 months after their quit date. (LOE = 1b-))
Moncada LV. Management of falls in older persons: a prescription for prevention. Am Fam Physician. 2011 Dec 1;84(11):1267-76.
Montani D, Bergot E, Gunther S, et al. **Pulmonary arterial hypertension** in patients treated by **dasatinib**. Circulation. 2012;125:2128–2137.
Morrow DA, de Lemos JA, Blazing MA, et al.; A to Z Investigators. Prognostic value of serial **B-type natriuretic peptide** testing during follow-up of patients with unstable coronary artery disease. JAMA. 2005 Dec 14;294(22):2866-71. (InfoPOEMs: Serial determination of B-type natriuretic peptide (BNP) during follow-up of patients after an acute coronary syndrome (ACS) helps predict the risk of subsequent death or congestive heart failure (CHF). It remains uncertain whether having this information will lead to a change in clinical management that improves patient-oriented outcomes or simply increases costs without any added benefit. (LOE = 1b))
Moser M, Setaro JF. Clinical practice. **Resistant** or difficult-to-control **hypertension**. N Engl J Med. 2006 Jul 27;355(4):385-92.
Mozaffarian D, Rimm EB. **Fish intake**, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006 Oct 18;296(15):1885-99.
Mozaffarian D, et al. **Trans fatty acids** and cardiovascular disease. N Engl J Med. 2006 Apr 13;354(15):1601-13.
Mueller C, Laule-Kilian K, Frana B, Rodriguez D, Scholer A, Schindler C, Perruchoud AP. Use of **B-type natriuretic peptide** in the management of acute dyspnea in patients with pulmonary disease. Am Heart J. 2006 Feb;151(2):471-7. (InfoPOEMs: In patients with pre-existing pulmonary disease, B-type natriuretic peptide (BNP) testing in the emergency department is effective at distinguishing an exacerbation due to heart failure (HF) from that caused by pulmonary disease. As a result, hospitalizations are fewer, probably because of initiation of more appropriate therapy in the emergency department. Also, the duration of the hospital stay is shorter and the cost is less. (LOE = 1b))
Mukamal KJ, Chiuve SE, Rimm EB. **Alcohol consumption** and risk for coronary heart disease in men with healthy lifestyles. Arch Intern Med. 2006 Oct 23;166(19):2145-50.
Murabito JM, Pencina MJ, Nam BH, et al. **Sibling cardiovascular disease** as a risk factor for cardiovascular disease in middle-aged adults. JAMA. 2005 Dec 28;294(24):3117-23.
Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for **hypertension in the elderly**. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD000028.
Myers Martin G, Godwin Marshall, Dawes Martin, et al. **Conventional versus automated measurement of blood pressure** in primary care patients with systolic hypertension: randomised parallel design controlled trial. BMJ 342:doi:10.1136/bmj.d286 (Published 7 Feb 2011).
Nahas R. **Complementary and alternative** medicine approaches to blood pressure reduction: An evidence-based review. Can Fam Physician. 2008 Nov;54(11):1529-33. Evidence from systematic reviews supports the blood pressure–lowering effects of coenzyme Q10, polyphenol-rich dark chocolate, Qigong, slow breathing, and transcendental meditation. Vitamin D deficiency is associated with hypertension and cardiovascular risk; supplementation lowered blood pressure in 2 trials. Acupuncture reduced blood pressure in 3 trials; in 1 of these it was no better than an invasive placebo. Melatonin was effective in 2 small trials, but caution is warranted in patients taking pharmacotherapy.
Naghavi M, Falk E, Hecht HS, et al. From vulnerable plaque to vulnerable patient: Part III. Introducing a new paradigm for the prevention of heart attack; identification and treatment of the asymptomatic vulnerable patient. Screening for Heart Attack Prevention and Education (SHAPE) task force report. Executive summary. *Am J Cardiol* 2006; DOI: 10.1016/j.amjcard.2006.03.002. Available at http://www.ajconline.org.
National High Blood Pressure Education Program Working Group on High Blood Pressure in **Children and Adolescents**. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004 Aug;114(2 Suppl 4th Report):555-76.
Nazer B, Humphreys BD, Moslehi J. Effects of novel **angiogenesis inhibitors** for the treatment of cancer on the cardiovascular system: focus on hypertension. Circulation. 2011 Oct 11;124(15):1687-91.
NICE: Hypertensive disorders during pregnancy Aug/10 http://guidance.nice.org.uk/CG/Wave15/10 (Visintin C, Mugglestone MA, Almerie MQ, et al. Guideline Development Group. Management of hypertensive

TOP

disorders during pregnancy: summary of NICE guidance. BMJ. 2010 Aug 25;341:c2207. doi: 10.1136/bmj.c2207).
NICE: National Institute for Health and Clinical Excellence. **Hypertension Guidelines**. Aug 2011. http://www.nice.org.uk/nicemedia/live/13561/56015/56015.pdf
Niiranen TJ, et al. A comparison of **home measurement** and **ambulatory monitoring** of blood pressure in the adjustment of antihypertensive treatment. Am J Hypertens. 2006 May;19(5):468-74.
Ogedegbe GO, Boutin-Foster C, Wells MT, et al. A randomized controlled trial of **positive affect intervention** and medication adherence in hypertensive African-Americans. *Arch Intern Med*. doi:10.1001/archinternmed.2011.1307.
Ohkubo T, Kikuya M, Metoki H, et al. Prognosis of "masked" hypertension & "white-coat" hypertension detected by 24-h **ambulatory blood pressure monitoring** 10-year follow-up from the Ohasama study. J Am Coll Cardiol.2005 Aug 2;46(3):508-15. (InfoPOEMs: Using 24-hour ambulatory blood pressure monitoring as the standard, some patients will have white-coat hypertension (that is, higher blood pressures in the office than at home) and some will also have masked hypertension as a result of lower blood pressure measurements in the office. White-coat hypertension does not confer added risk, but masked hypertension underestimates a patient's risk. Evidence is accumulating that blood pressure should be measured at home, either with a 24-hour monitor or via self-monitoring (J Am Coll Cardiol 2005;46:743-51), before labeling someone as hypertensive and treating them accordingly. (LOE = 2b))
Okin PM, et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of **new-onset atrial fibrillation** in patients with hypertension. (**LIFE** trial)JAMA. 2006 Sep 13;296(10):1242-8.
Okin PM, et al.; LIFE Study Investigators. **Electrocardiographic strain** pattern and prediction of new-onset congestive heart failure in hypertensive patients: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. Circulation. 2006 Jan 3;113(1):67-73. Epub 2005 Dec 19.
Okin PM, et al. Impact of Diabetes Mellitus on Regression of Electrocardiographic Left Ventricular Hypertrophy and the Prediction of Outcome During Antihypertensive Therapy. The Losartan Intervention For Endpoint (LIFE) eduction in Hypertension Study. Circulation. 2006 Mar 13; [Epub ahead of print]
Østergaard Pedersen J, Heitmann B L, Schnohr P, and Grønbæk M. The combined influence of leisure-time **physical activity and weekly alcohol** intake on fatal ischaemic heart disease and all-cause mortality. Eur Heart J 2008; DOI:10.1093/eurheartj/ehm574.
Osranek M, Bursi F, Bailey KR, et al. **Left atrial volume** predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. Eur Heart J. 2005 Dec;26(23):2556-61. Epub 2005 Sep 1.
Owan TE, et al. Trends in prevalence and outcome of **heart failure** with **preserved ejection fraction**. N Engl J Med. 2006 Jul 20;355(3):251-9.
Ovbiagele B, Diener H-C, Yusuf S, et al; **PROFESS** Investigators. Level of **systolic blood pressure** within the normal range and risk of recurrent **stroke**. JAMA. 2011;306(19):2137-2144.
Oveisgharan S, Hachinski V. **Hypertension**, executive dysfunction, and progression to **dementia**: the Canadian study of health and aging. Arch Neurol 2010; 67:187-192.
Pacak K. Preoperative management of the **pheochromocytoma** patient. J Clin Endocrinol Metab 2007;92:4069-4079.
Panagiotakos DB, et al. The Relation Between Pulse Pressure & Cardiovascular Mortality in 12 763 Middle-aged Men From Various Parts of the World: A 25-Year Follow-up of the Seven Countries Study. Arch Intern Med. 2005 Oct 10;165(18):2142-7. CONCLUSIONS: Pulse pressure followed by diastolic and systolic blood pressures were the best predictors for CVD mortality among other blood pressures, as well as age, physical activity, total serum cholesterol level, anthropometric indexes, and smoking habits. No significant differences were observed among the different populations studied.
Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the **ADVANCE** trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy. (InfoPOEMs: Perindopril (Aceon) plus indapamide (Lozol) is better than placebo in decreasing clinically relevant events in patients with type 2 diabetes who are at high risk of cardiovascular complications. Whether the combination is better than other medications -- like aspirin -- isn't addressed by this study. (LOE = 1b))
Pavy B, et al. Safety of **Exercise Training** for Cardiac Patients: Results of the French Registry of Complications During Cardiac Rehabilitation. Arch Intern Med. 2006 Nov 27;166(21):2329-2334.
Peila R, et al. Reducing the risk of **dementia**: efficacy of long-term treatment of hypertension. Stroke. 2006 May;37(5):1165-70. Epub 2006 Apr 6.
Peralta CA, Norris KC, Li S, et al. Blood Pressure Components **and End-stage Renal Disease** in Persons With Chronic Kidney Disease: The Kidney Early Evaluation Program (**KEEP**). Arch Intern Med. 2012 Jan 9;172(1):41-47.
Percutaneous Coronary Intervention: ACC/AHA/SCAI 2005 Guideline Update for (Update of the 2001 PCI Guidelines) (J Am Coll Cardiol, January 3, 2006 issue; Vol/Page Numbers pending) http://www.acc.org/clinical/guidelines/percutaneous/update/index.pdf
Perez M, Musini V. Pharmacological interventions for **hypertensive emergencies**. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003653. There is no RCT evidence demonstrating that anti-hypertensive drugs reduce mortality or morbidity in patients with hypertensive emergencies. Furthermore, there is insufficient RCT evidence to determine which drug or drug class is most effective in reducing mortality and morbidity. There were some minor differences in the degree of blood pressure lowering when one class of antihypertensive drug is compared to another. However, the clinical significance is unknown.
Perez MI, Musini VM, Wright JM. Effect of early treatment with **anti-hypertensive drugs on short and long-term mortality in patients with an acute cardiovascular event.** Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006743. Nitrates reduce mortality (4-8 deaths prevented per 1000) at 2 days when administered within 24 hours of symptom onset of an acute myocardial infarction. No mortality benefit was seen when treatment continued beyond 48 hours. Mortality benefit of immediate treatment with ACE inhibitors post MI at 2 days did not reach statistical significance but the effect was significant at 10 days (2-4 deaths prevented per 1000). There is good evidence for lack of a mortality benefit with immediate or short-term treatment with beta-blockers and calcium channel blockers for acute myocardial infarction.
Peripheral Arterial Disease: ACC/AHA Guidelines for the Management of Patients With (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic); A Collaborative Report From the AAVS/SVS, SCAI, SIR, SVMB, and the ACC/AHA Task Force on Practice Guidelines http://www.acc.org/clinical/guidelines/pad/summary.pdf (Abramson BL, et al.; **Canadian Cardiovascular Society**. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease - executive summary. Can J Cardiol. 2005 Oct;21(12):997-1006.)
Perk J, De Backer G, Gohlke H, et al. **European guidelines (ESC) on cardiovascular disease** in clinical practice (version 2012). Eur Heart J2012; DOI:10.1093/eurheartj/ehs092.
Pharmacists Letter. **New Blood Pressure Goal for Coronary Artery Disesease**. Aug 2007.
Pickering TG, Shimbo D, Haas D. **Ambulatory blood-pressure monitoring**. N Engl J Med. 2006 Jun 1;354(22):2368-74.
Pickering TG, Houston-Miller N, Ogedegbe G, et al. Call to action on use and reimbursement for **home blood pressure monitoring**. Hypertension 2008; DOI: 10.1161/hypertensionaha.107.189010.
Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with **heart failure** in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). Circulation. 2011;124:1811–1818.
PILL Collaborative Group (2011) An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill (‘‘**Polypill’’**) in People with Raised Cardiovascular Risk. PLoS ONE 6(5): e19857. doi:10.1371/journal.pone.0019857.
Pimenta E, Gaddam KK, Oparil S, et al. Effects of **Dietary Sodium Reduction** on Blood Pressure in Subjects With Resistant Hypertension. Results From a Randomized Trial. Hypertension. 2009 Jul 20. [Epub ahead of print]
Pimenta E and Calhoun DA. **Resistant hypertension**: Incidence, prevalence and prognosis. Circulation 2012; DOI:10.1161/_CIRCULATIONAHA.112.097345.
PK, Barzilay J, Cushman WC; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2005 Jun 27;165(12):1401-9.
Powers BJ, Olsen MK, Smith VA, et al. **Measuring blood pressure** for decision making and quality reporting: where and how many measures? Ann Intern Med. 2011;154:781-8.
P**rospective Studies Collaboration**, Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370(9602):1829-1839. This study reinforces what we already know: Higher cholesterol levels and blood pressure are each associated with an increased risk of vascular mortality. Be careful with these results; this kind of study doesn't tell us that lowering cholesterol levels and blood pressure will prevent deaths. For that, we'd need an intervention trial. (LOE = 1a)
Psaty BM, Weiss NS, Furberg CD. Recent trials in hypertension: compelling science or **commercial speech**? JAMA. 2006 Apr 12;295(14):1704-6.
Rastas S, et al. Association Between Blood Pressure and Survival over 9 Years in a General Population **Aged 85 elderly and Older**. J Am Geriatr Soc. 2006 Jun;54(6):912-8.
Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after **maternal placental syndromes** (CHAMPS): population-based retrospective cohort study. Lancet. 2005 Nov 19;366(9499):1797-803.
Raheem IA, Saaid R, Omar SZ, et al. **Oral nifedipine versus intravenous labetalol** for acute blood pressure control in **hypertensive emergencies of pregnancy**: a randomised trial. BJOG. 2012 Jan;119(1):78-85.
Rahman M, et al. ALLHAT Collaborative Research Group. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline **glomerular filtration rate**. Ann Intern Med. 2006 Feb 7;144(3):172-80.
Reboldi G, Gentile G, Angeli F, et al. Effects of **intensive blood pressure reduction on myocardial infarction and stroke in diabetes**: a meta-analysis in 73 913 patients. J Hypertens 2011; 29:1253-1269.
Redwine KM AA, Poffenbarger T, Portman RJ, Samuels J. Development of hypertension among **adolescents with pre-hypertension**. J Pediatr 2011.
Ried K, Sullivan T, Fakler P, Frank OR, Stocks NP. Does **chocolate** reduce blood pressure? A meta-analysis. BMC Med 2010;8:39.
Riley M. **High Blood Pressure in Children and Adolescents**. Am Fam Physician. 2012 Apr 1;85(7):693-700.
Ritter J M. Therapeutics: **Angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension**. BMJ 2011;342:doi:10.1136/bmj.d1673 (Published 7 April 2011)

TOP

Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop **Post-Stroke** Antihypertensives Collaborative Study (**COSSACS**): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol. 2010 Aug;9(8):767-75.
Robitaille C, Dai S, Waters C, et al. **Diagnosed hypertension in Canada**: incidence, prevalence and associated mortality. CMAJ. 2011 Nov 21.
Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. **Heart disease and stroke statistics**—2011 update: a report from the American Heart Association. Circulation. 2011;123:e18 – e209.
Roger V, Go A, Lloyd-Jones DM, et al. **Heart disease and stroke statistics—2012 update**. A report from the American Heart Association. Circulation 2012; DOI: 10.1161/CIR.0b013e31823ac046.
Romero-Ortuno R, Cogan L, et al. Continuous noninvasive **orthostatic blood pressure** measurements and their relationship with orthostatic intolerance, falls, and frailty in **older** people. J Am Geriatr Soc. 2011 Apr;59(4):655-65.
Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: A scientific statement from the **American Heart Association Council for High Blood Pressure** Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007; 2007; 115:2761-2788.
Rossi GP, Seccia TM, Maniero C, Pessina AC. **Drug-related hypertension** and resistance to antihypertensive treatment: a call for action. J Hypertens. 2011 Oct 13.
Rothenbacher D, Koenig W, Brenner H. Life Time **Physical Activity** Patterns and Risk of Coronary Heart Disease. Heart. 2006 Jul 19; [Epub ahead of print]
Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of **visit-to-visit variability**, maximum **systolic blood pressure**, and episodic hypertension. Lancet 2010; 375: 895-905.
Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of **variability, instability, and episodic**. Lancet 2010; 375:938-948.
Rothwell PM, Howard SC, Dolan E, et al. on behalf of the ASCOT-BPLA and MRC Trial Investigators. Effects of **beta blockers and calcium-channel blockers** on within-**individual variability** in blood pressure and risk of stroke. Lancet Neurol. 2010 Mar 11.
Ruggenenti P, Perna A, Loriga G, et al.; **REIN-2** Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease: multicentre, randomised controlled trial. Lancet. 2005 Mar 12;365(9463):939-46. (Interpretation: In pts with non-diabetic proteinuric nephropathies receiving background ACE-inhibitor therapy, no additional benefit from further blood-pressure reduction by felodipine could be shown.)
Sacks, Frank M., Campos, Hannia. **Dietary Therapy** in Hypertension. N Engl J Med 2010 362: 2102-2112.
Sacco Ralph L.. Achieving **Ideal Cardiovascular and Brain Health**: Opportunity Amid Crisis: Presidential Address at the American Heart Association (**AHA**) 2010 Scientific Sessions. Circulation 123: 2653-2657.
Salt Info: www.saltinstitute.org;
China Salt Substitute Study Collaborative Group. Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial. J Hypertens. 2007 Oct;25(10):2011-8.
Cohen HW, Hailpern SM, Fang J, Alderman MH. Sodium intake and mortality in the NHANES II follow-up study. Am J Med. 2006 Mar;119(3):275.e7-14.
Parikh NI, Gona P, Larson MG, et al. Plasma renin and risk of cardiovascular disease and mortality: the Framingham Heart Study. Eur Heart J. 2007 Nov;28(21):2644-52. Epub 2007 Sep 25.
Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT Study. The INTERSALT Co-operative Research Group.J Hypertens Suppl. 1988 Dec;6(4):S584-6.
Samuels, Martin A., Pomerantz, Benjamin J., Sadow, Peter M. Case 14-2010 -- A 54-Year-Old Woman with Dizziness and Falls. (**Pheochromocytoma**) N Engl J Med 2010 362: 1815-1823.
Sandset EC, Bath PMW, Boysen G et al. The angiotensin-receptor blocker **candesartan for treatment of acute stroke (SCAST):** A randomised, placebo-controlled, double-blind trial. *Lancet* 2011;DOI:10.1016/S0140-6736(11)60104-9.
Schmieder RE, Philipp T, Guerediaga J, et al. Long-term antihypertensive efficacy and safety of the oral direct renin inhibitor **aliskiren**: a 12-month randomized, double-blind comparator trial with hydrochlorothiazide. Circulation. 2009;119:417– 445.
Schuijf JD, et al. Diagnostic accuracy of **64-slice multislice computed tomography** in the noninvasive evaluation of significant coronary artery disease. Am J Cardiol. 2006 Jul 15;98(2):145-8. Epub 2006 May 19.
Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. **Renal sympathetic-nerve ablation** for uncontrolled hypertension. N Engl J Med. 2009 Aug 27;361(9):932-4.
Schulman SP, et al. **L-arginine** therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. JAMA. 2006 Jan 4;295(1):58-64.
Sciarretta Sebastiano; Palano Francesca; Tocci Giuliano; et al. Antihypertensive Treatment and Development of Heart Failure in Hypertension: A Bayesian Network Meta-analysis of Studies in Patients With Hypertension and High Cardiovascular Risk. Arch Intern Med. 2010;0(2010):archinternmed.2010.427.
Seely EW, Ecker J. Clinical practice. **Chronic hypertension in pregnancy**. N Engl J Med. 2011 Aug 4;365(5):439-46.
Serumaga B, Ross-Degnan D, Avery AJ, et al. Effect of **pay for performance** on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. An interrupted time-series study. BMJ 2011.
Sharma SK et al. **CPAP** for the metabolic syndrome in patients with obstructive sleep apnea. N Engl J Med. 2011 Dec 15;365(24):2277-86.
Shimbo D, Kuruvilla S, Haas D, Pickering TG, Schwartz JE, Gerin W. Preventing misdiagnosis of ambulatory hypertension: **algorithm using office and home blood pressures**. J Hypertens. 2009 Sep;27(9):1775-83.
Shlipak MG, et al. **Cystatin C** and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med. 2006 Aug 15;145(4):237-46.
Shook RP, Lee DC, Sui X, et al. **Cardiorespiratory fitness** reduces the risk of incident hypertension associated with a parental history of hypertension. Hypertension. 2012 Jun;59(6):1220-4.
Singer W, et al. **Pyridostigmine** treatment trial in **neurogenic orthostatic hypotension**. Arch Neurol. 2006 Apr;63(4):513-8. Epub 2006 Feb 13.
Sipahi I, Debanne SM, Rowland DT et al. **Angiotensin-receptor blockade** and risk of **cancer**: Meta-analysis of randomised controlled trials. Lancet Oncol 2010; DOI:10.1016/S1470-2045(10)70106-6.
Sipahi I, Swaminathan A, Natesan V, et al. Effect of antihypertensive therapy on incident **stroke in cohorts with prehypertensive** blood pressure levels: A meta-analysis of randomized controlled trials. Stroke 2011
Slagman Maartje C J, Waanders Femke, Hemmelder Marc H, et al. for the **HONEST** (HOlland NEphrology STudy) Group. Moderate dietary **sodium restriction added to angiotensin converting enzyme inhibition** compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. BMJ 2011;343:doi:10.1136/bmj.d4366 (26 July 2011)
Smith PK, et al. Selection of **surgical or percutaneous coronary intervention** provides differential longevity benefit. Ann Thorac Surg. 2006 Oct;82(4):1420-8; discussion 1428-9.
Smith S, Benjamin E, Bonow R, et al. **AHA/ACCF secondary prevention and risk reduction therapy** for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011; DOI:10.1161/CIR.0b013e318235eb4d.
Smith SC Jr, et al. **AHA/ACC** guidelines for **secondary prevention** for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. **2006** May 16;113(19):2363-72. http://circ.ahajournals.org/cgi/reprint/113/19/2363
Society of Obstetricians and Gynaecologists of Canada. **Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy**. J Obstet Gynaecol Can 2008;30:S1-S48.
Solomon SD, Hee Shin S, Shah A, et al. Effect of the direct rennin inhibitor aliskiren on left ventricular remodelling following myocardial infarction *with systolic dysfunction.(**ASPIRE**) Eur Heart J 2011; 32: 1227–34.*
Solomon SD, Appelbaum E, Manning WJ, et al.; for the Aliskiren in Left Ventricular Hypertrophy (**ALLAY**) Trial Investigators. Effect of the Direct Renin Inhibitor Aliskiren, the Angiotensin Receptor Blocker Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy. Circulation. 2009 Jan 19.
Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of **aldosterone** in the metabolic syndrome and **resistant hypertension**. Ann Intern Med. 2009 Jun 2;150(11):776-83.
Spahr A, et al. **Periodontal infections** & coronary heart disease: role of periodontal bacteria & total pathogen burden in the Coronary Event & Periodontal Disease (CORODONT) study. Arch Intern Med. 2006 Mar 13;166(5):554-9.
Staessen JA, et al. Risks of untreated and treated isolated systolic hypertension in the **elderly**: meta-analysis of outcome trials. Lancet. 2000 Mar 11;355(9207):865-72. Erratum in: Lancet 2001 Mar3;357(9257):724.
Staessen JA, Li Y, Richart T. Oral renin inhibitors. Lancet. 2006 Oct 21;368(9545):1449-56.
Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs **medical therapy alone for stable coronary artery disease**. Arch Intern Med 2012; 172:312-319.
Stone PH, Gratsiansky et al. **ERICA** Investigators. Antianginal efficacy of **ranolazine** when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol. 2006 Aug 1;48(3):566-75. Epub 2006 Jun 15. (InfoPOEMs: Ranolazine (Ranexa), added to maximum dosing of amlodipine, decreases angina episodes and nitroglycerin doses slightly more than placebo does; patients taking ranolazine experienced approximately 1 fewer episode, on average, every 2 weeks. These results occurred in patients with frequent symptoms -- at least 4 anginal episodes per week -- and its effect is likely to be less pronounced in patients with less frequent symptoms. (LOE = 1b)
Strandberg TE, et al. **Multifactorial intervention** to prevent recurrent cardiovascular events in patients **75 years or older**: the Drugs and Evidence-Based Medicine in the Elderly (**DEBATE**) study: a randomized, contr
Heart J. 2006 Sep;152(3):585-92. (InfoPOEMs: First, the good news: Researchers were able, without unusual effort, to apply evidence-based guidelines to older elderly patients with cardiovascular disease (CV

TOP

goal blood pressure and cholesterol levels in the majority. Now, the bad news: These interventions did not decrease the likelihood of the patients experiencing a cardiovascular problem over the next 3.4 years. The treated patients did not live any longer over this period, and the treatment did not delay deaths. (LOE = 1b))

Strazzullo Pasquale, D'Elia Lanfranco, et al. **Salt** intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567, doi: 10.1136/bmj.b4567 (24 November 2009).

Strippoli GF, Craig MC, Schena FP, Craig JC. Role of blood pressure targets and specific antihypertensive agents used to prevent **diabetic nephropathy** and delay its progression. J Am Soc Nephrol. 2006 Apr;17 Suppl 2:S153-5. On the basis of available RCT evidence, ACEi are the only agents with proven renal benefit in patients who have diabetes with no nephropathy and the only agents with proven survival benefit in patients who have diabetes with nephropathy.

Sudano I, Flammer AJ, Périat D, et al. **Acetaminophen increases blood pressure** in patients with coronary artery disease. Circulation. 2010 Nov 2;122(18):1789-96.

Sundquist K, Li X. Differences in maternal (**mother**) and paternal transmission of coronary heart disease. Am J Prev Med. 2006 Jun;30(6):480-6. Epub 2006 Apr 25.

Sundström J, Neovius M, Tynelius P, Rasmussen F. Association of **blood pressure ^{DBP} in late adolescence** with subsequent mortality: cohort study of Swedish male conscripts. BMJ. 2011 Feb 22;342:d643. doi: 10.1136/bmj.d643.

Sutaria S, Katbamna R, Underwood M. Effectiveness of interventions for the **treatment of acute and prevention of recurrent gout**--a systematic review. Rheumatology (Oxford). 2006 Nov;45(11):1422-31. Epub 2006 Apr 21.

Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-Selective Benefits of Medications in Treatment of **Acute Aortic Dissection** (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol. 2011 Sep 23.

Symplicity HTN-2 Investigators. **Renal sympathetic denervation** in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010; DOI:10.1016/S0140-6736(10)62039-9.

Taylor RS, Ashton KE, Moxham T, et al. **Reduced dietary salt** for the prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD009217. DOI: 10.1002/14651858.CD009217. Despite collating more event data than previous systematic reviews of randomised controlled trials (665 deaths in some 6,250 participants), there is still insufficient power to exclude clinically important effects of reduced dietary salt on mortality or cardiovascular morbidity in normotensive or hypertensive populations. Further RCT evidence is needed to confirm whether restriction of sodium is harmful for people with heart failure. Our estimates of benefits from dietary salt restriction are consistent with the predicted small effects on clinical events attributable to the small blood pressure reduction achieved.

The "**Triple Whammy**". Pharmaicst's Letter Dec/06 (Impaired renal function while involving an ACE &/or ARB, an NSAID &/or a diuretic)

Thijs L, Richart T, de Leeuw PW, et al. Morbidity and mortality on **combination** versus monotherapy: a posthoc analysis of the Systolic Hypertension in Europe trial. J Hypertens. 2010 Jan 5. [Epub ahead of print]

Thomas L. Managing **hypertensive emergencies** in the ED. Can Fam Physician. 2011 Oct;57(10):1137-97.

Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons **without hypertension**: a meta-analysis. JAMA 2011; 305:913-922.

Thornley-Brown D, et al. Differing effects of antihypertensive drugs on the incidence of diabetes mellitus among patients with hypertensive kidney disease. (**AASK**) Arch Intern Med. 2006 Apr 10;166(7):797-805.

Tissot AC, et al. Effect of **immunisation against angiotensin II** with CYT006-AngQb on ambulatory blood pressure: a double-blind, randomised, placebo-controlled phase IIa study. Lancet. 2008 Mar 8;371(9615):821-7.

Tobe SW, Stone JA, Brouwers M, et al. **Harmonization of guidelines** for the prevention and treatment of cardiovascular disease: the **C-CHANGE Initiative**. CMAJ. 2011 Sep 12.

Tocci G, Paneni F, Palano F, et al. **Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers** and **Diabetes**: A Meta-Analysis of Placebo-Controlled Clinical Trials. Am J Hypertens. 2011 May;24(5):582-90.

Tonelli M, et al. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial (**CARE**). BMJ. 2006 May 19; [Epub ahead of print] The presence or absence of proteinuria on dipstick urinalysis may be used to refine estimates of risk based on kidney function alone.

Trans CL, Ehrmann BJ, Messer KL, et al. Recent trends in healthcare utilization among **children and adolescents with hypertension** in the United States. Hypertension 2012.

Treatment Guidelines: Drugs for Treatment of **Heart Failure** from The Medical Letter April **2003** & Jan **2006.**

Turnbull F, Neal B, Algert C, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005 Jun 27;165(12):1410-9.

Turner ST, Schwartz GL, Chapman AB, et al. **Plasma renin activity** predicts blood pressure responses to beta-blocker and thiazide diuretics as monotherapy and add-on for hypertension. Am J Hypertens 2010.

UK Prospective Diabetes Study Group. Efficacy of **atenolol and captopril** in reducing risk of macrovascular and microvascular complications in type 2 diabetes: **UKPDS 39**. BMJ 1998;317:713-9.

Upadhyay Ashish, Earley Amy, Haynes Shana M., et al. Systematic Review: Blood Pressure Target in **Chronic Kidney Disease and Proteinuria** as an Effect Modifier. *Ann Intern Med* April 19, 2011 154:541-548.

U.S. Preventive Services Task Force (USPSTF). **Screening for high blood pressure**. U.S. Preventive Services Task Force reaffirmation recommendation statement. Rockville MD: Agency for Healthcare Research and Quality (AHRQ); 2007. 10 p. The USPSTF recommends screening for high blood pressure in adults aged 18 and older.

Václavík Jan, Sedlák Richard, Plachy Martin, et al. Addition of **Spironolactone** in Patients With **Resistant Arterial Hypertension (ASPIRANT)**: A Randomized, Double-Blind, Placebo-Controlled Trial. Hypertension 57: 1069-1075;

van Bemmel T, et al. In a population-based prospective study, no association between high blood pressure and mortality **after older age 85 years**. J Hypertens. 2006 Feb;24(2):287-92.

Van den Born BJ, Hulsman CA, Hoekstra JB, et al. Value of routine funduscopy in patients with hypertension: systematic review. BMJ 2005; 331:73-6. (InfoPOEMs: It is uncommon to see retinal changes by funduscopic examination in patients with hypertension, although when retinal changes occur they are almost always associated with hypertension. Though no studies have been performed to check the reliability of an actual funduscopic examination, there was only moderate agreement between 2 clinicians evaluating photographs of the retina of hypertensive patients for early changes. (LOE = 4))Whelton

van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors **reduce mortality in hypertension**: A meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. Eur Heart J2012.

Van Vliet BN, Campbell NR; Canadian Hypertension Education Program. Efforts to **reduce sodium intake** in Canada: why, what, and when? Can J Cardiol. 2011 Jul-Aug;27(4):437-45.

Verberk WJ, Kroon AA, Kessels AG, de Leeuw PW. **Home blood pressure measurement**: a systematic review. J Am Coll Cardiol. 2005 Sep 6;46(5):743-51. (InfoPOEMs: Blood pressure measurements taken at home with validated automatic monitors average lower than readings obtained in the office. They are also better prognostic indicators of the detrimental effects of hypertension. Before consigning patients to a diagnosis and treatment of hypertension, or before changing drug therapy, try a few days of at-home monitoring; it might avoid overdiagnosis and overtreatment. (LOE = 1a))

Verdecchia P, Staessen JA, Angeli F, et al. Usual versus tight control of systolic blood pressure in nondiabetic patients with hypertension (**CARDIO-SIS**): an open-label randomised trial. *Lancet* 2009; 374: 525-33.

Verhamme K, Mosis et al. **Spironolactone** and risk of upper gastrointestinal events: population based case-control study. BMJ. 2006 Aug 12;333(7563):330. Epub 2006 Jul 13.

Viera Anthony J., Hinderliter Alan L., Evaluation and Management of the Patient with Difficult-to-Control or **Resistant Hypertension** Am Fam Physician. 2009;79(10):863-869.

Viera AJ, Neutze DM. Diagnosis of **secondary hypertension**: an age-based approach. Am Fam Physician. 2010 Dec 15;82(12):1471-8.

von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean **arterial pressure and fetal growth restriction in pregnancy** hypertension: a meta-analysis. Lancet 2000;355:87-92.

Wald DS, Bestwick JP, Wald NJ. **Child-parent screening for familial hypercholesterolaemia**: screening strategy based on a meta-analysis. BMJ. 2007 Sep 22;335(7620):599. Epub 2007 Sep 13. The proposed strategy of screening children and parents for familial hypercholesterolaemia could have considerable impact in preventing the medical consequences of this disorder in two generations simultaneously.

Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. **Combination therapy** versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009 Mar;122(3):290-300.

Wan Y, Heneghan C, Stevens R, McManus RJ, Ward A, Perera R, et al. Determining which **automatic digital blood pressure device** performs adequately: a systematic review. J Hum Hypertens. 2010 Jul;24(7):431-8.

Wang L, Sharifi BG, Pan T, et al. Bone marrow transplantation shows superior atheroprotective effects of gene therapy with **apolipoprotein A-1 Milano** compared with wild-type apolipoprotein A-1 in hyperlipidemic mice. J Am Coll Cardiol 2006; 48:1459-68.

Walsh JM, et al. **Quality improvement strategies** for hypertension management: a systematic review.Med Care. 2006 Jul;44(7):646-57.

Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic Syndrome vs **Framingham Risk Score** for Prediction of Coronary Heart Disease, Stroke, and Type 2 Diabetes Mellitus. Arch Intern Med. 2005 Dec 26;165(22):2644-50.

Ward, Alison M.; Takahashi, Osamu; Stevens, Richard; Heneghan, Carl. **Home measurement of blood pressure** and cardiovascular disease: systematic review and meta-analysis of prospective studies. Journal of Hypertension Jan 11,12.

Weber Cynthia A.; Ernst Michael E.; Sezate Genesis S.; et al. Pharmacist-Physician Comanagement of Hypertension and Reduction in 24-Hour Ambulatory Blood Pressures. *Arch Intern Med*. 2010;170(18):1634-1639.

Webb AJS, Fischer U, Mehta Z, et al. Effects of antihypertensive-drug class on **interindividual variation** in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 2010; 375:906-915.

Webb AJS, Fischer U, Rothwell PM. Effects of **beta-blocker selectivity** on **blood pressure variability and stroke**: a systematic review. Neurology 2011;77:731–737.

Webb AJ, Rothwell PM. Effect of **dose and combination of antihypertensives on interindividual blood pressure variability**: a systematic review. Stroke. 2011 Oct;42(10):2860-5.

Wen CP, Wai JPM, Tsai MK, et al. Minimum amount of **physical activity** for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011. (15min a day or 90 min a week of moderate intensity exercise)

White WB et al. **Average daily blood pressure**, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. Circulation. 2011 Nov 22;124(21):2312-9.

Wijeysundera HC, Nallamothu BK, Krumholz HM, Tu JV, Ko DT. Meta-analysis: Effects of **Percutaneous Coronary Intervention Versus Medical Therapy** on Angina Relief. Ann Intern Med. 2010 Mar 16;152(6):370-9.

Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, Gulanick M, Laing ST, Stewart KJ. **Resistance Exercise** in Individuals With and Without Cardiovascular Disease: 2007 Update. A Scien
From the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2007 Jul 16; [Epub ahead of print]

TOP

Wong ND, Lopez VA, L'italien G, Chen R, Kline SE, Franklin SS. **Inadequate Control of Hypertension** in US Adults With Cardiovascular Disease Comorbidities in 2003-2004. Arch Intern Med. 2007 Dec 10;167(22):2431-6.
Winkelmayer WC, Stampfer MJ, Willett WC, Curhan GC. Habitual **caffeine** intake and the risk of hypertension in women. JAMA. 2005 Nov 9;294(18):2330-5. (InfoPOEMs: Habitual caffeine consumption does not appear to increase the risk of hypertension in women. In particular, coffee and tea are not associated with increased risk. The development of hypertension is, however, significantly associated with the intake of cola drinks, including both sugared and diet versions. (LOE = 2b))
Wright JT, JA, et al, for the **ALLHAT** Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. JAMA 2005;293:1595- 608 & ACP Journal Club . (InfoPOEMs: Thiazide-type diuretics are the best initial agents for the treatment of hypertension for most patients, including both blacks and nonblacks. (LOE = 1b-))
Wright JM, Musini VM. **First-line drugs** for hypertension. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD001841. First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.
Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with **sorafenib** in patients with cancer: a systematic review and meta-analysis. Lancet Oncol. 2008 Feb;9(2):117-23. Epub 2008 Jan 24.
Yancy William S Jr; Westman Eric C.; McDuffie Jennifer R.; et al. A Randomized Trial of a **Low-Carbohydrate** Diet vs **Orlistat Plus a Low-Fat** Diet for Weight Loss. Arch Intern Med. 2010;170(2):136-145.
Yang Q, Liu T, Kuklina EV, et al. **Sodium and potassium intake and mortality** among US adults: prospective data from the Third National Health and Examination Survey. Arch Intern Med. 2011;171(13):1183-1191.
Yoon C, Yang HS, Jeon I, et al. Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and **cancer risk**: a meta-analysis of observational studies. CMAJ. 2011 Oct 4;183(14):E1073-84.
Yusuf S, Islam S, Chow CK, et al. Use of **secondary prevention drugs** for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011; DOI:10.1016/ S0140-6736(11)61215-4.
Zhao P, Xu P, Wan C, Wang Z. **Evening versus morning dosing regimen** drug therapy for hypertension. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD004184. DOI: 10.1002/14651858.CD004184.pub2. No RCT reported on clinically relevant outcome measures - all cause mortality, cardiovascular morbidity and morbidity. There were no significant differences in overall adverse events and withdrawals due to adverse events among the evening versus morning dosing regimens. In terms of BP lowering efficacy, for 24-hour SBP and DBP, the data suggests that better blood pressure control was achieved with bedtime dosing than morning administration of antihypertensive medication, the clinical significance of which is not known.
Zatonski W, Willett W. Changes in **dietary fat** and declining coronary heart disease in Poland: population based study. BMJ. July 23, 2005;331:187-88.
Zillich AJ, Sutherland JM, Kumbera PA, Carter BL. Hypertension outcomes through blood pressure monitoring and evaluation by pharmacists (HOME study). J Gen Intern Med. 2005 Dec;20(12):1091-6.

Web Sties:

American College of Physicians: ACP Special Report: Living with Hypertension www.doctorsforadults.com/images/healthpdfs/hypertension_report.pdf
American Heart Association: High Blood Pressure www.americanheart.org/presenter.jhtml?identifier=2114
National Heart, Lung, and Blood Institute: Your Guide to Lowering Blood Pressure www.nhlbi.nih.gov/health/public/heart/hbp/hbp_low/hbp_low.pdf
National Kidney Foundation: High Blood Pressure (Hypertension) www.kidney.org/atoz/atozTopic.cfm?topic=1

TOP

Antihypertensives: Landmark & Recent Trials – Summary

[1] Wright JT Jr, Bakris G, Greene T, Agodoa LY, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the **AASK trial**.; African American Study of Kidney Disease and Hypertension Study Group. JAMA 2002;288:2421-31.

Appel LJ, Wright JT Jr, Greene T, Kusek JW, et al. for the African American Study of Kidney Disease and Hypertension Collaborative Research Group. (AASK trial) Long-term Effects of Renin-Angiotensin System-Blocking Therapy and a Low Blood Pressure Goal on Progression of Hypertensive Chronic Kidney Disease in African Americans. Arch Intern Med. 2008 Apr 28;168(8):832-839. Despite the benefits of renin-angiotensin system-blocking therapy on CKD progression, most African Americans with hypertensive CKD who are treated with currently recommended BP therapy continue to progress during the long term.

Weinberg Joy M.; Appel Lawrence J.; Bakris George; et al.; for the African American Study of Hypertension and Kidney Disease Collaborative Research Group. Risk of Hyperkalemia in Nondiabetic Patients With Chronic Kidney Disease Receiving Antihypertensive Therapy. Arch Intern Med. 2009;169(17):1587-1594.

Appel LJ, Wright JT Jr, Greene T, et al. Intensive bloodpressure control in hypertensive chronic kidney disease. (**AASK**) N Engl J Med 2010;363:918-29.

[2] ALLHAT Officers and Coordinators for the **ALLHAT** Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel block vs. diuretic. JAMA. 2002;288:2981–2997.

ALLHAT Working Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT-LLT**). JAMA. 2002;288:2998- 3007.

Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up (8.9yr) of participants with heart failure in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Circulation. 2011;124:1811–1818.

Alderman MH, Piller LB, Ford CE, et al. for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Clinical Significance of Incident Hypokalemia and Hyperkalemia in Treated Hypertensive Patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Hypertension. 2012 May;59(5):926-933.

[3] Dahlof B, Sever PS, Poulter NR, et al. ASCOT investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (**ASCOT-BPLA**): a multicentre randomised controlled trial. Lancet. 2005 Sep 10;366(9489):895-906. Web: http://www.ascotstudy.co.uk (see also **Q&A Ascot-BPLA** http://www.rxfiles.ca/acrobat/HTN-Q&A-ASCOT.pdf)

[4] Poulter NR, Wedel H, Dahlof B, Sever PS, et al.; for the ASCOT investigators. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the **ASCOT-BPLA**. Lancet. 2005 Sep 10;366(9489):907-13.

Ostergren J, Poulter NR, Sever PS, et al. for the ASCOT investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. J Hypertens. 2008 Nov;26(11):2103-2111. In the large diabetic subgroup in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial, the benefits of amlodipine-based treatment, compared with atenolol-based treatment, on the incidence of total cardiovascular events and procedures was significant (14% reduction) and similar to that observed in the total trial population (16% reduction).

Sever PS, Poulter NR, et al. on behalf of the ASCOT Investigators. Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin: observations from the Anglo-Scandinavian Cardiac Outcomes Trial. Eur Heart J. 2011 Jul 28.

[5] Mogensen CE, Neldam S, Tikkanen I, Oren S, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (**CALM**) study. BMJ 2000;321:1440-4.

[6] Nakao N, Yoshimura A, Morita H et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease (**COOPERATE**): a randomised controlled trial. Lancet 2003;361:117-24.

Kunz R, Wolbers M, Glass T, Mann JF. The COOPERATE trial: a letter of concern. Lancet. 2008 May 10;371(9624):1575-6.

The Editors Of The Lancet. **Retraction**-Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet. 2009 Oct 10;374(9697):1226.

[7] Hansson L, Lindholm LH, Niskanen L, Lanke J et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (**CAPPP**) randomised trial. Lancet 1999;353:611-6.

[8] Pitt B, Poole-Wilson PA, Segal R, Martinez FA et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial-the Losartan Heart Failure Survival Study **ELITE II**. Lancet 2000;355:1582-7.

[9] Tatti P, Pahor M, Byington RP, Di Mauro P et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (**FACET**) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.

[10] Yusuf S, Sleight P, Pogue J, Bosch J, et al. The Heart Outcomes Prevention Evaluation (**HOPE**) Study. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-153.

[11] Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular & microvascular outcomes in people with diabetes mellitus: results of the HOPE study and **MICRO-HOPE** substudy. Lancet 2000;355:253-9.

[12] Bosch J, Yusuf S, Pogue J, Sleight P et al . Use of ramipril in preventing stroke: double blind randomised trial.; **HOPE** Investigators. Heart outcomes prevention evaluation. BMJ 2002;324:699-702.

[13] Sleight P, Yusuf S, Pogue J, Tsuyuki R, Diaz R, Probstfield J. Blood-pressure reduction and cardiovascular risk in HOPE study. Lancet. 2001;358:2130-1.

[14] Svensson P, de Faire U, Sleight P, Yusuf S, Ostergren J. Hypertension 2001;38:E28-32 Comparative effects of ramipril on ambulatory and office blood pressures: a **HOPE** Substudy.

[15] Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment randomised trial. **HOT** Study Group. Lancet 1998;351:1755-62.

Jardine, Meg J., Ninomiya, Toshiharu, Perkovic, Vlado, et al. Aspirin Is Beneficial in Hypertensive Patients With **Chronic Kidney Disease**: A Post-Hoc Subgroup Analysis of a Randomized Controlled Trial (**HOT**). J Am Coll Cardiol 2010 56: 956-965.

[16] Lewis EJ, Hunsicker LG, Clarke WR, Berl T et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes (**IDNT**); Collaborative Study Group. N Engl J Med 2001 Sep 20;345(12):851-60.

[17] Brown MJ, Palmer CR, Castaigne A, de Leeuw PW et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (**INSIGHT**). Lancet 2000;356:366-72.

[18] Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes (**IRMA II**). N Engl J Med 2001;345:870-8.

[19] Dahlof B, Devereux RB, Kjeldsen SE, Julius S et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (**LIFE**): a randomised trial against atenolol. Lancet 2002;359:995-1003.

[20] Lindholm LH, Ibsen H, Dahlof B, Devereux RB et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (**LIFE**): a randomised trial against atenolol. Lancet 2002;359:1004-10. (Note: in patients with left ventricular hypertrophy)

[21] Kjeldsen SE, Dahlof B, Devereux RB, Julius S et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (**LIFE**) substudy. JAMA 2002;288:1491-8.

[22] Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (**NORDIL**) study. Lancet 2000;356:359-65.

[23] Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the **OPTIMAAL** randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002;360:752-60.

[24] **PROGRESS** Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41.

Arima H, Anderson C, Omae T, et al; for the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Collaborative Group. Effects of Blood Pressure Lowering on Intracranial and Extracranial Bleeding in Patients on Antithrombotic Therapy: The PROGRESS Trial. Stroke. 2012 Jun;43(6):1675-1677.

[25] Pitt B, O'Neill B, Feldman R, et al. The QUinapril Ischemic Event Trial (**QUIET**): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. The QUIET Study Group. Am J Cardiol 2001;87:1058-63.

[26] Brenner BM, Cooper ME, de Zeeuw D, Keane et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy; **RENAAL** Study Investigators. N Engl J Med 2001;345:861-9.

[27] SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (**SHEP**). JAMA 1991 Jun 26;265(24):3255-64.

[28] Curb JD, Pressel SL, Cutler JA, Savage PJ et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension (**SHEP**). JAMA 1996;276:1886-92.

Kostis JB, Wilson AC, et al.; **SHEP** Collaborative Research Group. Long-term effect (14.3 yrs) of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. Am J Cardiol. 2005 Jan 1;95(1):29-35.

Kostis JB, Cabrera J, Cheng JQ, et al. Association between chlorthalidone treatment of systolic hypertension and long-term survival (SHEP). JAMA. 2011 Dec 21;306(23):2588-93. In the SHEP trial, treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up.

[29] Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB. The role of diastolic blood pressure when treating isolated systolic hypertension (**SHEP program**). Arch Intern Med 1999;159:2004-9.

[30] Hansson L, Lindholm LH, Ekbom T, Dahlof B et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study (**STOP Hypertension-2**). Lancet 1999;354:1751-6.

[31] Staessen JA, Fagard R, Thijs L, Celis H et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (**Syst-Eur**) Trial Investigators. Lancet 1997;350:757-64.

[32] Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators (**Syst-Eur**). N Engl J Med 1999;340:677-84.

Thijs L, Richart T, de Leeuw PW, et al. Morbidity and mortality on **combination** versus monotherapy: a posthoc analysis of the Systolic Hypertension in Europe trial. (**Syst-Eur**). J Hypertens. 2010 Jan 5. [Epub ahead of print]

[33] Forette F, Seux ML, Staessen JA, Thijs L et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (**Syst-Eur**) study. Arch Intern Med 2002;162:2046-52.

TOP

[34] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: **UKPDS 38**. BMJ 1998;317:703-13.

[35] UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: **UKPDS 39**. BMJ 1998;317:713-20.

[36] Cohn JN, Tognoni G . A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure (**Val-HeFT**); Valsartan Heart Failure Trial Investigators. N Engl J Med 2001;345:1667-75.

[37] Maggioni AP, Anand I, Gottlieb SO, et al. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. **Val-HeFT** Investigators (Valsartan Heart Failure Trial). J Am Coll Cardiol 2002;40:1414-21.
Anand IS, Bishu K, Rector TS, et al. Proteinuria, Chronic Kidney Disease, and the Effect of an Angiotensin Receptor Blocker in Addition to an Angiotensin-Converting Enzyme Inhibitor in Patients With Moderate to Severe Heart Failure. Circulation. 2009 Oct 5.

[38] Jamerson KA, Weber MA, Bakris GL, et al. Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension, the early termination of the **ACCOMPLISH** trial for efficacy. Session 407; ACC 57th Annual Scientific Session; March 29-April 1, 2008. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. (**ACCOMPLISH**)N Engl J Med. 2008 Dec 4;359(23):2417-2428.
The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.
Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized, controlled trial. Lancet 2010; DOI:10.1016/S0140-6736(09)62100-0.
Jamerson KA, Bakris GL, Weber MA. 24-hour ambulatory blood pressure in the ACCOMPLISH trial. N Engl J Med. 2010 Jul 1;363(1):98.
Weber MA, Bakris GL, Jamerson K, et al. Cardiovascular events during differing hypertension therapies in patients with **diabetes**. (**Accomplish**) J Am Coll Cardiol. 2010 June 29;56(1):77-85.
Jamerson KA, Devereux R, Bakris GL, et al. Efficacy and Duration of Benazepril Plus Amlodipine or Hydrochlorthiazide on **24-Hour Ambulatory** Systolic Blood Pressure Control. (Accomplish) Hypertension. 2010 Dec 28.

[39] **ACCORD** Study Group, Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001286.

[40] Patel A; **ADVANCE** Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40.
Heerspink HJ, Ninomiya T, Perkovic V, et al. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. Eur Heart J. 2010 Dec;31(23):2888-96.

[41] Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, et al.; the **HYVET** Study Group. Treatment of Hypertension in Patients 80 Years of Age or Older.N Engl J Med. 2008 Mar 31; [Epub ahead of print].
Allan, G. Michael, Mallery, Laurie, Ivers, Noah. Treating hypertension in the very elderly. Can Fam Physician 2010 56: 1141.
Beckett N, Peters R, Tuomilehto J, et al. for the HYVET Study Group. Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial. BMJ. 2011 Jan 4;344:d7541. doi: 10.1136/bmj.d7541.

[42] Schrader J, Lüders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener HC; MOSES Study Group. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005 Jun;36(6):1218-26. Epub 2005 May 5. (Yusuf S, Diener HC, Sacco RL, et al. the **PRoFESS** Study Group. Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events. N Engl J Med. 2008 Aug 27. [Epub ahead of print] (20,332 patients) Therapy with telmisartan initiated soon after an ischemic stroke and continued for 2.5 years did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes.)
Ovbiagele B, Diener H-C, Yusuf S, et al; **PROFESS** Investigators. Level of **systolic blood pressure** within the normal range and risk of recurrent **stroke**. JAMA. 2011;306(19):2137-2144.

[43] Yusuf S, Teo KK, Pogue J, et al for the **ONTARGET** investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008: 358:1547-1559. The angiotensin-converting enzyme inhibitor (ACEI) ramipril and the angiotensin receptor blocker (ARB) telmisartan are equally effective for secondary cardiovascular prevention. The combination of both drugs is no more effective and causes more adverse effects at greater cost. ACEIs should remain the drug of choice for secondary prevention in high risk cardiovascular patients unless the drug is not tolerated because of angioedema or cough, in which case ARBs provide an effective alternative. (LOE = 1b). Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, et al.; ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008 Aug 16;372(9638):547-53. In people at high vascular risk, telmisartan's effects on major renal outcomes are similar to ramipril. Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes. The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008 Aug 29.
Sleight P, Redon J, Verdecchia P, et al.; on behalf of the ONTARGET investigators. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. J Hypertens. 2009 Jun 5. [Epub ahead of print] In high-risk patients, the benefits from SBP lowering below 130 mmHg are driven mostly by a reduction of stroke; myocardial infarction is unaffected and cardiovascular mortality is unchanged or increased. Future trials should be designed to test the value of SBP lowering in high-risk patients with SBP in the range of 130-150 mmHg. { FDA July/09: After carefully weighing the evidence, a US Food and Drug Administration advisory panel voted unanimously against expanding the indication for the angiotensin receptor blocker (ARB) telmisartan (Micardis, Boehringer Ingelheim Pharmaceuticals) for the reduction of cardiovascular events in high-risk patients. The decision, however, does provide physicians with an alternative first-line treatment in patients 55 years or older intolerant to ACE inhibitors but who are at high risk for cardiovascular events. In these patients, the Cardiovascular and Renal Drugs Advisory Committee voted 5 to 2 in favor of approving telmisartan to reduce the risk of MI, stroke, death from cardiovascular causes, or hospitalization for congestive heart failure. Complicating the whole affair was the fact that Boehringer Ingelheim and the FDA failed to come to an agreement in 2001 regarding the statistical plan for the noninferiority end point to determine efficacy. The sponsor chose a margin of 13%, or a hazard ratio of 1.13, which the FDA considered too liberal. Instead, the agency wanted a more conservative margin of 8%, or a hazard ratio of 1.08. Dr Salim Yusuf (McMaster University, Hamilton, ON), the lead investigator of the ONTARGET study, defended the decision to adopt the liberal noninferiority margin, noting that while his approach to clinical trials is to conduct the largest study possible, the margin requested by the FDA would have doubled ONTARGET to more than 50 000 patients, something that just wasn't feasible}
Mann JF, Schmieder RE, Dyal L, et al.; TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) Investigators. Effect of telmisartan on renal outcomes: a randomized trial. Ann Intern Med. 2009 Jul 7;151(1):1-10, W1-2. Epub 2009 May 18.
Cowan BR, Young AA, Anderson C, et al.; ONTARGET Investigators. Left ventricular mass and volume with telmisartan, ramipril, or combination in patients with previous atherosclerotic events or with diabetes mellitus (from the ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET]). Am J Cardiol. 2009 Dec 1;104(11):1484-9. Epub 2009 Oct 14.
Anderson Craig, Teo Koon, Gao Peggy, et al. and for the ONTARGET and TRANSCEND Investigators, Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies, The Lancet Neurology, Volume 10, Issue 1, January 2011, Pages 43-53, ISSN 1474-4422, DOI: 10.1016/S1474-4422(10)70250-7.
Barzilay Joshua I.; Gao Peggy; O'Donnell Martin; et al. for the ONTARGET and TRANSCEND Investigators. Albuminuria and Decline in Cognitive Function: The ONTARGET/TRANSCEND Studies. Arch Intern Med. 2011;171(2):142-150.
Clase CM, Gao P, Tobe SW, et al. on behalf of the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in Angiotensin-Converting-Enzyme-Inhibitor Intolerant Subjects with Cardiovascular Disease). **Estimated Glomerular Filtration Rate and Albuminuria** as Predictors of Outcomes in Patients With High Cardiovascular Risk: A Cohort Study. Ann Intern Med. 2011 Mar 1;154(5):310-318.
Tobe SW, Clase CM, Gao P, et al; on behalf of the ONTARGET and TRANSCEND Investigators. **Cardiovascular and Renal Outcomes** With Telmisartan, Ramipril, or Both in People at High **Renal Risk**: Results From the ONTARGET and TRANSCEND Studies. Circulation. 2011 Mar 15;123(10):1098-1107.
Redon J, Sleight P, Mancia G, Gao O, Verdecchia P, Fagard R, Schumacher H, Weber M, Boehm M, Williams B, et al. Safety and efficacy of aggressive blood pressure lowering among patients with **diabetes**: subgroup analyses from the ONTARGET trial. J Hypertens. 2009;27(Suppl. 4):S16.
Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, Fagard R, Verdecchia P, Weber M, Böhm M, et al. Safety and efficacy of low blood pressure among patients with **diabetes**: sub-group analyses from the ONTARGET trial. J Hypertens. 2011;29(e-Suppl. A):e113.
Mancia G, Schumacher H, Redon J, et al. **Blood pressure targets** recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (**ONTARGET**). Circulation. 2011;124:1727–1736.

Additional trials:

ACTIVE I Investigators. Irbesartan in Patients with Atrial Fibrillation. N Engl J Med 2011; 364:928-938. (Not reduce CV events)
Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP; for the PROVE IT-TIMI 22 Trial Investigators. What Is the **Optimal Blood Pressure in Patients After Acute Coronary Syndromes**?: Relationship of Blood Pressure and Cardiovascular Events in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 Trial. Circulation. 2010 Nov 8.
Cooper-DeHoff Rhonda M.; Gong Yan; Handberg Eileen M.; et al. Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease. (**INVEST**) JAMA. 2010;304(1):61-68.
Tight control of systolic BP among patients with diabetes and CAD was not associated with improved cardiovascular outcomes compared with usual control.
Filippone EJ. Foy A, Newman E. Goal-directed antihypertensive therapy: **Lower may not always be better.** *Cleveland Clinic Journal of Medicine* 2011; 78(2):123-133; doi:10.3949/ccjm.78a.10101.
Haller H, Ito S, Izzo JL Jr, et al. **Olmesartan** for the delay or prevention of microalbuminuria in type 2 diabetes. (**ROADMAP**) N Engl J Med 2011;364:907-17. (n=4447 over 3.2yr. Improved microalbuminuria, but increased fatal CV events)
Hypertension Detection and Follow-up Program Cooperative Group (**HDFP**). Five-year findings of the Hypertension Detection and Follow-up Program, I: reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA. 1979;242(23):2562-2571.
JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008; 31:2115–2127. (n=4418 over 2yrs)
Multiple Risk Factor Intervention Trial Research Group (**MRFIT**) . Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. JAMA. 1982;248(12):1465-1477.
Sandset EC, Bath PMW, Boysen G et al. The angiotensin-receptor blocker **candesartan for treatment of acute stroke** (**SCAST**): A randomised, placebo-controlled, double-blind trial. Lancet 2011;DOI:10.1016/S0140-6736(11)60104-9.
Upadhyay Ashish, Earley Amy, Haynes Shana M., et al. Systematic Review: **Blood Pressure Target in Chronic Kidney Disease and Proteinuria** as an Effect Modifier. Ann Intern Med E-335published ahead of print March 14, 2011, doi:10.1059/0003-4819-154-8-201104190-00335
Veterans Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967;202(11):1028-1034.

TOP

Extra, extra, extra….read if you want to….Other information….

Risk Stratification Schemes Use to Predict Warfarin-Associated Hemorrhage

Risk Scheme (publication year)	Risk Factors	Risk Category	Points	Major Bleeding Rates in Validation Cohorts	Comment
ATRIA Risk Score [24] (2011) Adults with nonvalvular, nontransient atrial fibrillation on warfarin & enrolled in Kaiser Permanente of Northern California	Anemia (3 points) Severe renal disease=eGFR<30mL/min (3 points) Age ≥ 75 yrs (2 points) Any prior hemorrhage diagnosis (1 point) Diagnosed Hypertension (1 point)	Low Intermediate High	0-3 4 5-10	0.72%/yr 2.71%/yr 5.99%/yr	Clinical risk factors based on computerized databases Anemia not defined Simple to use Data on ethanol abuse, drug abuse, aspirin, OTCs, & genetic factors not available
RIETE risk scheme [25] (2008) Developed in patients with acute venous thromboembolism	Recent major bleeding (<15 days before thrombotic event) (1.5 points) Creatinine>106 mmol/L (1.5 points) Anemia (1.5 points) Malignancy (1 point) Clinically overt pulmonary embolism (1 point) Age > 75 yrs (1 point)	Low Intermediate High	0 1-4 >4	0.1% at 3 months 2.8% at 3 months 6.2% at 3 months	
$HEMORR_2HAGES$ [26] (2006) Developed in hospitalized Medicare patients with atrial fibrillation discharged on warfarin	Hepatic or renal disease (1 point) Ethanol abuse (1 point) Malignancy (1 point) Older age > 75 yrs (1 point) Reduced platelet count or function (1 point) Rebleeding risk (2 points) Hypertension (1 point) Anemia (1 point) Genetic factors (1 point) Excessive fall risk or neuropsychiatric disease (1 point) Stroke (1 point)	Low Intermediate High	0-1 2-3 ≥4	1.9-2.5%/yr 5.3-8.4%/yr 10.4-12.3%/yr	
Shireman et al. [48] (2006) Developed in hospitalized Medicare patients with atrial fibrillation discharged on warfarin	Age ≥ 70 yrs Female Remote bleeding event Alcohol or drug abuse Diabetes mellitus Anemia (Hct<30% during index hospitalization) Antiplatelet drugs (aspirin, clopidogrel, or ticlopidine at discharge) Risk score = 0.49 (age ≥ 70) + 0.32 (female) + 0.58 (remote bleed) + 0.62 (recent bleed) + 0.71 (alcohol/drug abuse) + 0.25 (diabetes) + 0.86 (anemia) + 0.32 (antiplatelet use)	Low Intermediate High	≤ 1.07 1.07-2.18 ≥2.19	0.9% within 90 days 2.0% within 90 days 5.4% within 90 days	Complicated risk score formula
Kearon et al.[49] (2003) Developed in patients with acute venous thromboembolism enrolled in clinical trial. Risk score categories developed & validated by Gage et al.	Age ≥ 65 yrs (1 point) Prior stroke (1 point) Prior peptic ulcer disease (1 point) Prior GI bleeding (1 point) Creatinine > 141 mmol/L (1 point) Anemia or thrombocytopenia (1 point) Liver disease (1 point) Diabetes mellitus (1 point) Antiplatelet therapy (1 point)	Low Intermediate High	0-1 2 3 ≥4	2.5%/yr 6.5%/yr 9.3%/yr 15.3%/yr	
Kuijer et al.[50] (1999) Developed in patients with acute thromboembolism	Age>60 yrs (1.6 points) Female (1.3 points) Malignancy (2.2 points)	Low Intermediate High	0 1-2.9 ≥3	0.6% at 3 months 2% at 3 months 7% at 3 months	
Outpatient Bleeding Index[51] (1998) Developed in patients newly starting warfarin after hospital discharge	Age≥65 yrs (1 point) Prior stroke (1 point) Prior GI bleeding (1 point) Recent MI, diabetes mellitus, hematocrit < 30%, creatinine > 141 mmol/L (1 point if any of the above)	Low Intermediate High	0 1-2 3-4	3%/yr 8%/yr 30%/yr	

eGFR=estimated glomerular filtration rate, RIETE=Registro Informatizado de la Enfermedad TromboEmbolica

Bleeding risk ↑ as anti-thrombotic intensity ↑. Antithrombotics listed from lowest to highest bleeding risk: (note: based on extrapolated data from different studies & different populations)
1) ASA 75-325mg daily or clopidogrel 75mg daily alone, 2) ASA 75-325mg daily + clopidogrel, 3) apixaban 5mg BID (but ↑ bleed in ACS pts) or dabigatran 110mg BID, 4) dabigatran 150mg BID, rivaroxaban 20mg daily or warfarin.

TOP

ROCKET-AF, ARISTOTLE & RELY: Comparison Tables of Baseline Characteristics (Adapted with permission from M.Louie, PharmD)

Baseline	Age median	Male	HTN	DM	Prior TIA/S	Prior MI	$Time_{spent}$ INR 2-3	$CHADS_2$ (mean)	Trial design	n	Follow up
Dabigatran 110mg bid	71.5	63.3%	78.9%	23.2%	20%	16.5%	64% (mean)	2.1	RCT Open blinded assessment	18k	2 yr
Dabigatran 150mg bid								2.2			
Rivaroxaban 20mg od	73	60%	90.5%	39.5%	55%	17.5%	55% (mean)	3.4	RCT DB DD	14k	1.94 yr
Apixaban 5mg bid	70	65%	87.5%	25%	19.4%	14.2%	62% (mean)	2.1	RCT DB DD	18k	1.8 yr

ROCKET-AF, ARISTOTLE & RELY: Comparison Table of Results

Results	Stroke or systemic embolism	Ischemic stroke	Hemor-rhagic stroke	All cause death	MI/ACS	Major bleed	Intra-cranial bleed	GI bleed	Discontinue rate
Dabigatran 110 vs warf	NSS 3.0vs3.3%	NSS 2.6vs2.4%	0.2vs0.7% RR 0.31	NSS 7.4vs8.1%	NSS 1.4vs1.0%	5.4vs6.6% RR0.81	0.4vs1.4% RR 0.31	NSS 2.2vs2.0%	20.7vs16.6%
Dabigatran 150 vs warf	2.2vs3.3% RR 0.67	1.8vs2.4% RR 0.77	0.2vs0.7% RR 0.26	NSS 7.2vs8.1%	1.5vs1.0% RR 1.40?	NSS 6.2vs6.6%	0.6vs1.4% RR 0.41	3.0vs2.0% RR 1.5	21.2vs16.6%
Rivaroxaban vs warf	3.8vs4.3% RR 0.88_{pp}	NSS 2.1vs2.3%	0.4vs0.7% RR 0.58	NSS 2.9vs3.5&	NSS 1.4vs1.8%	NSS 5.6vs5.4%	0.8vs1.2%RR 0.66	NSS 3.2vs2.2%	23.9vs22.4%
Apixaban vs warf	2.3vs2.9% RR 0.80	NSS 1.8vs1.9%	0.4vs0.9% RR 0.51	6.6vs7.4 RR 0.90	NSS 1.0vs1.1%	3.6vs5.1% RR 0.70	0.6vs1.3% RR 0.42	NSS 1.2vs1.3%	25.3vs27.5%

ROCKET-AF, ARISTOTLE & RELY: Comparision Table of NNT & NNH

NNT NNH	Stroke or systemic embolism	Ischemic stroke	Hemor-rhagic stroke	All cause death	MI/ACS	Major bleed	Dyspesia	GI bleed	Antidote
Dabigatran 110 vs warf			192			77	17 11.8vs5.8%		?
Dabigatran 150 vs warf	88	132	182		239-284?		18 11.3vs5.8%	100	?
Rivaroxaban vs warf	135_{pp}		333						Octaplex
Apixaban vs warf	167		238	132		67			Octaplex?

Concluding comments:

Dabigatran (RELY)

RELY has been criticized for it's open label design. Tolerance is an issue with the higher discontinuation rates than warfarin driven by dyspepsia. The tartaric acid in the formulation is likely driving the increased dyspepsia rates. Although not statistically significant after re-analysis, the increasing trend for MIs is worrisome. The 150mg dosage has the best NNT for the stroke and systemtic embolism, hemorrhagic stroke and the only statistically significant NNT for ischemic stroke. The 110mg dosage may be appropriate for those at high risk for major bleeding.

Rivaroxaban (ROCKET-AF)

The trial design was superior to RELY in that it was double blinded with sham INR for both comparator and control groups. Their patient population was also sicker with $CHADS_2$ score mean of 3.4 compared to 2.1-2.2 from RELY. However, a criticism has been that the time within TTR (INR2-3) for the warfarin group was only 55%, which is lower than RELY and ROCKET-AF. This is understandable because sicker patients are more difficult to dose to TTR with warfarin. Also rivaroxaban was shown to be non-inferior to warfarin for the intention to treat analysis and was only superior in the per protocol group. As far as efficacy for the primary endpoint, it could be considered second to last before dabigatran 110mg dosage.

Apixaban (ARISTOLE)

This drug reduced all cause mortality compared to warfarin, which is already a very efficacious drug. This endpoint trumps the other two trials. On the safety side there is 30% less major bleeding (a combination of less intracranial and a decreasing trend for GI bleeds). It has not yet been approved in Canada or the US for stroke prevention in AF patients.

Recommendations for the prevention of stroke in patients with atrial fibrillation

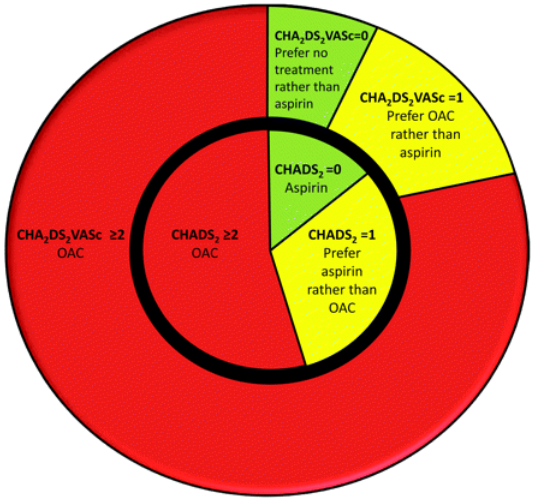


Figure. Recommendations for the prevention of stroke in patients with atrial fibrillation. The inner circle represents treatment recommendations based on the use of the $CHADS_2$ score, as in US guidelines. The outer circle represents recommendations based on the CHA_2DS_2–VASc model, as outlined in the European guidelines, which advise anticoagulant therapy in a larger proportion of patients with atrial fibrillation. Bleeding risk assessment is recommended for patients at intermediate stroke risk (yellow-shaded area), with particular caution and regular patient review for those on warfarin therapy when the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score is ≥3. For patients at very high risk of bleeding (eg, those with malignant hypertension or prior episodes of major bleeding), conservative monitoring without treatment should be considered. OAC indicates oral anticoagulation.

Reference:

Fuster V, Chinitz JS. Net clinical benefit of warfarin: extending the reach of antithrombotic therapy for atrial fibrillation. Circulation. 2012 May 15;125(19):2285-7.

TOP

Management of Recent-Onset AF & Flutter in the Emergency Department (ED):[52]

- Rate-control vs. Rhythm Control Treatment (Tx)
- Rate Control Tx = ventricular rate control, oral anticoagulation, no attempt to return the patient to sinus rhythm in the ED, & delayed cardioversion after 4 weeks, if indicated
- Rhythm Control Tx = cardiovert patients to sinus rhythm in ED (pharmacologically or electrically), then discharge home in sinus rhythm

TOP

ORAL ANTIPLATELET & ANTITHROMBOTIC AGENTS

1. Micromedex 2011; Drugs in Pregnancy and Lactation, 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Baltimore, MD: 2011.; Hansten & Horn-Drug Interactions 2008.
2. Antithrombotic Trialists' Collaboration. (ATT) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86.
   Collins R et al. for the Antithrombotic Trialists' (**ATT**) Collaboration. **Aspirin in the primary and secondary prevention** of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009 May 30; 373:1849.
3. CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel vs aspirin in patients at risk of ischemic events (**CAPRIE**). Lancet 1996; 348:1329-39.
4. Bertrand ME et al. Double blind study of the safety of clopidogrel with and without loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting. (**CLASSICS**). Circulation 2000; 102: 624-29.
5. Yusuf S et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation (Clopidogrel in unstable angina to prevent recurrent events (**CURE**). N Engl J Med 2001; 345: 494-502.
6. Diener HC et al. European Stroke Prevention Study 2 (**ESPS2**). Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143: 1-13.
7. Hirsh J, Dalen J Guyatt G. The **sixth (2000) ACCP Guidelines** for antithrombotic therapy for prevention & treatment of thrombosis. **CHEST** 2001;119:1s-370s. The **Seventh ACCP** Evidence-Based Guidelines. **Chest 2004 September 2004**
   (**see also CHEST ACCP-AT9 Antithrombotic and Thrombolytic 9th Edition 2012**).
   Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American college of chest physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:160-98.
   Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American college of chest physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:299S-339S.
   Bell AD, Cartier R, Chan WS. Canadian Cardiovascular Society (**CCS**) Anti-Platelet Guideline 2010.
   Bell Alan D., Roussin André, Cartier Raymond, et al. The Use of **Antiplatelet Therapy in the Outpatient Setting**: Canadian Cardiovascular Society (**CCS**) Guidelines. Can J Cardiol. 2011 May-Jun;27 Suppl A:S1-59.
   Chassot PG, Marcucci C, Delabays A, Spahn DR. Perioperative antiplatelet therapy. Am Fam Physician. 2010 Dec 15;82(12):1484-9.
   Bartolucci AA, Tendera M, and Howard G. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. Am J Cardiol 2011; DOI:10.1016/j.amjcard.2011.02.325.
   Seshasai SRK, Wijesuriya S, Sivakumaran R, et al. Effect of **aspirin** on **vascular and nonvascular outcomes**: meta-analysis of randomized controlled trials [online Jan 9, 2012]. Archives Intern Med. doi:10.1001/archinternmed.2011.628.
   Lip GY, Felmeden DC, Dwivedi G. **Antiplatelet agents and anticoagulants** for **hypertension**. Cochrane Database Syst Rev. 2011 Dec7;12:CD003186. Antiplatelet therapy with ASA for primary prevention in patients with elevated blood pressure provides a benefit, reduction in myocardial infarction, which is negated by a harm of similar magnitude, increase in major haemorrhage.The benefit of antiplatelet therapy for secondary prevention in patients with elevated blood pressure is many times greater than the harm.Benefit has not been demonstrated for warfarin therapy alone or in combination with aspirin in patients with elevated blood pressure.
   Guyatt Gordon H., Akl EA., Crowther M. **Executive Summary**: Antithrombotic Therapy and Prevention of Thrombosis,**9th ed**: American College of Chest Physicians (**ACCP-AT9**). Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2)(Suppl):7S–47S.
   Lansberg MG, et al. Antithrombotic & thrombolytic therapy for **ischemic stroke**: antithrombotic therapy & prevention of thrombosis, 9th ed: American College of Chest Physicians (**ACCP-AT9**) evidence-based guidelines. Chest. 2012;141(2)(supp):e601S-e636S.
   You JJ, Singer DE, et al. Antithrombotic therapy for **atrial fibrillation**: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence(**ACCP-AT9**) -based clinical guidelines. Chest. 2012;141(2)(suppl):e531S-575S.
   Vandvik PO, Lincoff AM, Gore JM, et al. American College of Chest Physicians. **Primary and secondary prevention of cardiovascular disease**: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e637S-68S.
8. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989;2:1215-1220.
9. Hass WK, Easton JD, Adams HP, et al. A randomized trial comparing ticlopidine with aspirin for the prevention of stroke in high risk patients (**TASS**). N Engl J Med 1989;321:501-507.
10. Steering Committee of the Physicians Health Study Research Group. Final report on the aspirin component of the ongoing Physicians Health Study (**PHS**). N Eng J Med 1989;321:129-135.
11. Hansson L Zanchetti A, Carruthers SG, et al. Effects of intensive blood pressure lowering & low dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (**HOT**) randomized trial. Lancet 1998;351:1755-1762.
    Jardine, Meg J., Ninomiya, Toshiharu, Perkovic, Vlado, et al. Aspirin Is Beneficial in Hypertensive Patients With **Chronic Kidney Disease**: A Post-Hoc Subgroup Analysis of a Randomized Controlled Trial (HOT). J Am Coll Cardiol 2010 56: 956-965.
12. Progress Collaborative Group. Randomized trial of a perindopril based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. (**PROGRESS**) Lancet 2001;358:1033-1041.
    (Arima H, et al.; for the PROGRESS Collaborative Group. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens. 2006 Jun;24(6):1201-1208.)
13. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin converting enzyme inhibitor, ramipril on cardiovascular events in high risk patients (**HOPE**). N Engl J Med 2000;342:145-153.
14. The SALT Collaborators Group. Swedish Aspirin Low-dose Trial (**SALT**) of 75mg aspirin as secondary prophylaxis after cerebrovascular eschemic events. Lancet 1991;338:1345-9.
15. SPIRIT Study Group. A randomized trial of **anticoagulants versus aspirin** after cerebral ischemia presumed arterial origin. The Stroke Prevention in Reversible Ischemia Trial (**SPIRIT**) Study Group. Ann Neuro 1997;42:857-65.
16. Kovacs MJ, Rodger M, et al. Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism. Ann Intern Med. 2003 May 6;138(9):714-9.
17. Ridker PM, Goldhaber SZ, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism (**PREVENT**). N Engl J Med. 2003 Apr 10;348(15):1425-34.
18. Gorelick PB, Richardson D, Kelly M, Ruland S, Hung E, Harris Y, Kittner S, Leurgans S. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. (**AAASPS**) JAMA. 2003 Jun 11;289(22):2947-57.
19. Pearson TA, et al. **AHA Guidelines** for Primary Prevention of Cardiovascular Disease and Stroke: **2002** Update. Circulation. 2002 Jul 16;106(3):388-91. (Pharmacists Letter. Using Aspirin in Hypertensive patients. Oct 2007.)
    Pignone Michael, Alberts Mark J., Colwell John A., et al. **Aspirin for Primary Prevention of Cardiovascular Events in People With Diabetes**. A Position Statement of the American Diabetes Association (**ADA**), a Scientific Statement of the American Heart Association (**AHA**), and an Expert Consensus Document of the American College of Cardiology Foundation (ACCF). Circulation published May 27, 2010, doi:10.1161/CIR.0b013e3181e3b133 http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181e3b133v1
    Furie Karen L., Kasner Scott E., Adams Robert J., et al., and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the **Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack** (Secondary Prevention). A Guideline for Healthcare Professionals From the American Heart Association (**AHA**) /American Stroke Association (**ASA**). Stroke published October 21, 2010, doi:10.1161/STR.0b013e3181f7d043 http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181f7d043v1
    Goldstein Larry B., Bushnell Cheryl D., Adams Robert J., et al., and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quali Guidelines for the **Primary Prevention of Stroke**. A Guideline for Healthcare Professionals From the American Heart Association (**AHA**) /American Stroke Association (**ASA**). Stroke published December 2, 2010, doi:10.1161/STR.0b013e3181fcb238
    ADA- American Diabetes Association. Standards of Medical Care in Diabetes—**2011 Diabetes Care.** January 2011 34:S11-S61; doi:10.2337/dc11-S011. http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html
20. Hurlen M, Abdelnoor M, Smith P, Eriksen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. (**WARIS-II**) N Engl J Med. 2002 Sep 26;347(13):969-74.
21. Kearon C, et al. (**ELATE** Investigators). Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003 Aug 14;349(7):631-9.
22. Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003;349:1133-1138.
23. **U.S. Preventive Services** Task Force: **Aspirin** for the **Primary Prevention** of Cardiovascular Events: Recommendation and Rationale Ann Intern Med. 2002;136:157–160
24. Rachel S. Eidelman et al. An Update on Aspirin in the Primary Prevention of Cardiovascular Disease**.** Arch Intern Med. 2003;163:2006-2010.
25. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S. Effects of Aspirin Dose When Used Alone or in Combination With Clopidogrel in Patients With Acute Coronary Syndromes. Observations From the Clopidogrel in Unstable angina to prevent Recurrent Events (**CURE**) Study. Circulation. 2003 Sep 22 . (Budaj A, Yusuf S, Mehta SR, Fox KA, Tognoni G, Zhao F, Chrolavicius S, Hunt D, Keltai M, Franzosi MG; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation. 2002 Sep 24;106(13):1622-6.)
26. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ; **CREDO** Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002 Nov 20;288(19):2411-20.
27. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, Venco A, Ageno W. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med. 2002 Aug 20;137(4):251-4.
28. Possidente CJ, Howe JG, Cushman M. Evaluation of very low-dose subcutaneous vitamin K during postoperative warfarin therapy. Pharmacotherapy. 2001 Mar;21(3):295-300.
29. Crowther MA, Julian J, McCarty D, Douketis J, Kovacs M, Biagoni L, Schnurr T, McGinnis J, Gent M, Hirsh J, Ginsberg J. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. Lancet. 2000 Nov 4;356(9241):1551-3.
30. Nee R, Doppenschmidt D, Donovan DJ, Andrews TC. Intravenous versus subcutaneous vitamin K1 in reversing excessive oral anticoagulation. Am J Cardiol. 1999 Jan 15;83(2):286-8, A6-7.
31. Lubetsky A, Yonath H, Olchovsky D, Loebstein R, et al.. Comparison of Oral vs Intravenous Phytonadione (Vitamin K1) in Patients With Excessive Anticoagulation: A Prospective Randomized Controlled Study. Arch Intern Med. 2003 Nov 10;163(20):2469-73.
32. Weibert RT, Le DT, Kayser SR, Rapaport SI. Correction of excessive anticoagulation with low-dose oral vitamin K1. Ann Intern Med. 1997 Jun 15;126(12):959-62.
33 Wilson SE, et al. Low-dose oral vitamin K therapy for the management of asymptomatic patients with elevated international normalized ratios: a brief review. CMAJ. 2004 Mar 2;170(5):821-4. (Dezee KJ, et al.Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. Arch Intern Med. 2006 Feb 27;166(4):391-7.)
34. Eidelman RS, Hebert PR, Weisman SM, Hennekens CH. An update on aspirin in the primary prevention of cardiovascular disease. Arch Intern Med. 2003 Sep 22;163(17):2006-10.
35. Lauer MS. Clinical practice. Aspirin for primary prevention of coronary events. N Engl J Med. 2002 May 9;346(19):1468-74.
36. Messerli FH, Grossman E, Lever AF. Do thiazide diuretics confer specific protection against strokes? Arch Intern Med. 2003 Nov 24;163(21):2557-60.
37. Lip GY, Kamath S, Hart RG. ABC of antithrombotic therapy: Antithrombotic therapy for cerebrovascular disorders. BMJ. 2002 Nov 16;325(7373):1161-3.
38. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. JAMA. 2002 Sep 18; 288(11): 1388-95.
39. Diabetes Care 27:S72-S73, 2004. Aspirin Therapy in Diabetes -American Diabetes Association. (American Diabetes Association (ADA). Standards of medical care in diabetes. VI. **Prevention and management of diabetes complications. Diabetes Care 2007** Jan;30(Suppl 1): S15-24. http://care.diabetesjournals.org/cgi/content/full/30/suppl_1/S4#SEC14)
    American Diabetes Association (ADA). Standards of medical care in diabetes--2008. Diabetes Care. 2008 Jan;31 Suppl 1:S12-54. http://care.diabetesjournals.org/cgi/content/full/31/Supplement_1/S12
    American Diabetes Assoc. Standards of Medical Care in Diabetes—**2009** Diabetes Care January 2009 32:S13-S61; doi:10.2337/dc09-S013. http://care.diabetesjournals.org/content/32/Supplement_1/S13.full http://care.diabetesjournals.org/content/32/Supplement_1/S13.full
    American Diabetes Assoc-ADA. Standards of Medical Care in Diabetes—2010 Diabetes Care Diabetes Care January 2010 33:S11-S61; doi:10.2337/dc10-S011 http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html
40. Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W. Benefit of Clopidogrel Over Aspirin Is Amplified in Patients With a History of Ischemic Events. Stroke. 2004 Jan 22.
41. Toole J.F., et al. Lowering Homocysteine in Patients With Ischemic Stroke to Prevent Recurrent Stroke, Myocardial Infarction, and Death. The Vitamin Intervention for Stroke Prevention (**VISP**) Randomized Controlled Trial. JAMA. 2004;291:5

TOP

Bang H, Chambless LE, Stampfer MJ. Vitamin Intervention For Stroke Prevention trial: an efficacy analysis. Stroke. 2005 Nov;36(11):2404-9. Epub 2005 Oct 20.)
(Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD, Gaziano JM; Veterans Affairs Site Investigators. Effect of homocysteine lowering on mortality & vascular disease in **advanced chronic kidney disease** & end-stage renal disease: a randomized controlled trial. JAMA. 2007 Sep 12;298(10):1163-70.Treatment with high doses of folic acid and B vitamins did not improve survival or reduce the incidence of vascular disease in patients with advanced chronic kidney disease or end-stage renal disease.)

42. VITATOPS Trial Study Group. The **VITATOPS** (Vitamins to Prevent Stroke) Trial: rationale and design of an international, large, simple, randomised trial of homocysteine-lowering multivitamin therapy in patients with recent transient ischaemic attack or stroke. Cerebrovasc Dis. 2002;13(2):120-6. (McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med. 2006 Jun 29;354(26):2764-72. (InfoPOEMs: There is no evidence from this well-designed study that vitamin supplementation to lower homocysteine levels has any beneficial effect on cognition. Although cognition actually appeared to worsen with the use of vitamins in one of the tests, this may be a spurious finding given the large number of comparisons made by the researchers. (LOE = 1b)))
VITATOPS Trial Study Group. B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. Lancet Neurol. 2010 Aug 3.
Hankey GJ, Eikelboom JW, Yi Q, et al. Antiplatelet therapy and the effects of B vitamins in patients with previous stroke or transient ischaemic attack: a post-hoc subanalysis of VITATOPS, a randomised, placebo-controlled trial. Lancet Neurol 2012; online May 2.
43. Linkins LA, Choi PT, Douketis JD. Clinical **impact of bleeding in patients taking oral anticoagulant** therapy for venous thromboembolism: a meta-analysis. Ann Intern Med. 2003 Dec 2;139(11):893-900.
44. Koennecke HC. Secondary prevention of stroke: a practical guide to drug treatment. CNS Drugs. 2004;18(4):221-41.
45. ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction **2004**. http://www.acc.org/clinical/guidelines/stemi/index.pdf
Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). *Circulation* **2007**: DOI: 10.1161/CIRCULATIONAHA.107.188209. Available at: http://circ.ahajournals.org. *J Am Coll Cardiol* 2007: DOI:10.1016/j.jacc.2007.10.001. Available at: http://content.onlinejacc.org. http://content.onlinejacc.org/cgi/content/full/j.jacc.2007.10.001v1
Kushner, Frederick G., Hand, Mary, Smith, Sidney C., et al. **2009 Focused Updates**: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009 0: j.jacc.2009.10.015
http://content.onlinejacc.org/cgi/reprint/j.jacc.2009.10.015v1.pdf
46. Bates SM, Ginsberg JS. Clinical practice. Treatment of deep-vein thrombosis. N Engl J Med. **2004** Jul 15;351(3):268-77.
47. Ramzi DW, Leeper KV. DVT & pulmonary embolism: **Part I**. Diagnosis. Am Fam Physician. 2004 Jun 15;69(12):2829-36 & DVT and pulmonary embolism: **Part II**. Treatment and prevention. Am Fam Physician. 2004 Jun 15;69(12):2841-8
48. Diener HC, Bogousslavsky J, Brass LM, et al.; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004 Jul 24;364(9431):331-7.
49. Hirsh J, Guyatt G, Albers G, Schunemann HJ. The **seventh ACCP** conference on antithrombotic and thrombolytic therapy. Evidence-Based Guidelines. **Chest 2004 September 2004** Supplement; 126:172S-696S.
(**see also ACCP Antithrombotic and Thrombolytic 8th Edition 2008**).
50. Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. JAMA. 2004 Oct 20;292(15):1867-74.
51. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the CAPRIE and CURE studies. Arch Intern Med. 2004 Oct 25;164(19):2106-10.
52. Chan FKL, et al Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding. N Engl J Med 2005;352:238-44. n=320 1yr (InfoPOEMs: For patients with a history of bleeding peptic ulcer, **aspirin and a proton pump inhibitor** twice a day was safer in terms of bleeding side effects than clopidogrel. While esomeprazole was used in this study, generic omeprazole 20 mg give twice a day provides nearly the same degree of acid suppression at a much lower cost. This study calls into question the overall safety of clopidogrel, which has been promoted as not increasing the risk of bleeding significantly. (LOE = 1b)) (Lai KC, et al. **Esomeprazole 20mg/d + ASA (100mg/d)** vs clopidogrel 75mg od for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol. 2006 Jul;4(7):860-5. Epub 2006 Jun 22. n=170 1yr 0 esomeprazole + ASA vs 13.6% clopidogrel recurrent ulcer complications)
Bhatt DL, Scheiman J, Abraham NS, et al. **ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID** use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2008; *Circulation*. 2008; DOI: DOI: 10.1161/CIRCULATIONAHA.108.191087. Available at: http://circ.ahajournals.org
American College of Cardiology Foundation Task Force on Expert Consensus Documents, , Abraham, Neena S., Hlatky, Mark A., Antman, Elliott M., Bhatt, Deepak L., et al. **ACCF/ACG/AHA 2010** Expert Consensus Document on the Concomitant Use of Proton **Pump Inhibitors and Thienopyridines**: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use J Am Coll Cardiol 2010 0: j.jacc.2010.09.010 http://content.onlinejacc.org/cgi/reprint/j.jacc.2010.09.010v1.pdf
American College of Cardiology Foundation Task Force on Expert Consensus Documents, , Abraham, Neena S., Hlatky, Mark A., Antman, Elliott M., Bhatt, Deepak L., et al. ACCF/ACG/AHA **2010** Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use J Am Coll Cardiol 2010 0: j.jacc.2010.09.010
Hsu PI, Lai KH, Liu CP. Esomeprazole with Clopidogrel Reduces Peptic Ulcer Recurrence, Compared to Clopidogrel Alone, in Patients with Atherosclerosis. Gastroenterology. 2010 Dec 6. (n=165, 6months).
Luo JC, Huang KW, Leu HB, et al. Randomised clinical trial: **rabeprazole plus aspirin is not inferior to rabeprazole plus clopidogrel** for the healing of aspirin-related peptic ulcer. Aliment Pharmacol Ther. 2011 Sep;34(5):519-25.
53. Ridker PM, et al. A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women (**WHS**). N Engl J Med. 2005 Mar 7 pre release electronic;352. N Engl J Med 2005;352:1293-304.
(InfoPOEMs: Aspirin reduces the risk of stroke and transient ischemic attack in women but does not reduce the risk of myocardial infarction or cardiovascular death. The reduction in strokes over 10 years (number needed to treat = 444) must be balanced against an increase in serious gastrointestinal bleeds (number needed to treat to harm = 553). No change was seen in this large, long study regarding all-cause mortality. (LOE = 1b)) {Low dose Aspirin in the Primary Prevention of Cancer WHS study JAMA. 2005;294:47-55. Conclusions: Results from this large scale, long-term trial suggest that alternate day use of 100mg every other day for an average of 10yrs does not lower the risk of total, breast, colorectal, or other site-specific cancers. A protective effect on lung cancer or a benefit of higher doses of aspirin cannot be ruled out}
Kurth T, Barr RG, Gaziano JM, Buring J. Randomised Aspirin Assignment And Risk Of Adult-Onset Asthma In The Women's Health Study. (**WHS**) Thorax. 2008 Mar 13; [Epub ahead of print] In this large, randomised clinical trial of apparently healthy adult women, assignment of 100 mg of aspirin on alternate days reduced the relative risk of newly reported diagnosis of **asthma**.
54. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: Stroke risk stratification in patients taking aspirin. Circulation 2004; 110:2287-92. (InfoPOEMs: Clinical decision rules, especially the well-validated Stroke Prevention in Atrial Fibrillation (SPAF) score, can help identify which groups of patients with atrial fibrillation are likely and unlikely to benefit from anticoagulation. (LOE = 1a).If the risk of stroke is low (< 2%), the harms of anticoagulation generally outweigh the benefits. If the risk of stroke is high (> 4%), the benefits of anticoagulation outweigh the risks for most pts. If the patient's stroke risk is in between both extremes, we have to look carefully at his or her risk for hemorrhage.)
55. Sabatine MS, et al. Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation (**CLARITY-TIMI 28**). N Engl J Med. 2005 Mar 9; [Epub] (N=3491,Groups: Plavix 300mg x1 then 75mg od (median **4 doses** given) until angiography vs placebo had 30 day mortality of less than 5%, age <75yr, excluded high bleeding risk pts, few CABG performed, thus select pts were studied, mechanism may be to prevent reocclusion) (InfoPOEMs: Adding clopidogrel to aspirin and fibrinolytic therapy during the first week in patients with ST-segment elevation myocardial infarction reduces the likelihood of recurrent myocardial infarction and ischemia leading to revascularization over a 30-day period (number needed to treat = 15). The short-term risk of major bleeding was low. This trial does not address how long patients should continue to take clopidogrel after the first week of treatment. (LOE = 1b)) {Sabatine MS, Cannon CP, Gibson CM, et al.; Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the **PCI-CLARITY** study. JAMA. 2005 Sep 14;294(10):1224-32. Epub 2005 Sep 4. CONCLUSIONS: Clopidogrel pretreatment significantly reduces the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding. These data add further support to the early use of clopidogrel in STEMI and the strategy of routine clopidogrel pretreatment in patients undergoing PCI. (InfoPOEMs: Pretreatment with clopidogrel before percutaneous coronary intervention (PCI) reduces the risk of cardiovascular disease complications without increasing the risk of bleeding complications. This study only followed patients for 30 days after the intervention, so further long-term studies are needed before a general recommendation can be made. (LOE = 1b-)) } (Scirica BM, et al. The role of clopidogrel in early & sustained arterial patency after fibrinolysis for ST-segment elevation MI: the ECG CLARITY-TIMI 28 Study. J Am Coll Cardiol. 2006 Jul 4;48(1):37-42. Epub 2006Jun 12.)
56. Chen ZM, Jiang LX, Chen YP, et al. **COMMIT** (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5;366(9497):1607-21. COMMIT/CCS-2 trial (Mean age 61, n=45,852, <24hr since MI symptom onset, primary PCI or high risk bleeding were excluded, 54% rec'd thrombolysis, Plavix 75mg od + ASA162mg od vs ASA 162mg od for a mean of **15 days**, Death/MI/stroke 9.2 vs 10.1%, Death 7.5 vs 8.1%, Major Bleeding both equal ~0.6%, Minor bleeds 3.6 vs 3.1%) INTERPRETATION: In a wide range of patients with acute MI, adding clopidogrel 75 mg daily to aspirin and other standard treatments (such as fibrinolytic therapy) safely reduces mortality and major vascular events in hospital, and should be considered routinely.(InfoPOEMs: Patients with acute myocardial infarction treated with aspirin plus clopidogrel have better in-hospital or 28-day survival and fewer deaths, reinfarctions, or strokes than patients treated with aspirin alone. This study doesn't tell us if patients are better off 6 months to 1 year after their myocardial infarction. (LOE = 1b))
57. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al.; Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and **aspirin** for symptomatic intracranial arterial stenosis. (**WASID**). N Engl J Med. 2005 Mar 31;352(13):1305-16. (InfoPOEMs: Warfarin instead of aspirin causes 1 extra death every 2 years for patients with **intracranial arterial stenosis** and a recent stroke or transient ischemic attack. Given the risk and cost of the imaging studies done to diagnose intracranial arterial stenosis, one has to wonder whether we should just prescribe 650 mg aspirin twice a day for these patients and leave it at that. (LOE = 1b))
58. Dobkin BH. Rehabilitation after Stroke. N Engl J Med 2005;352:1677-85. (Langhorne P, Taylor G, Murray G, Dennis M, Anderson C, Bautz-Holter E, Dey P, Indredavik B, Mayo N, Power M, Rodgers H, Ronning OM, Rudd A, Suwanwela N, Widen-Holmqvist L, Wolfe C. **Early supported discharge** services for stroke patients: a meta-analysis of individual patients' data. Lancet. 2005 Feb 5-11;365(9458):501-6.)
59. Siguret V, Gouin I, et al. Initiation of warfarin therapy in elderly medical inpatients: A safe and accurate regimen. Am J Med 2005; 118:137-42. ((InfoPOEMS: This algorithm, which starts with a lower dose than other algorithms, is effective in predicting the final dose of warfarin required by patients older than 70 years. (LOE = 2b) Here is the nomogram: Days 1, 2, 3 -- Give warfarin 4 mg Day 4 -- Check INR in the morning; according to the result, give the following dose (daily): 1.0 to < 1.3 = 5 mg, 1.3 to < 1.5 = 4 mg, 1.5 to < 1.7 = 3 mg, 1.7 to < 1.9 = 2 mg, 1.9 to < 2.5 =1mg, 2.5 or higher = Measure INR daily and hold warfarin until INR drops to < 2.5, then resume at 1 mg.)
60. Ergin A, Ergin N. Is thrombolytic therapy associated with increased mortality? Meta-analysis of randomized controlled trials. Arch Neurol 2005; 62:362-66. (InfoPOEMs: This meta-analysis suggests there is a small, but statistically insignificant, risk of death in patients with acute ischemic stroke receiving thrombolytics within either 3 or 6 hours, which is consistent with other meta-analyses. The available data are too limited to know if important differences exist between agents. (LOE = 1a-))
61. Zimarino M, Renda G, De Caterina R. Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. Drugs. 2005;65(6):725-32.
62. Weinberger J. Adverse effects and drug interactions of antithrombotic agents used in prevention of ischaemic stroke. Drugs. 2005;65(4):461-71.
63. Kyrle PA, Eichinger S. **Deep vein thrombosis**. Lancet. 2005 Mar 26;365(9465):1163-74. & Bates SM, Ginsberg JS. Clinical practice. Treatment of **deep-vein thrombosis**. N Engl J Med. 2004 Jul 15;351(3):268-77.
64. Nelson MR, Liew D, Bertram M, Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged >=70. BMJ. 2005 May 20; [Epub ahead of print]
65. Kerr CR, Humphries KH, Talajic M, et al. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: Results from the Canadian Registry of Atrial Fibrillation. Am Heart J 2005;149:489-96. (InfoPOEMs: After the first episode of paroxysmal atrial fibrillation, most patients (84.5%) will have at least one more episode of atrial fibrillation over the next 5 years. In this same period 24.7% of patients will develop chronic atrial fibrillation. (LOE = 1b))
66. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, Wells PS. Systematic overview of **warfarin and its drug and food interactions**. Arch Intern Med. 2005 May 23;165(10):1095-106.
67. Sherman DG, Kim SG, Boop BS, et al.; NHLBI AFFIRM Investigators. Occurrence & characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (**AFFIRM**). Arch Intern Med. 2005 May 23;165(10):1185-91.
68. Quiroz R, Kucher N, Zou KH, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism. A systematic review. JAMA 2005; 293:2012-17. (InfoPOEMs: A negative computed tomography (CT) scan is as accurate as pulmonary angiography in ruling out suspected pulmonary embolism (PE). Clinicians should strongly consider using clinical decision rules to accurately assess the pretest probability of PE in a individual patient, and then interpret diagnostic tests in light of this probability. For example, a negative CT in a low-risk patient rules out PE, while a negative CT in a high-risk patient may require further confirmation. (LOE = 2a-))
69. Christiansen SC, Cannegieter SC, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA 2005; 293:2352-61. (InfoPOEMs: The risk of recurrence after a first venous thrombotic event (VTE) is increased in men, patients whose

TOP

idiopathic, and women using oral contraceptives after the initial VTE. This study found no increased risk for recurrence in patients with prothrombotic abnormalities. Testing for prothrombotic abnormalities should be considered only in patients with a recurrent VTE. (LOE = 1b-))

70. Perrier A, Roy PM, Sanchez O, et al. **Multidetector-row computed tomography** in suspected pulmonary embolism. N Engl J Med 2005; 352:1760-68. (InfoPOEMs: An algorithm that includes a careful, structured clinical assessment (D-dimer, lower extremity ultrasound, and multidetector-row computed tomography depending on risk status, and other testing as needed based on this initial assessment) provides a safe, and presumably cost-effective, evaluation for patients with suspected pulmonary embolism (PE). The authors argue that omitting the lower extremity ultrasound is a reasonable option given its low yield in this study, although further evaluation of that step is needed in subsequent studies. (LOE = 1a))
71. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical **pharmacy anticoagulation service** on the outcomes of anticoagulation therapy. Chest. 2005 May;127(5):1515-22.
72. Ost D, Tepper J, Mihara H, Lander O, Heinzer R, Fein A. **Duration of anticoagulation** following venous thromboembolism: a meta-analysis. JAMA. 2005 Aug 10;294(6):706-15. CONCLUSIONS: Patients who receive extended anticoagulation are protected from recurrent VTE while receiving long-term therapy. The clinical benefit is maintained after anticoagulation is discontinued, but the magnitude of the benefit is less pronounced. (InfoPOEMs: The optimal duration of anticoagulation following an initial venous thromboembolism (VTE) event is 6 months or more. The risk of a major bleeding event is most pronounced in the first month of treatment and the rate is similar to short-term (3 months or less) treatment. Since the magnitude of benefit appears to lessen beyond 6 months, physicians and patients should reassess individual risk/benefit profiles beyond this timeframe. (LOE = 1a))

Matchar David B., Jacobson Alan, Dolor Rowena, et al. for the **THINRS** Executive Committee and Site Investigators. Effect of **Home Testing of International Normalized Ratio** on Clinical Events**.** N Engl J Med 2010; 363:1608-1620.

73. Roy PM, Colombet I, Durieux P, Chatellier G, Sors H, Meyer G. Systematic review and meta-analysis of strategies for the **diagnosis of suspected pulmonary embolism**. BMJ. 2005 Jul 30;331(7511):259. (InfoPOEMs: Some tests are better at diagnosing pulmonary embolism (PE) and some are better at excluding it. To exclude PE in patients with a low likelihood of disease, use a lung scan, spiral computed tomography (CT) plus leg ultrasound, or D-dimer by ELISA. To diagnose PE in patients with a high likelihood of disease, use a ventilation perfusion scan, spiral CT, or leg ultrasound. (LOE = 1a))
74. Drummond AE, Pearson B, Lincoln NB, Berman P. Ten year follow-up of a randomised controlled trial of care in a stroke **rehabilitation unit**. BMJ. 2005 Aug 10; [Epub ahead of print]
75. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Low-dose **aspirin** in the primary prevention of **cancer**: the Women's Health Study (WHS) : a randomized controlled trial. JAMA. 2005 Jul 6;294(1):47-55. Results from this large-scale, long-term trial suggest that alternate day use of low-dose aspirin (100 mg) for an average 10 years of treatment does not lower risk of total, breast, colorectal, or other site-specific cancers. A protective effect on lung cancer or a benefit of higher doses of aspirin cannot be ruled out. (InfoPOEMs: Low-dose aspirin does not reduce the risk of lung, breast, colorectal, or other site cancer in healthy women 45 years and older. There may be a protective effect on reducing lung cancer mortality, but overall mortality is not reduced. (LOE = 1b))
76. Andrew T. Chan, MD, MPH; Edward L. et al. Long-term Use of Aspirin and Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Cancer JAMA. 2005;294:914-923. CONCLUSIONS: Regular, long-term aspirin use reduces risk of colorectal cancer. Nonaspirin NSAIDs appear to have a similar effect. However, a significant benefit of aspirin is not apparent until more than a decade of use, with maximal risk reduction at doses greater than 14 tablets per week. These results suggest that optimal chemoprevention for colorectal cancer requires long-term use of aspirin doses substantially higher than those recommended for prevention of cardiovascular disease, but the dose-related risk of gastrointestinal bleeding must also be considered. (InfoPOEMs: Regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), especially more than 14 doses per week for at least 10 years, reduces the risk of colon cancer while also increasing the risk of a major gastrointestinal bleeding event. All-cause mortality is not affected by regular use. We need additional methods (gene testing?) to determine who is at high risk of colorectal cancer before making specific recommendations for prevention. (LOE = 2b))
77. Goodacre S, Sutton AJ, Sampson FC. Meta-analysis: The value of clinical assessment in the diagnosis of deep venous thrombosis. Ann Intern Med. 2005 Jul 19;143(2):129-39. CONCLUSION: Individual clinical features are of limited value in diagnosing DVT. Overall assessment of clinical probability by using the Wells score is more useful. (InfoPOEMs: With the exception of either a previous deep vein thrombosis (DVT) or a previous malignancy, no other clinical feature effectively increases or decreases the odds of having a DVT. The Wells Clinical Probability Score, which combines several clinical features, is much more effective. (LOE = 1a))
78. Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. **Risks** of **oral anticoagulant** therapy with increasing **age**. Arch Intern Med. 2005 Jul 11;165(13):1527-32.
79. Tapson VF, Hyers TM, Waldo AL, et al.; NABOR (National Anticoagulation Benchmark and Outcomes Report) Steering Committee. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. Arch Intern Med. 2005 Jul 11;165(13):1458-64.
80. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet. 2005 Jul 2;366(9479):29-36. (InfoPOEMs: Easy-to-assess clinical and demographic variables can be used to predict which patients with transient ischemic attacks (TIAs) are at greatest risk of stroke in the subsequent week. (LOE = 1b-))
Sciolla R, Melis F; SINPAC Group. Rapid identification of high-risk transient ischemic attacks: prospective validation of the ABCD score. Stroke. 2008 Feb;39(2):297-302. Epub 2008 Jan 3.
81. van Wijk I, Kappelle LJ, van Gijn J, et al.; LiLAC study gp. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. Lancet. 2005 Jul 7;365(9477):2098-104. (48% survive 10yrs free of another vaxcular event)
82. Hankey GJ. Redefining risks after TIA and minor ischaemic stroke. Lancet. 2005 Jul 7;365(9477):2065-6. (Looking forward from the time of a TIA, the risk of a stroke is as high as 5% within the first 48hr and 12% within the first 30 days.)
Shah KH, Metz HA, Edlow JA. Clinical prediction rules to stratify short-term risk of stroke among patients diagnosed in the emergency department with a transient ischemic attack. Ann Emerg Med. 2009 May;53(5):662-73.
83. Schrader J, Luders S, et al; **MOSES** Study Group. Morbidity and Mortality After Stroke, **Eprosartan** Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005 Jun;36(6):1218-26.
84. Drummond AE, Pearson B, Lincoln NB, Berman P. Ten year follow-up of a randomised controlled trial of care in a stroke rehabilitation unit. BMJ. 2005 Sep 3;331(7515):491-2. Epub 2005 Aug 10.
85. Rothwell PM, Warlow CP. Timing of **TIAs** preceding stroke: time window for prevention is very short. Neurology. 2005 Mar 8;64(5):817-20.
86. Duncan PW, Zorowitz R, Bates B, Choi JY, Glasberg JJ, Graham GD, Katz RC, Lamberty K, Reker D. Management of Adult Stroke **Rehabilitation Care**: a clinical practice guideline. Stroke. 2005 Sep;36(9):e100-43.
87. Wolak A, Amit G, Cafri C, Gilutz H, Ilia R, Zahger D. Increased long term rates of stent thrombosis and mortality in patients given clopidogrel as compared to **ticlopidine** following coronary stent implantation. Int J Cardiol. 2005 Sep 1;103(3):293-7.
88. Hermida RC, Ayala DE, Calvo C, Lopez JE. Aspirin administered at bedtime, but not on awakening, has an effect on ambulatory blood pressure in hypertensive patients. J Am Coll Cardiol. 2005 Sep 20;46(6):975-83.
89. Andreotti F, Testa L, Biondi-Zoccai G, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25 307 patients. Eur Heart J. 2005 Sep 5; [Epub ahead of print] CONCLUSION: For patients recovering from ACS, a combined strategy of A + W at INR values of 2-3 doubles the risk of MB, but is nonetheless superior to aspirin alone in preventing MAE. Whether this combined regimen is also superior to a 'double' anti-platelet strategy or to newer evolving treatments warrants further investigation.
90. Bonaa KH for the NORVIT Study Group. **NORVIT**: Randomised trial of homocysteine-lowering with B vitamins for secondary prevention of cardiovascular disease after acute myocardial infarction. European Society of Cardiology, Sept 3-7, 2005, Abstract 1334.
91. Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. **Warfarin plus aspirin after myocardial infarction** or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. Ann Intern Med. 2005 Aug 16;143(4):241-50. Summary for patients in: Ann Intern Med. 2005 Aug 16;143(4):I14. (InfoPOEMs: Adding warfarin to aspirin prophylaxis does not affect overall death rates, though the combination decreases subsequent myocardial infarction risk (number needed to treat [NNT] = 56) and, to a lesser degree, ischemic stroke risk (NNT = 221). As one might expect, major bleeding episodes occur more often with the added warfarin, though only in a small number of patients (1.5% vs 0.56%). (LOE = 1a))
92. Fitzmaurice DA, Murray ET, McCahon D, et al. **Self management of oral anticoagulation**: randomised trial. BMJ. 2005 Nov 5;331(7524):1057. Epub 2005 Oct 10. (Menendez-Jandula B, Souto JC, et al. Comparing **self-management** of oral anticoagulant therapy with clinic management: a randomized trial. Ann Intern Med. 2005 Jan 4;142(1):1-10. (InfoPOEMs: Although many patients will not wish to do so, home monitoring of anticoagulation status and subsequent self-adjustment of dosing is safe and effective. Self-monitoring of anticoagulation is a bit trickier than home blood glucose monitoring, and approximately 30% of patients dropped out during the training period. The testing equipment is expensive ($1300 US), a cost-effectiveness analysis has not been done, and there is no evidence that it leads to better clinical outcomes (ie, less bleeding and less recurrent embolic events) . (LOE = 1b))
Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, Heneghan CJ. Self-monitoring and self-management of oral anticoagulation. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD003839.
Stafford Leanne, Peterson Gregory M, Bereznicki Luke RE, et al..Clinical Outcomes of a Collaborative, Home-Based Postdischarge **Warfarin Management Service** (March). Articles Ahead of Print published 8 March 2011, DOI 10.1345/aph.1P617.
Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, et al. Meta-analysis: effect of patient **self-testing and self-management of longterm anticoagulation** on major clinical outcomes. Ann Intern Med. 2011;154: 472-82.
Grunau BE, Wiens MO, Harder KK. Patient **self-management of warfarin** therapy: Pragmatic feasibility study in Canadian primary care. Can Fam Physician. 2011 Aug;57(8):e292-8.
Cho HJ, On YK, Bang OY, et al. Development and Comparison of a Warfarin-Dosing **Algorithm** for Korean Patients With Atrial Fibrillation. Clin Ther. 2011 Oct 5.
Heneghan C, Ward, A, Perera R, and The Self-Monitoring Trialist Collaboration. **Self-monitoring** of oral anticoagulation: systematic review and meta-analysis of individual patient data. Lancet 2011; published online Dec 1.
Carlquist JF, Anderson JL. Using **pharmacogenetics in real time to guide warfarin** initiation: a clinician update. Circulation. 2011 Dec 6;124(23):2554-9.
Valentin II, Vazquez J, Rivera-Miranda G, et al. Prediction of Warfarin Dose Reductions in Puerto Rican Patients, Based on Combinatorial **CYP2C9 and VKORC1 Genotypes** (February). Ann Pharmacother. 2012 Jan 24.
Horne BD, Lenzini PA, Wadelius M, et al. **Pharmacogenetic warfarin** dose refinements remain significantly influenced by genetic factors after one week of therapy. Thromb Haemost 2012; 107:232-240.
Anderson JL, Horne BD, Stevens SM, et al. A randomized and clinical effectiveness trial comparing two **pharmacogenetic algorithms** and standard care for individualizing warfarin dosing (**Coumagen-II**). Circulation. 2012;125:1997–2005.
93. ACTIVE Writing Group on behalf of the ACTIVE Investigators; Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (**ACTIVE W**): a randomised controlled trial. Lancet. 2006 Jun 10;367(9526):1903-12. There were 165 primary events in patients on oral anticoagulation therapy (**annual risk 3.93%**) and 234 in those on clopidogrel plus aspirin (**annual risk 5.60%**; relative risk 1.44 (1.18-1.76; p=0.0003). Patients on oral anticoagulation therapy who were already receiving this treatment at study entry had a trend towards a greater reduction in vascular events (relative risk 1.50, 95% CI 1.19-1.89) and a significantly (p=0.03 for interaction) **lower risk of major bleeding with oral anticoagulation** therapy (**2.2 vs 2.4% per year**) (1.30; 0.94-1.79) than patients not on this treatment at study entry (1.27, 0.85-1.89 and 0.59, 0.32-1.08, respectively). (InfoPOEMs: Warfarin is superior to the combination of clopidogrel (Plavix) plus aspirin in preventing strokes and systemic emboli in high-risk patients with atrial fibrillation. (LOE = 2b)) Healey JS, Hart RG, Pogue J, et al. Risks and Benefits of Oral Anticoagulation Compared With Clopidogrel Plus Aspirin in Patients With Atrial Fibrillation According to Stroke Risk. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W). Stroke. 2008 Mar 6. In this clinical trial, patients with a CHADS2=1 had a low risk of stroke, yet still derived a modest (<1% per year) but statistically significant absolute reduction in stroke with OAC and had low rates of major hemorrhage on OAC.
De Caterina R, Connolly SJ, Pogue J, Chrolavicius S, Budaj A, Morais J, Renda G, Yusuf S; on behalf of the ACTIVE Investigators. Mortality predictors and effects of antithrombotic therapies in atrial fibrillation: insights from ACTIVE-W. Eur Heart J. 2010 Aug 4. Non-fatal strokes increased mortality in ACTIVE-W, but non-disabling strokes did not. Among major bleeding events, only those also classified as severe increased mortality. Future research should emphasize the prevention of disabling strokes and severe bleeds and place less emphasis on non-disabling stroke or major bleeds that are not severe.
EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fi brillation after transient ischaemic attack or minor stroke. Lancet 1993; 342: 1255–62.
Stroke Prevention in Atrial Fibrillation (**SPAF**) Investigators. Adjusted-dose warfarin versus low-intensity, fi xed-dose warfarin plus aspirin for high-risk patients with atrial fi brillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet 1996; 348: 633–38.
94. von Beckerath N, Taubert D, et al.. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the **ISAR-CHOICE** (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. Circulation. 2005 Nov 8;112(19):2946-50. Epub 2005 Oct 31. (Montalescot G, et al.; **ALBION** Trial Investigators. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. J Am Coll Cardiol. 2006 Sep 5;48(5):931-8. Epub 2006 Aug 17.)
King SB, Smith SC, Hirshfeld JW, et al. **2007** focused update of the ACC/AHA/SCAI 2005 Guideline Update for **Percutaneous Coronary Intervention**: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: (2007 Writing Group to Review New Evidence and Update the 2005 ACC/AHA/SCAI Guideline Update for Percutaneous Coronary Intervention). Circulation 2007; DOI: 10.1161/CIRCULATIONAHA.107.188208. http://circ.ahajournals.org.
American College of Cardiology Foundation, , American Heart Association Task Force on Practice Guidelines, , Society for Cardiovascular Angiography and Interventions, , Levine, Glenn N., Bates, Eric R., et al.
2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: Executive Summary. J Am Coll Cardiol 2011 0: j.jacc.2011.08.006. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.08.006v1.pdf
American College of Cardiology Foundation, , American Heart Association Task Force on Practice Guidelines, , American Association for Thoracic Surgery, , Society of Cardiovascular Anesthesiologists, , Society of Thoracic Surgeons, Hillis, L. David, Smith, Peter K., Anderson, Jeffrey L., et al. **2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery**: Executive Summary. J Am Coll Cardiol 2011 0: j.jacc.2011.08.008. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.08.008v1.pdf
95. Aujesky D, Smith KJ, Cornuz J, Roberts MS. **Cost-effectiveness of low-molecular-weight heparin** for treatment of pulmonary embolism. Chest. 2005 Sep;128(3):1601-10.
95. Foerster V, et al. **CT and MRI** for selected clinical disorders: A systematic review of clinical systematic reviews Oct/05 https://www.ccohta.ca/publications/pdf/322_ctmri_tr_e.pdf
96. James AH, et al. Incidence & risk factors for stroke in **pregnancy** and the puerperium. Obstet Gynecol. 2005 Sep;106(3):509-16. (InfoPOEMs: Hospitalization with a diagnosis of stroke in pregnancy or puerperium occurs in 34 per 100,000 deliveries in the United States. It occurs in more that 50 per 100,000 in African American women and women older than 35 years. The most common comorbid conditions associated with increased risk are migraine headache and hypertension (including gestational hypertension). (LOE = 2c))
97. Doukas G, Samani NJ, Alexiou C, Oc M, Chin DT, Stafford PG, Ng LL, Spyt TJ. Left **atrial radiofrequency ablation during mitral valve surgery** for continuous atrial fibrillation: a randomized controlled trial. JAMA. 2005 Nov 9;294(18):232

TOP

98. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous **thromboembolism during pregnancy** or postpartum: a 30-year population-based study. Ann Intern Med. 2005 Nov 15;143(10):697-706.
99. Ballantyne CM, Hoogeveen RC, Bang H, et al. **Lipoprotein-Associated Phospholipase A2**, High-Sensitivity **C-Reactive Protein**, and Risk for Incident Ischemic Stroke in Middle-aged Men and Women in the Atherosclerosis Risk in Communities (ARIC) Study. Arch Intern Med. 2005 Nov 28;165(21):2479-84.
101. Patrono C et al. Low-Dose **Aspirin** for the Prevention of Atherothrombosis. N Engl J Med 2005;353:2373-83.
102. Capone ML, Sciulli MG, Tacconelli S, Grana M, Ricciotti E, Renda G, Di Gregorio P, Merciaro G, Patrignani P. Pharmacodynamic interaction of **naproxen with low-dose aspirin** in healthy subjects. J Am Coll Cardiol. 2005 Apr 19;45(8):1295-301.
103. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. **Cyclooxygenase inhibitors** and the antiplatelet effects of **aspirin**. N Engl J Med. 2001 Dec 20;345(25):1809-17.
104. Corman SL, Fedutes BA, Ansani NT. Impact of **nonsteroidal antiinflammatory drugs** on the cardioprotective effects of **aspirin**. Ann Pharmacother. 2005 Jun;39(6):1073-9. Epub 2005 May 3.
105. Teo KK, Yusuf S, Pfeffer M, et al.; ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors (**ACEI**) in the presence or absence of **aspirin**: a systematic review. Lancet. 2002 Oct 5;360(9339):1037-43. Erratum in: Lancet 2003 Jan 4;361(9351):90.
106. Latini R, Tognoni G, Maggioni AP, et al. Clinical effects of early angiotensin-converting enzyme inhibitor (**ACEI**) treatment for acute myocardial infarction are similar in the presence and absence of **aspirin**: systematic overview of individual data from 96,712 randomized patients. Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group. J Am Coll Cardiol. 2000 Jun;35(7):1801-7.
107. PREPIC Study Group. Eight-year follow-up of patients with **permanent vena cava filters** in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation.2005Jul 19;112(3): 416-22. Epub 2005 Jul 11. (InfoPOEMs: In a fairly high-risk group of patients with venous thromboembolism (VTE), vena cava filters reduce the risk of pulmonary embolism (PE), increase the risk of deep vein thrombosis (DVT), and do not alter the risk of death. However, this group was not typical of the group that is usually given these filters in clinical practice. (LOE = 1b))
108. Poole KE, Loveridge N, Barker PJ, et al. Reduced **Vitamin D** in Acute Stroke. Stroke. 2005 Dec 1; [Epub ahead of print]
109. Chambers B, Donnan G, Chambers B. **Carotid endarterectomy** for asymptomatic carotid stenosis. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001923. AUTHORS' CONCLUSIONS: Despite about a 3% perioperative stroke or death rate, CEA for asymptomatic carotid stenosis reduces the risk of ipsilateral stroke, and any stroke, by approximately 30% over three years. However, the absolute risk reduction is small (approximately 1% per annum over the first few years of follow up in the two largest and most recent trials) but it could be higher with longer follow up.
110. Mahaffey KW, et al. **SYNERGY** Trial Investigators. High-risk patients with acute coronary syndromes treated with low-molecular-weight or unfractionated heparin: outcomes at 6 months and 1 year in the SYNERGY trial. JAMA. 2005 Nov 23;294(20):2594-600. (InfoPOEMs: Low-molecular-weight heparin (enoxaparin) is no more effective than unfractionated heparin in the treatment of patients with acute coronary syndromes (ACS). (LOE = 1b-)) (Ferguson JJ, et al. SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA. 2004 Jul 7;292(1):45-54.)
111. Martel N, Lee J, Wells PS. Risk for **heparin-induced thrombocytopenia** with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005 Oct 15;106(8):2710-5. Epub 2005 Jun 28. The inverse variance-weighted average that determined the absolute risk for HIT with LMWH was 0.2%, and with UFH the risk was 2.6%. Most studies were of patients after orthopedic surgery.
112. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, Singer DE. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004 Nov 16;141(10):745-52.
113. Witt BJ, Brown RD Jr, Jacobsen SJ, et al. A community-based study of stroke incidence after myocardial infarction. Ann Intern Med. 2005 Dec 6;143(11):785-92.
114. Albers GW, Diener HC, Frison L, et al.; SPORTIF Executive Steering Committee for the SPORTIF V Investigators. **Ximelagatran** vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA. 2005 Feb 9;293(6):690-8.
115. McKeown PP, et al.; American College of Chest Physicians. Executive summary: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005 Aug;128(2 Suppl):1S-5S.
116. Alexander KP, Chen AY, Roe MT, et al.; CRUSADE Investigators. **Excess dosing of antiplatelet and antithrombin agents** in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA. 2005 Dec 28;294(24):3108-16.
117. Eikelboom JW, et al. Unfractionated & low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute MI: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67. Epub 2005 Dec 12.
118. Hayashino Y, Goto M, Noguchi Y, Fukui T. Ventilation-perfusion scanning and helical CT in suspected pulmonary embolism: meta-analysis of diagnostic performance. Radiology. 2005 Mar;234(3):740-8.
119. van Belle A, et al. Writing Group for the Christopher Study Investigators. Effectiveness of managing suspected **pulmonary embolism** using an **algorithm** combining clinical probability, D-dimer testing, & computed tomography. JAMA. 2006 Jan 11;295(2):172-9.
120. Roderick P, et al. Towards **evidence-based guidelines** for the prevention of venous thromboembolism: systematic reviews of mechanical, oral anticoagulation, dextran & regional anaesthesia as thromboprophylaxis. Health Technol Assess. 2005 Dec;9(49):1-94.
121. Choudhry NK, Anderson GM, Laupacis A, Ross-Degnan D, Normand SL, Soumerai SB. Impact of **adverse events on prescribing warfarin** in patients with atrial fibrillation: matched pair analysis. BMJ. 2006 Jan 10; [Epub ahead of print]
122. Berger JS, et al. **Aspirin for the primary** prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006 Jan 18;295(3):306-13. CONCLUSIONS: For women and men, aspirin therapy reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischemic stroke in women and MI in men. Aspirin significantly increased the risk of bleeding to a similar degree among women and men. (InfoPOEMs: Primary prevention with aspirin reduces the risk of adverse cardiovascular events in both women and men. In particular, aspirin reduces the risk of stroke in women and the risk of myocardial infarction (MI) in men. The risk of major bleeding is significantly increased with regular aspirin therapy in both sexes and overall mortality is unchanged. Patients and their clinicians should weigh their independent risks and benefits before deciding on regular aspirin use. (LOE = 1a))
123. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic **fracture** in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Arch Intern Med. 2006 Jan 23;166(2):241-6.
124. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. A **prediction rule** to identify low-risk patients with pulmonary embolism. Arch Intern Med. 2006 Jan 23;166(2):169-75.
125. Blann AD, Lip GY. Venous thromboembolism. BMJ. 2006 Jan 28;332(7535):215-9.
126. Sacco RL, et al. Guidelines for **Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack**: A Statement for Healthcare Professionals From the **American Heart Association/American Stroke Association** Council on Stroke: Co-Sponsored by the Council on Cardiovascular Radiology and Intervention: The American Academy of Neurology affirms the value of this guideline. Stroke. 2006 Feb;37(2):577-617. http://stroke.ahajournals.org/cgi/reprint/37/2/577
Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Sacco RL, Schwamm LH, American Heart Association, American Stroke Association. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008 May;39(5):1647-52. http://stroke.ahajournals.org/cgi/reprint/39/5/1647
127. Touze E, Varenne O, Chatellier G, et al. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke. 2005 Dec;36(12):2748-55. Epub 2005 Oct 27. (InfoPOEMs: Following a stroke or transient ischemic attack (TIA), the annual rate of nonstroke vascular **death and myocardial infarction (MI) is approximately 2% per year**. This information can be used to inform patients about the clinical course of their disease. (LOE = 1a-))
128. **Dalhousie** University Academic Detailing Service: Acute Coronary SyndromeJan 2006 http://cme.medicine.dal.ca/files/clop%20handout.pdf
129. Rodger MA, et al. The bedside investigation of pulmonary embolism diagnosis study: a double-blind randomized controlled trial comparing combinations of 3 bedside tests vs ventilation-perfusion scan for the initial investigation of suspected pulmonary embolism. Arch Intern Med. 2006 Jan 23;166(2):181-7.
130. Lim W, Crowther MA, et al. Management of antiphospholipid antibody syndrome: a systematic review. JAMA. 2006 Mar 1;295(9):1050-7. (InfoPOEMs: Patients who test positive for antiphospholipid antibodies are at an increased risk of thrombotic events. Similarly afflicted pregnant women are at an increased risk of fetal loss. Moderate-intensity anticoagulation with warfarin (target international normalized ratio (INR) = 2.0 - 3.0) prevents recurrent venous thrombosis. The optimal management of other thrombotic aspects of patients with antiphospholipid antibodies remains uncertain. (LOE = 1a-))
Cohen Danielle, Berger Stefan P, Steup-Beekman Gerda M et al., Diagnosis and management of the **antiphospholipid syndrome**. BMJ 2010;340
Ruiz-Irastorza Guillermo, Crowther Mark, Branch Ware, et al. **Antiphospholipid syndrome**, The Lancet, In Press, Corrected Proof, Available online 6 September 2010, ISSN 0140-6736, DOI: 10.1016/S0140-6736(10)60709-X.
131 Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. N Engl J Med. 2006 Mar 12; (**Charisma**) [Epub ahead of print] (InfoPOEMs: The use of the combination of clopidogrel (Plavix) and aspirin should be limited to carefully defined groups of patients with acute coronary syndromes. It is not recommended for the broader group of patients with coronary disease, cerebrovascular disease, or multiple risk factors such as diabetes, hyperlipidemia, and hypertension. (LOE = 1b)) Wang TH, Bhatt DL, Fox KA, Steinhubl SR, Brennan DM, Hacke W, Mak KH, Pearson TA, Boden WE, Steg PG, Flather MD, Montalescot G, Topol EJ; on behalf of the CHARISMA Investigators. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. Eur Heart J. 2007 Aug 2; [Epub ahead of print] These findings do not support the use of dual-antiplatelet therapy with clopidogrel and aspirin in a primary prevention population. In this subgroup analysis, CV death occurred more frequently than anticipated.
Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. (Charisma) Ann Intern Med 2009; 150:379-386.
Dasgupta A, Steinhubl SR, Bhatt DL, et al.; CHARISMA Investigators. Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance [CHARISMA] trial). Am J Cardiol. 2009 May 15;103(10):1359-63. Epub 2009 Apr 1
Berger PB, Bhatt DL, Fuster V, et al. for the CHARISMA Investigators. Bleeding Complications With Dual Antiplatelet Therapy Among Patients With Stable Vascular Disease or Risk Factors for Vascular Disease: Results From the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) Trial. Circulation. 2010 Jun 15;121(23):2575-2583.
Hankey GJ, Hacke W, Easton JD, et al. on behalf of the CHARISMA Trial Investigators. Effect of Clopidogrel on the Rate and Functional Severity of Stroke Among High Vascular Risk Patients. A Prespecified Substudy of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) Trial. Stroke. 2010 Jul 1.
132. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine Lowering and Cardiovascular Events after Acute Myocardial Infarction. (**NORVIT**) N Engl J Med. 2006 Mar 12; [Epub ahead of print]
Ebbing Marta; Bonaa Kaare Harald; Nygard Ottar; et al. Cancer Incidence and Mortality After Treatment With Folic Acid and Vitamin B12 (Norvit & Wenbit). JAMA. 2009;302(19):2119-2126.
Langan RC, Zawistoski KJ. Update on **Vitamin B12 Deficiency**. Am Fam Physician. 2011 Jun 15;83(12):1425-1430.
133. Lonn E, Yusuf S, Arnold MJ, et al.; Heart Outcomes Prevention Evaluation **(HOPE) 2** Investigators. **Homocysteine** lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006 Apr 13;354(15):1567-77. Epub 2006 Mar 12. (InfoPOEMs: Supplementation with folic acid and B vitamins is ineffective for adults 55 years and older with known cardiovascular disease (CVD) or diabetes. A second report in the same issue found that similar supplementation in patients with a recent acute myocardial infarction was not helpful and may actually increase the risk of a bad cardiovascular outcome (relative risk = 1.22; 95% CI, 1.0 - 1.5). (LOE = 1b))
134. Choi-Kwon S, Han SW, Kwon SU, Kang DW, Choi JM, Kim JS. Fluoxetine treatment in poststroke depression, emotional incontinence, and anger proneness: a double-blind, placebo-controlled study.Stroke. 2006 Jan;37(1):156-61. Epub 2005 Nov 23.
135. Yusuf S, et al.; Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006 Apr 6;354(14):1464-76. Epub 2006 Mar 14. Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. (OASIS-5) N Engl J Med. 2006 Mar 14; [Epub ahead of print] Conclusions Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long term mortality and morbidity. (InfoPOEMs: **Fondaparinux** is a safer alternative to enoxaparin in patients with acute coronary syndrome (ACS), and has slightly better long-term efficacy, as well. (LOE = 1b))
136. Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction: The **OASIS-6** Randomized Trial. JAMA. 2006 Mar 14; [Epub ahead of print] CONCLUSION: In patients with STEMI, particularly those not undergoing primary percutaneous coronary intervention, **fondaparinux** significantly reduces mortality & reinfarction without increasing bleeding and strokes. (InfoPOEMs: Fondaparinux (Arixtra) reduces the risk of mortality and reinfarction without increasing the risk of severe bleeding events in patients with acute ST-segment elevation myocardial infarction. Patients undergoing primary percutaneous coronary intervention (PCI) received no additional benefit from fondaparinux compared with unfractionated heparin (UFH). (LOE = 1b-)) Mehta SR, et al.; ASPIRE Investigators. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation (ASPIRE) Pilot Trial. Circulation. 2005 Mar 22;111(11):1390-7.
137. Mohr JP, et al. Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. (WARSS) N Engl J Med. 2001 Nov 15;345(20):1444-51.
138. Kastrati A, et al. **Abciximab** in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention After Clopidogrel Pretreatment: The **ISAR-REACT 2** Randomized Trial. JAMA. 2006 Mar 13; [Epub ahead of print]

TOP

Abciximab reduces the risk of adverse events in patients with non-ST-segment elevation ACS undergoing PCI after pretreatment with 600 mg of clopidogrel. The benefits provided by abciximab appear to be confined to patients presenting with an elevated troponin level.
139. Sacco RL et al **American Heart Association**/American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for **prevention of stroke** in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Circulation. **2006** Mar 14;113(10):e409-49. http://circ.ahajournals.org/cgi/content/full/113/10/e409
140. Becker DM, et al. Sex differences in platelet reactivity and response to low-dose aspirin therapy. JAMA. 2006 Mar 22;295(12):1420-7.
141 **Peripheral Arterial Disease**: ACC/AHA 2005 Guideline for Management of Patients With (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic); A Collaborative Report From the AAVS/SVS, SCAI, SIR, SVMB, and the ACC/AHA Task Force on Practice Guidelines http://content.onlinejacc.org/cgi/content/full/47/6/e1 (Abramson BL, et al.; Canadian Cardiovascular Society. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease - executive summary. Can J Cardiol. 2005 Oct;21(12):997-1006.)
142. Antman EM, et al. Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction. (**EXTRACT-TIMI 25**)N Engl J Med. 2006 Mar 20; [Epub ahead of print] Conclusions In patients receiving fibrinolysis for ST-elevation myocardial infarction, treatment with enoxaparin throughout the index hospitalization is superior to treatment with unfractionated heparin for 48 hours but is associated with an increase in major bleeding episodes. (InfoPOEMs: For every 1000 patients treated with enoxaparin instead of unfractionated heparin there were 15 fewer nonfatal myocardial infarctions (MIs), 7 fewer urgent revascularizations, and 6 fewer deaths, but there were 4 additional episodes of nonfatal major bleeding. (LOE = 1b))
143. Morice MC, et al. REALITY Trial Investigators. **Sirolimus- vs paclitaxel**-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. JAMA. 2006 Feb 22;295(8):895-904.
144. Kaplan RC, et al. Vascular events, mortality, and preventive therapy following ischemic stroke in the elderly. Neurology. 2005 Sep 27;65(6):835-42. Erratum in: Neurology. 2006 Feb 28;66(4):493.
145. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after **transbronchial** biopsy in humans. Chest. 2006 Mar;129(3):734-7.
146. Purkayastha S, et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart. 2006 Apr;92(4):531-2. (More blood lost & transfusions)
147. Stabile G, et al. Catheter ablation treatment in pts with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (**Catheter Ablation For The Cure Of Atrial Fibrillation Study**). Eur Heart J.2006Jan;27(2):216-21.Epub 2005Oct 7.
148. Cohen AT, et al.; ARTEMIS Investigators. Efficacy and safety of **fondaparinux** for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ. 2006 Feb 11;332(7537):325-9. Epub 2006 Jan 26.
149. Wolfram RM, et al. Clopidogrel Loading Dose (**300** Versus 600 mg) Strategies for Patients With Stable Angina Pectoris Subjected to Percutaneous Coronary Intervention. Am J Cardiol. 2006 Apr 1;97(7):984-9. Epub 2006 Feb 13.
150. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet. 2006 Feb 4;367(9508):404-11. (InfoPOEMs: Patients who self-monitor oral anticoagulation had fewer thromboembolic events than those using standard approaches to monitoring. However, self-monitoring should only be offered to literate and motivated patients. Additionally, the machines are costly and not universally covered by insurance. (LOE = 1a))
151. Glueck CJ, Khalil Q, Winiarska M, Wang P. Interaction of **duloxetine and warfarin** causing severe elevation of international normalized ratio. JAMA. 2006 Apr 5;295(13):1517-8.
152. Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common **thrombophilia**: a systematic review. Arch Intern Med. 2006 Apr 10;166(7):729-36.
153. Tricoci P, Roe MT, Mulgund J, et al. Clopidogrel to treat patients with non-ST-segment elevation acute coronary syndromes after hospital discharge. Arch Intern Med 2006; 166:806-811.
154. Pignone M, Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Ann Intern Med. 2006 Mar 7;144(5):326-36. Summary for patients in: Ann Intern Med. 2006 Mar 7;144(5):I29. (InfoPOEMs: From the viewpoint of cost to a third-party payer, the costs of aspirin alone are reasonable in men at low-risk for coronary heart disease (CHD); the addition of a statin to aspirin therapy in these men is above what is considered to be reasonable cost for prevention. However, the combination of aspirin and a statin is cost-effective when men are at high risk (10% or above). (LOE = 2a))
155. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: **low-molecular-weight heparin** and **bleeding** in patients with severe **renal** insufficiency. Ann Intern Med. 2006 May 2;144(9):673-84.
156. Smith SC Jr, et al. **AHA/ACC guidelines for secondary prevention** for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006 May 16;113(19):2363-72. http://circ.ahajournals.org/cgi/reprint/113/19/2363
Furie Karen L., Kasner Scott E., Adams Robert J., et al., and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the **Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack**. (Secondary Prevention) A Guideline for Healthcare Professionals From the American Heart Association (AHA)/American Stroke Association (ASA). Stroke published October 21, 2010, doi:10.1161/STR.0b013e3181f7d043. http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181f7d043v1
157. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing between stroke and mimic at the bedside: the brain attack study. Stroke. 2006 Mar;37(3):769-75. Epub 2006 Feb 16. (InfoPOEMs: In this study, 31% of patients with suspected stroke actually had a stroke mimic. Eight clinical factors helped distinguish these patients from those with stroke. (LOE = 2b))
158. Rasoul S, et al. A comparison of dual vs. **triple antiplatelet** therapy in patients with non-ST-segment elevation acute coronary syndrome: results of the ELISA-2 trial. Eur Heart J. 2006 May 8; [Epub ahead of print]
159. Toff WD, et al. Effect of hypobaric hypoxia, simulating conditions during long-haul **air travel**, on coagulation, fibrinolysis, platelet function, and endothelial activation. JAMA. 2006 May 17;295(19):2251-61. (but up 5min/hr, not alcohol/narcotics)
160. ESPRIT Study Group; et al. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (**ESPRIT**): randomised controlled trial. Lancet. 2006 May 20;367(9523):1665-73. Norrving B. Dipyridamole with aspirin for secondary stroke prevention. Lancet. 2006 May 20;367(9523):1638-9. (InfoPOEMs: In this unblinded study, the combination of aspirin plus dipyridamole is more effective than aspirin alone in preventing death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complications. However, patients taking dipyridamole are much more likely to experience headaches sufficient to stop taking it. (LOE = 2b)) (The ESPRIT Study Group; Algra A. Medium intensity oral **anticoagulants versus aspirin** after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol. 2007 Feb;6(2):115-24. Oral anticoagulants (target INR range 2.0-3.0) are not more effective than aspirin for secondary prevention after transient ischaemic attack or minor stroke of arterial origin. A possible protective effect against ischaemic events is offset by increased bleeding complications.) (Sudlow C. Dipyridamole with aspirin is better than aspirin alone in preventing vascular events after ischaemic stroke or TIA. BMJ. 2007 Apr 28;334(7599):901.)
161. Bhatt DL, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006 Jan 11;295(2):180-9.
162. Kumar S, Savitz S, Schlaug G, Caplan L, Selim M. **Antiplatelets, ACE inhibitors, and statins** combination reduces stroke severity and tissue at risk. Neurology. 2006 Apr 25;66(8):1153-8; discussion 1135.
163. Stein PD, et al.; PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006 Jun 1;354(22):2317-27. (InfoPOEMs: Patients with high or intermediate probability of pulmonary embolism (PE) and an abnormal result on computed tomographic angiography (CTA) or CTA combined with venous-phase imaging (CTA-CTV) are very likely to have PE. Those with low or intermediate probability and a negative CTA or CTA-CTV result are unlikely to have PE. All other patients -- that is, those with discordant findings between the clinical examination and CTA or CTA-CTV -- need either further testing or close clinical follow-up to confirm or exclude the diagnosis. Clinical evaluation using a validated decision rule remains an important part of the evaluation. (LOE = 2b))
164. Kearon C, et al.; Canadian Pulmonary Embolism Diagnosis Study (CANPEDS) Group. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial.Ann Intern Med. 2006 Jun 6;144(11):812-21.
165. Khurram Z, et al. Combination therapy with **aspirin, clopidogrel and warfarin** following coronary stenting is associated with a significant risk of bleeding. J Invasive Cardiol. 2006 Apr;18(4):162-4. In patients requiring warfarin therapy, the addition of dual antiplatelet therapy is associated with an approximately 7% major bleeding risk. Thus, novel regimens are needed to reduce the bleeding risk.
166. Staresinic AG, Sorkness CA, Goodman BM, Pigarelli DW. Comparison of outcomes using 2 delivery models of anticoagulation care. Arch Intern Med. 2006 May 8;166(9):997-1002.
167. Regier DA, et al. Cost-effectiveness of **self-managed versus physician**-managed oral anticoagulation therapy. CMAJ. 2006 Jun 20;174(13):1847-52.
168. Cokkinos DV, et al. Efficacy of antithrombotic therapy in chronic **heart failure**: The **HELAS** study. Eur J Heart Fail. 2006 Jun;8(4):428-32. Epub 2006 Jun 5. Overall embolic events are rare in heart failure regardless of treatment & treatment does not seem to affect outcome.(Massie BM, et al. The Warfarin and Antiplatelet Therapy in Heart Failure trial (**WATCH**): rationale, design, and baseline patient characteristics. J Card Fail. 2004 Apr;10(2):101-12.) (Cleland JG, The Warfarin/Aspirin Study in Heart failure (**WASH**): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J. 2004 Jul;148(1):157-64.)
169. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: Stroke risk stratification in patients taking aspirin. Circulation 2004; 110:2287-92. (InfoPOEMs: Clinical decision rules, especially the well-validated Stroke Prevention in Atrial Fibrillation (SPAF) score, can help identify which groups of patients with atrial fibrillation are likely and unlikely to benefit from anticoagulation. (LOE = 1a).If the risk of stroke is low (< 2%), the harms of anticoagulation generally outweigh the benefits. If the risk of stroke is high (> 4%), the benefits of anticoagulation outweigh the risks for most pts. If the patient's stroke risk is in between both extremes, we have to look carefully at his or her risk for hemorrhage.)
Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed comparison of stroke prevention treatments in individuals with **nonrheumatic atrial fibrillation**. Arch Intern Med. 2006 Jun 26;166(12):1269-75. A lower rate of ischemic stroke and a higher rate of major bleeding episodes were found to be associated with oral anticoagulants compared with aspirin, and both anticoagulants and aspirin were found to be associated with a reduction in the rate of stroke compared with placebo. Assuming a baseline risk of 51 ischemic stroke events per 1000 person-years, it can be estimated that adjusted standard-dose warfarin could prevent 28 (95% CrI, -37 to -19) ischemic strokes at the expense of 11 (95% CrI, -1 to +39) major or fatal bleeding episodes. In comparison, aspirin could prevent 16 (95% CrI, -26 to -5) ischemic strokes at the expense of 6 (95% CrI, -3 to +27) major or fatal bleeding episodes. (Fuster V, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. **ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation**: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) http://www.acc.org/qualityandscience/clinical/guidelines/atrial_fib/pdfs/AF_Full_Text.pdf developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006 Aug 15;114(7):e257-354.)
Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-867.
Estes NAM, Halperin JL, Calkins H, et al. ACC/AHA physician consortium 2008 clinical performance measures for adults with nonvalvular atrial fibrillation or atrial flutter. J Am Coll Cardiol 2008; 51:865-884.
Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ; American College of Chest Physicians. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). **Chest. 2008** Jun;133(6 Suppl):546S-592S.
Lip GYH, Nieuwlaat R, et al. Refi ning clinical risk stratifi cation for predicting stroke and thromboembolism in atrial fi brillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fi brillation. Chest 2010; 137: 263–72. (**CHA_2DS_2-VASc**)
ACCF- AHA-HRS Atrial Fibrillation 2011 Focused Update. Circulation 2011. http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181fa3cf4v1
Wann L. Samuel, Curtis Anne B., Ellenbogen Kenneth A., et al. **2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Circulation published February 14, 2011, doi:10.1161/CIR.0b013e31820f14c0 http://circ.ahajournals.org/cgi/reprint/CIR.0b013e31820f14c0v1
Olesen JB, Lip G, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:doi:10.1136/bmj.d124 (31 Jan 11). CHADS2 vs **CHA2DS2-VASc**
Cairns JA, Connolly S, McMurtry S, et al. CCS Atrial Fibrillation Guidelines Committee. **Canadian cardiovascular society atrial fibrillation guidelines 2010**: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol. 2011 Jan-Feb;27(1):74-90.
Hobbs F D R, Roalfe A K, Lip G Y H, et al. on behalf of Birmingham Atrial Fibrillation in the Aged (BAFTA) investigators and Midland Research Practices Consortium (MidReC) network. **Performance of stroke risk scores** in older people with atrial fibrillation not taking warfarin: comparative cohort study from BAFTA trial. BMJ 2011;342:doi:10.1136/bmj.d3653 (23 June 2011)
Klein D, Levine M. Are family physicians using the CHADS2 score?: is it useful for assessing risk of stroke in patients with atrial fibrillation? Can Fam Physician. 2011 Aug;57(8):e305-9.

TOP

170. Tung R, Kaul S, Diamond GA, Shah PK. Narrative review: **drug-eluting stents** for the management of restenosis: a critical appraisal of the evidence. Ann Intern Med. 2006 Jun 20;144(12):913-9.
171. Ricci S, Lewis S, Sandercock P; IST Collaborative Group. **Previous use of aspirin** and baseline stroke severity: an analysis of 17,850 patients in the International Stroke Trial. Stroke. 2006 Jul;37(7):1737-40. Epub 2006 Jun 1.
172. Goldstein LB, et al. American Heart Association; American Stroke Association Stroke Council. **Primary prevention of ischemic stroke**: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2006 Jun 20;113(24):e873-923. http://circ.ahajournals.org/cgi/reprint/113/24/e873
173. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's **sex** on risk of recurrent venous thromboembolism: a meta-analysis. Lancet. 2006 Jul 29;368(9533):371-8.
174. Hron G, Kollars M, Binder BR, Eichinger S, Kyrle PA. Identification of patients at low risk for recurrent venous thromboembolism by measuring **thrombin generation**. JAMA. 2006 Jul 26;296(4):397-402.
175. Munoz R, Duran-Cantolla J, Martinez-Vila E, et al. Severe **sleep apnea** and risk of ischemic stroke in the elderly. Stroke 2006; DOI: 10.1161/01.STR.0000236560.15735.0f. Available at: http://stroke.ahajournals.org
176. Goodacre S, et al. How should we **diagnose suspected deep-vein thrombosis**? QJM. 2006 Jun;99(6):377-88. (InfoPOEMs: The most cost-effective algorithm for managing patients with suspected deep vein thrombosis (DVT) was identified, although several are nearly as good. The main message is that the best approach uses a combination of a validated clinical decision rule, D-dimer test, and venous ultrasound. (LOE = 1b))
177. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of **low-dose aspirin** and clopidogrel in randomized controlled trials. Am J Med. 2006 Aug;119(8):624-38.
178. Park DW, Park SW, Park KH, Lee BK, Kim YH, Lee CW, Hong MK, Kim JJ, Park SJ. Frequency of and risk factors for **stent thrombosis** after drug-eluting stent implantation during long-term follow-up. Am J Cardiol. 2006 Aug 1;98(3):352-6. Epub 2006 Jun 12.
179. Almeida OP, Waterreus A, Hankey GJ. Preventing depression after stroke: Results from a randomized (**sertaline NS**) placebo-controlled trial. J Clin Psychiatry. 2006 Jul;67(7):1104-9.
180. Amarenco P, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (**SPARCL**) Investigators. High-dose **atorvastatin** after stroke or transient ischemic attack. N Engl J Med. 2006 Aug 10;355(6):549-59. (InfoPOEMs: High-dose atorvastatin reduces the risk of recurrent stroke, but does not improve mortality rates. A reduction in the risk of transient ischemic attack (TIA) or unclassified stroke was partially offset by an increase in the risk of hemorrhagic stroke. (LOE = 1b)) Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, Hennerici M, Simunovic L, Zivin JA, Welch KM; SPARCL Investigators. Effects of Intense Low-Density Lipoprotein Cholesterol Reduction in Patients With Stroke or Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2007 Oct 25; [Epub ahead of print] As compared with having no change or an increase in LDL-C, achieving a >/=50% lowering was associated with a greater reduction in the risk of stroke and major coronary events with no increase in brain hemorrhages. Goldstein LB, Amarenco P, Szarek M, Callahan A 3rd, Hennerici M, Sillesen H, Zivin JA, Welch KM; On behalf of the SPARCL Investigators. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology. 2007 Dec 12; [Epub ahead of print] Hemorrhagic stroke was more frequent in those treated with atorvastatin, in those with a hemorrhagic stroke as an entry event, in men, and increased with age. Those with Stage 2 hypertension at the last visit prior to the hemorrhagic stroke were also at increased risk. Treatment did not disproportionately affect the hemorrhagic stroke risk associated with these other factors. There were no relationships between hemorrhage risk and baseline low-density lipoprotein (LDL) cholesterol level or recent LDL cholesterol level in treated patients.
Sillesen H, Amarenco P, Hennerici MG, et al. on Behalf of the SPARCL Investigators. Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis. A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2008 Oct 9. [Epub ahead of print] Consistent with the overall results of the SPARCL intention to treat population, intense lipid lowering with atorvastatin reduced the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis. The carotid stenosis group may have greater benefit.
Amarenco P, Benavente O, Goldstein LB, et al.; on behalf of the SPARCL Investigators. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes. Stroke. 2009 Feb 19. [Epub ahead of print] Atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other cardiovascular events, irrespective of baseline ischemic stroke subtype.
Goldstein LB, Amarenco P, Zivin J, Messig M, Altafullah I, Callahan A, Hennerici M, Macleod MJ, Sillesen H, Zweifler R, Welch KM; on behalf of the SPARCL Investigators. Statin Treatment and Stroke Outcome in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2009 Sep 10.
Amarenco P, Goldstein LB, Sillesen H, Benavente O, Zweifler RM, Callahan A 3rd, Hennerici MG, Zivin JA, Welch KM; on behalf of the SPARCL Investigators. Coronary Heart Disease Risk in Patients With Stroke or Transient Ischemic Attack and No Known Coronary Heart Disease. Findings From the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2010 Jan 28.
181. Eisenstein EL, Anstrom KJ, Kong DF, et al. **Clopidogrel use** and long-term clinical outcomes after **drug-eluting stent** implantation. JAMA 2006; 297:DOI:10.1001/jama.297.2.joc60179. Available at: http://jama.ama-assn.org. The extended use of clopidogrel in patients with DES may be associated with a reduced risk for death and death or MI. However, the appropriate duration for clopidogrel administration can only be determined within the context of a large-scale randomized clinical trial.
182. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after **clopidogrel discontinuation** may limit the benefit of **drug-eluting stents**. J Am Coll Cardiol 2006; 48:2584-2591. The primary focus of this observation was cardiac death/MI. Rates of 18-month cardiac death/MI were not different between DES and BMS patients. However, after the discontinuation of clopidogrel (between months 7 and 18), these events occurred in 4.9% after DES vs 1.3% after BMS implantation. Target vessel revascularization remained lower after DES, resulting in similar rates of all clinical events for this time period (DES 9.3%, BMS 7.9%). Documented late stent thrombosis & related death/target vessel MI were twice as frequent after DES versus BMS (2.6% vs. 1.3%).
183. Harrington, RA, Califf RM, et al. Late ischemic events after **clopidogrel cessation** following drug-eluting stenting. Should we be worried? J Am Coll Cardiol 2006; 48:2592-2594.
184 Zeymer U, et al. Acute COronary Syndromes (**ACOS**) registry investigators. Effect of clopidogrel on 1-year mortality in hospital survivors of acute ST-segment elevation myocardial infarction in clinical practice. Eur Heart J. 2006 Nov;27(22):2661-6.
185. Shuchman M. Trading **restenosis for thrombosis**? New questions about **drug-eluting stents**. N Engl J Med. 2006 Nov 9;355(19):1949-52.
186. Shireman TI, et al. Development of a contemporary **bleeding risk model** for **elderly warfarin** recipients. Chest. 2006 Nov;130(5):1390-6.
187. Wald DS, Wald NJ, Morris JK, Law M. **Folic acid, homocysteine**, and cardiovascular disease: judging causality in the face of inconclusive trial evidence. BMJ. 2006 Nov 25;333(7578):1114-7.
188. Stone GW, et al. Bivalirudin for Patients with Acute Coronary Syndromes. (**ACUITY**)N Engl J Med. 2006 Nov 23;355(21):2203-2216. .
189. Hennerici M, Kay R, Bogousslavsky J, et al. Intravenous **ancrod** for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: A randomised controlled trial. Lancet 2006; 368:1871-1878.
190 Bos MJ, et al. High serum **C-reactive protein** level is not an independent predictor for stroke: the Rotterdam Study. Circulation. 2006 Oct 10;114(15):1591-8. Epub 2006 Oct 2.
191 Albert C. A randomized trial of **folic acid and B-vitamins** in the secondary prevention of cardiovascular events in women: Results from the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS). American Heart Association 2006 Scientific Sessions; November 13, 2006; Chicago, IL. PS.03.Late-Breaking Clinical Trials I. The Women's Antioxidant and Folic Acid Cardiovascular Study (**WAFACS**) enrolled 5,442 women at least 40 years of age, with established cardiovascular disease or at least 3 cardiovascular risk factors, who were already participating in a randomized study of antioxidant supplementation. Women who had been randomized to receive vitamins C and E plus beta-carotene were further randomized to receive either placebo or daily doses of 2.5 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12. Albert CM, Cook NR, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. (**WAFACS**) JAMA. 2008 May 7;299(17):2027-36. After 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B6, and vitamin B12 did not reduce a combined end point of total cardiovascular events among high-risk women, despite significant homocysteine lowering.
Cook NR, Albert CM, et al.. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study (**WACS**). Arch Intern Med. 2007 Aug 13-27;167(15):1610-8. There were no overall effects of ascorbic acid, vitamin E, or beta carotene on cardiovascular events among women at high risk for CVD.
192. Marcucci R, et al. Usefulness of **Aspirin Resistance** After Percutaneous Coronary Intervention for Acute Myocardial Infarction in Predicting One-Year Major Adverse Coronary Events. Am J Cardiol. 2006 Nov 1;98(9):1156-1159. Epub 2006 Aug 31. A significantly higher percentage of patients with MACEs had aspirin resistance (39.1% vs 23.2%, p <0.05).
193. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity **C-reactive protein**, **lipoprotein-associated phospholipase A2**, and outcome after ischemic stroke. Arch Intern Med. 2006 Oct 23;166(19):2073-80.
194. Wolf SL, et al. **EXCITE** Investigators. Effect of **constraint-induced movement therapy** on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006 Nov 1;296(17):2095-104. Among patients who had a stroke within the previous 3 to 9 months, CIMT produced statistically significant and clinically relevant improvements in arm motor function that persisted for at least 1 year.
Langhorne P, Bernhardt J, Kwakkel G. **Stroke rehabilitation**. Lancet. 2011 May 14;377(9778):1693-702.
Laver KE, George S, Thomas S, Deutsch JE, Crotty M. **Virtual reality** for stroke rehabilitation. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD008349. DOI: 10.1002/14651858.CD008349.pub2. We found limited evidence that the use of virtual reality and interactive video gaming may be beneficial in improving arm function and ADL function when compared with the same dose of conventional therapy.
195. Paterson JM, Mamdani M, Juurlink DN, et al. Clinical consequences of **generic warfarin substitution**: an ecological study. JAMA. 2006 Oct 25;296(16):1969-72.
196. Dolitzky M, et al. A randomized study of **thromboprophylaxis** in women with unexplained consecutive recurrent miscarriages. Fertil Steril. 2006 Aug;86(2):362-6. Epub 2006 Jun 12. (InfoPOEMs: Daily treatment with aspirin or enoxaparin (Lovenox) each results in a high live birth rate for women with history of unexplained recurrent miscarriages. The lack of a control group is an important limitation of this study. (LOE = 1b-))
197. Budnitz DS, et al. National surveillance of emergency department visits for outpatient **adverse drug events**. JAMA. 2006 Oct 18;296(15):1858-66. In an analysis of routine surveillance data from 63 US hospitals, adverse drug events accounted for an estimated 2.5% of emergency department visits for unintentional injury and 0.6% of visits for all causes. About a third were allergic reactions and another third were unintentional overdoses, particularly of drugs that need regular monitoring such as digoxin and warfarin. Insulin and warfarin were implicated in over a quarter of all serious events. Insulin, warfarin, and digoxin accounted for more than 40% of serious events among people aged over 65.
198. Palareti G et al. for the **PROLONG** Investigators. **D-dimer** testing to determine the duration of anticoagulation therapy. N Engl J Med 2006 Oct 26; 355:1780-9.
199. Sellier E, et al. Effectiveness of a guideline for venous **thromboembolism prophylaxis** in **elderly post-acute care** patients: a multicenter study with systematic ultrasonographic examination. Arch Intern Med. 2006 Oct 23;166(19):2065-71.
200. Mas JL, et al.; **EVA-3S** Investigators. **Endarterectomy versus stenting** in patients with symptomatic severe carotid stenosis. N Engl J Med. 2006 Oct 19;355(16):1660-71. In this study of patients with symptomatic carotid stenosis of 60% or more, the rates of death and stroke at 1 and 6 months were lower with endarterectomy than with stenting. (But await NIH **CREST** trial) (InfoPOEMs: Carotid stenting as currently practiced should be abandoned. It significantly increases the risk of stroke in patients with symptomatic carotid stenosis. (LOE = 1b))
201. Blann AD, Lip GY. **Venous thromboembolism**. BMJ. 2006 Jan 28;332(7535):215-9.
202. SPACE Collaborative Group; Ringleb PA, et al. 30 day results from the **SPACE** trial of **stent-protected angioplasty versus carotid endarterectomy** in symptomatic patients: a randomised non-inferiority trial. Lancet. 2006 Oct 7;368(9543):1239-47.
203. Howard VJ, et al. High **Prevalence of Stroke** Symptoms Among Persons Without a Diagnosis of Stroke or Transient Ischemic Attack in a General Population: The REasons for Geographic And Racial Differences in Stroke (**REGARDS**) Study. Arch Intern Med. 2006 Oct 9;166(18):1952-8.
204. Hernandez-Diaz S, Garcia Rodriguez LA. Cardioprotective **aspirin** users and their excess **risk of upper gastrointestinal complications**. BMC Med. 2006 Sep 20;4:22.

TOP

205. Fairhead JF, Rothwell PM. **Underinvestigation and undertreatment** of carotid disease in **elderly** patients with transient ischaemic attack and stroke: comparative population based study. BMJ. 2006 Sep 9;333(7567):525-7. Epub 2006 Jul 18.
206 Spertus JA, et al. Prevalence, predictors, and outcomes of **premature discontinuation** of **thienopyridine therapy** after **drug-eluting stent** placement: results from the **PREMIER** registry. Circulation. 2006 Jun 20;113(24):2803-9. Epub 2006 Jun 12.
207. Morice MC, et al. **REALITY** Trial Investigators. **Sirolimus- vs paclitaxel-eluting stents** in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. JAMA. 2006 Feb 22;295(8):895-904.
208. Montalescot G, et al. **STEEPLE** Investigators. **Enoxaparin versus unfractionated heparin** in elective percutaneous coronary intervention. N Engl J Med. 2006 Sep 7;355(10):1006-17.
209. Lagerqvist B, et al. Fast Revascularisation during InStability in Coronary artery disease (**FRISC-II**) Investigators. 5-year outcomes in the FRISC-II randomised trial of an **invasive versus a non-invasive** strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet. 2006 Sep 16;368(9540):998-1004. (InfoPOEMs: In this study of patients with non-ST-elevation acute coronary syndromes, patients treated invasively had fewer subsequent myocardial infarctions after 5 years than patients treated medically. The benefits are seen mainly in men, nonsmokers, and patients with at least 2 risk factors. (LOE = 1b))
210. George-Phillips KL, Bungard TJ. Use of **low-molecular-weight heparin** to bridge therapy in **obese** patients and in patients with **renal dysfunction**. Pharmacotherapy. 2006 Oct;26(10):1479-90.
211. Mirkhel A, et al. Frequency of **aspirin resistance** in a community hospital. Am J Cardiol. 2006 Sep 1;98(5):577-9. Epub 2006 Jun 30. In conclusion, this study estimates aspirin resistance prevalence and shows a strong association of **smoking** with platelet hyperactivity in a diverse community hospital population. Nonresponders to 81 mg/day frequently responded to 325 mg/day or to the addition of clopidogrel.
212. Casele H, et al. **Bone density changes** in women who receive **thromboprophylaxis** in pregnancy. Am J Obstet Gynecol. 2006 Oct;195(4):1109-13. In this study, the incidence of clinically significant bone loss (> or = 10%) in the femur in women who received thromboprophylaxis in pregnancy is approximately 2% to 2.5% and appears to be similar, regardless of whether the patient receives low molecular weight heparin therapy or unfractionated heparin therapy.
213. Alexander KP, Chen AY, Newby K, et al. **Sex** differences in major **bleeding with glycoprotein IIb/IIIa inhibitors.** Circulation 2006; 114: 1380-1387.
214. Levine RL, McCollum D, Hursting MJ. How frequently is venous thromboembolism in heparin-treated patients associated with **heparin-induced thrombocytopenia**? Chest. 2006 Sep;130(3):681-7. VTE is associated with HIT infrequently (< 1%) in LMWH-treated patients, yet often (approximately one in eight cases) in unfractionated heparin-treated patients. Physicians should suspect the possibility of HIT if VTE develops during or soon after unfractionated heparin use; if thrombocytopenia is present, alternative anticoagulation should be used until HIT is excluded.
215. Suk Danik J, Rifai N, Buring JE, Ridker PM. **Lipoprotein(a)**, measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. JAMA. 2006 Sep 20;296(11):1363-70.
216. Hallas J, et al. Use of **single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding**: population based case-control study. BMJ. 2006 Sep 19; [Epub ahead of print] Adjusted odds ratios associating drug use with upper gastrointestinal bleeding were 1.8 (95% confidence interval 1.5 to 2.1) for low dose aspirin, 1.1 (0.6 to 2.1) for clopidogrel, 1.9 (1.3 to 2.8) for dipyridamole, and 1.8 (1.3 to 2.4) for vitamin K antagonists. Corresponding figures for combined use were 7.4 (3.5 to 15) for clopidogrel and aspirin, 5.3 (2.9 to 9.5) for vitamin K antagonists and aspirin, and 2.3 (1.7 to 3.3) for dipyridamole and aspirin.
217. Gibson CM, et al.; **TIMI** Study Group. Usefulness of **Clopidogrel** in Abolishing the Increased Risk of Reinfarction Associated With **Higher Platelet Counts** in Patients With ST-Elevation Myocardial Infarction (Results from **CLARITY-TIMI 28**). Am J Cardiol. 2006 Sep 15;98(6):761-763. Epub 2006 Aug 2.
218. Laarman GJ, et al. **Paclitaxel-eluting versus uncoated stents** in primary percutaneous coronary intervention.N Engl J Med. 2006 Sep 14;355(11):1105-13.
219. Spaulding C, et al.; **TYPHOON** Investigators. **Sirolimus-eluting versus uncoated stents** in acute myocardial infarction. N Engl J Med. 2006 Sep 14;355(11):1093-104.
220. McQuaid KR, et al. Systematic review and meta-analysis of **adverse events of low-dose aspirin and clopidogrel** in randomized controlled trials. Am J Med. 2006 Aug;119(8):624-38. Aspirin increased the risk of major bleeding (RR=1.71; 95% confidence interval [CI], 1.41-2.08), major gastrointestinal (GI) bleeding (RR=2.07; 95% CI, 1.61-2.66), and intracranial bleeding (RR=1.65; 95% CI, 1.06-5.99) versus placebo. No difference between 75-162.5 mg/day and >162.5-325 mg/day aspirin versus placebo was seen. The absolute annual increases attributable to aspirin were major bleeding: 0.13% (95% CI, 0.08-0.20); major GI bleeding: 0.12% (95% CI, 0.07-0.19), intracranial bleeding: 0.03% (95% CI, 0.01-0.08). No study compared clopidogrel with placebo. One study showed increased major GI bleeding (but not non-GI bleeding endpoints) with aspirin versus clopidogrel (RR=1.45; 95% CI, 1.00-2.10). The absolute annual increase was 0.12% (95% CI, 0.00-0.28). CONCLUSIONS: Low-dose aspirin increases the risk of major bleeding by approximately 70%, but the absolute increase is modest: 769 patients (95% CI, 500-1250) need to be treated with aspirin to cause one additional major bleeding episode annually. Compared with clopidogrel, aspirin increases the risk of GI bleeding but not other bleeding; however, 883 patients (95% CI, 357-infinity) would need to be treated with clopidogrel versus aspirin to prevent one major GI bleeding episode annually at a cost of over 1 million dollars.
221. Laine L. Review article: **gastrointestinal bleeding with low-dose aspirin** - what's the risk? Aliment Pharmacol Ther. 2006 Sep 15;24(6):897-908. The single endoscopic trial assessing ulcers showed no significant difference in 12-week ulcer incidence: 6% of 381 given placebo vs. 7% of 387 given 81 mg enteric-coated aspirin. The relative risk of major gastrointestinal bleeding with low-dose aspirin in a meta-analysis of placebo-controlled trials of vascular protection was 2.07 (95% CI: 1.61-2.66). The absolute rate increase with aspirin above placebo was 0.12% per year (95% CI: 0.07-0.19%) with a number-needed-to-harm of 833 patients (95% CI: 526-1429). A meta-analysis of aspirin 50-1500 mg daily reported an odds ratio for any gastrointestinal bleeding of 1.68 (95% CI: 1.51-1.88) with an number-needed-to-harm at 1 year of 247. The relative risk of hospitalization for upper gastrointestinal bleeding with low-dose aspirin in a large Danish cohort study was 2.6 (95% CI: 2.2-2.9) with an absolute annual incidence of 0.6%. Factors that may increase the risk of gastrointestinal bleeding include prior history of ulcers or gastrointestinal bleeding, corticosteroid use, anticoagulant therapy and addition of a non-aspirin non-steroidal anti-inflammatory drug.
222. Algra A, et al. Oral **anticoagulants versus antiplatelet** therapy for preventing further vascular events after transient ischaemic attack or minor **stroke** of presumed arterial origin. Cochrane Database Syst Rev. 2006 Jul 19;3:CD001342.
223. Brophy JM, et al. A pharmacoepidemiology study of the interaction between **atorvastatin and clopidogrel** after percutaneous coronary intervention. Am Heart J. 2006 Aug;152(2):263-9.
224.Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of **bleeding** on prognosis in patients with acute coronary syndromes. Circulation 2006; 114: 774 - 782.
225.Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of **high clopidogrel loading doses** in patients with non-ST-segment elevation acute coronary syndromes. The **ALBION** (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. J Am Coll Cardiol 2006; 48:931-938.
226. Kearon C, et al., Gent M; Fixed-Dose Heparin (**FIDO**) Investigators. Comparison of fixed-dose weight-adjusted unfractionated **heparin and low-molecular-weight heparin** for acute treatment of venous thromboembolism. JAMA. 2006 Aug 23;296(8):935-42. (InfoPOEMs: In this study, fixed-dose weight-adjusted unfractionated heparin (UFH) administered subcutaneously was as safe and effective as low-molecular-weight heparin (LMWH) in the treatment of venous thromboembolism (VTE). Estimated drug costs for a 6-day course are $712 for LMWH and $37 for UFH. Most clinicians will want to see similar results from at least 1 additional well-done clinical trial, including more patients with symptomatic pulmonary embolism, before routinely treating VTE with subcutaneous UFH. (LOE = 1b))
227. Turrentine MA. Single-dose **fluconazole** for vulvovaginal candidiasis: impact on **prothrombin** time in women taking **warfarin**. Obstet Gynecol. 2006 Feb;107(2 Pt 1):310-3.
228. Mehta RH, et al. Acute **clopidogrel** use and outcomes in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. J Am Coll Cardiol. 2006 Jul 18;48(2):281-6. Epub 2006 Jun 21.
229. Quiroz R, et al. Comparison of a Single End Point to Determine Optimal Initial **Warfarin Dosing** (5 mg Versus 10 mg) for Venous Thromboembolism. Am J Cardiol. 2006 Aug 15;98(4):535-537. Epub 2006 Jun 28.
230. Meune C, et al. Effects of **aspirin and clopidogrel** on plasma brain **natriuretic peptide** in patients with heart failure receiving ACE inhibitors. Eur J Heart Fail. 2006 Aug 14; [Epub ahead of print]
231. O'donnell M, et al.; on behalf of the Investigators of the Registry of the Canadian Stroke Network. **Preadmission antithrombotic treatment** and **stroke severity** in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol. 2006 Sep;5(9):749-54.
232. Cox D, Maree AO, Dooley M, Conroy R, Byrne MF, Fitzgerald DJ. Effect of **enteric coating** on antiplatelet activity of low-dose **aspirin** in healthy volunteers. Stroke. 2006 Aug;37(8):2153-8. Epub 2006 Jun 22.
233. Dec/06 Health Canada: Association of increased mortality and risk of serious adverse events when prophylactic low-dose heparin is abruptly discontinued in patients to be started on Xigris [drotrecogin alfa (activated)] therapy for severe sepsis.
234. Aguilar M, Hart R. **Antiplatelet therapy** for preventing stroke in patients with non-valvular **atrial fibrillation** and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001925. Aspirin appears to reduce stroke and major vascular events in patients with non-valvular AF similar to its effect in other high-risk patients (ie by about 25%). For primary prevention among AF patients with an average stroke rate of 4% per year, about 10 strokes would likely be prevented yearly for every 1000 AF patients given aspirin.
235. Aguilar MI, Hart R. **Oral anticoagulants** for preventing stroke in patients with non-valvular **atrial fibrillation** and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001927. Treatment with adjusted-dose warfarin to achieved INRs of 2 to 3 reduces stroke, disabling or fatal stroke, and death for patients with non-valvular AF. The benefits were not substantially offset by increased bleeding among these participants in randomized clinical trials. Limitations include relatively short follow up and imprecise estimates of bleeding risks from the selected participants enrolled in the trials. For primary prevention of stroke in AF patients, about 25 strokes and about 12 disabling or fatal strokes would be prevented yearly for every 1000 atrial fibrillation patients given OACs.
236. Grines CL, Bonow RO, Casey DE. Prevention of premature **discontinuation of dual antiplatelet** therapy in patients with coronary artery **stents**. Circulation 2007; DOI: 10.1161/CIRCULATIONAHA.106.180944. Available at: http://www.circulationaha.org.
237. Pharmacist's Letter: FDA Statement of Coronary **Drug-Eluting Stents** Jan 07
238. Sarkiss MG, Yusuf SW, Warneke CL, et al. Impact of **aspirin** therapy in cancer patients with **thrombocytopenia** and acute coronary syndromes. Cancer. 2006 Dec 13;109(3):621-627 [Epub ahead of print] Therapy with ASA was associated with a significantly improved 7-day survival after ACS in cancer patients, with or without thrombocytopenia, and not associated with more severe bleeding.
239. Dentali F, Douketis JD, Lim W, Crowther M. Combined **Aspirin-Oral Anticoagulant Therapy Compared With Oral Anticoagulant Therapy Alone** Among Patients at Risk for Cardiovascular Disease: A Meta-analysis of Randomized Trials. Arch Intern Med. 2007 Jan 22;167(2):117-24. Our findings question the current practice of using combined aspirin-OAC therapy except in patients with a mechanical heart valve, given the questionable benefits in reducing thromboembolic events and the increased risk of major bleeding. (InfoPOEMs: **Except for patients with mechanical heart valves, the addition of aspirin to therapeutic warfarin doses does not decrease** the risk of death or of thromboembolism and does not increase the risk of a major bleed. (LOE = 1a))
240. The **ESPRIT** Study Group; Algra A. Medium **intensity oral anticoagulants versus aspirin** after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol. 2007 Feb;6(2):115-24.
241. Hull RD, et al. **Self-managed long-term low-molecular-weight heparin** therapy: the balance of benefits and harms. Am J Med. 2007 Jan;120(1):72-82.
242. Durga J, van Boxtel MPJ, Schouten EG, et al. Effect of 3-year **folic acid** supplementation on **cognitive function** in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 2007; 369:208-216. Folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age.
243. Biondi-Zoccai GG, et al. A systematic review and meta-analysis on the hazards of **discontinuing or not adhering to aspirin** among 50,279 patients at risk for coronary artery disease. Eur Heart J. 2006 Nov;27(22):2667-74. Epub 2006 Oct 19. Overall, aspirin non-adherence/withdrawal was associated with three-fold higher risk of major adverse cardiac events (OR=3.14 [1.75-5.61], P=0.0001). This risk was magnified in patients with intracoronary stents, as discontinuation of antiplatelet treatment was associated with an even higher risk of adverse events (OR=89.78 [29.90-269.60]).
244. Hodgson JM, et al. **Late stent thrombosis**: Considerations and practical advice for the use of drug-eluting stents: A report from the society for cardiovascular angiography and interventions drug-eluting stent task force. Catheter Cardiovasc Interv. 2007 Jan 11; [Epub ahead of print]
245. Serebruany VL, Atar D. **Assessment of bleeding events** in clinical trials-proposal of a new classification. Am J Cardiol. 2007 Jan 15;99(2):288-90. Epub 2006 Nov 27.
246. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing **drug-eluting vs. bare metal stents** in coronary artery disease: a meta-analysis. Eur Heart J. 2006 Dec;27(23):2784-814. Epub 2006 Oct 4. Drug-eluting stents for the treatment of coronary artery disease do not reduce total mortality when compared with bare metal stents. Preliminary evidence suggests that sirolimus- but not paclitaxel-eluting stents may lead to increased non-cardiac mortality.
247. Dubinsky RM, Lai SM. Mortality from combined **carotid endarterectomy and coronary artery bypass** surgery in the US. Neurology. 2007 Jan 16;68(3):195-7.

TOP

248. Burton JR, Burton I, Pearson GJ. **Clopidogrel-precipitated rhabdomyolysis** in a stable heart transplant patient. Ann Pharmacother. 2007 Jan;41(1):133-7. Epub 2007 Jan 2.
249. Millan M, et al. Increased body **iron stores** are associated with **poor** outcome after **thrombolytic treatment** in acute stroke. Stroke. 2007 Jan;38(1):90-5. Epub 2006 Nov 30.
250. Subramaniam RM, et al. **Diagnosis** of lower limb **deep venous thrombosis** in emergency department patients: performance of Hamilton and modified Wells scores. Ann Emerg Med. 2006 Dec;48(6):678-85. Epub 2006 Jun 9.
251. Ferretti G, et al. Is recurrent venous thromboembolism after therapy reduced by **low-molecular-weight heparin** compared with **oral anticoagulants**? Chest. 2006 Dec;130(6):1808-16.
252. Steffen LM, Folsom AR, Cushman M, et al. Greater **fish, fruit, and vegetable** intakes are related to lower incidence of venous thromboembolism. The Longitudinal Investigation of Thromboembolism Etiology. Circulation 2006; DOI:10.1161/CIRCULATIONAHA.106.641688.
253. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of **stroke** over the past 50 years. JAMA 2006; 296:2939-2946.
254. Health Canada Dec /06 Increased mortality and risk of serious adverse events when prophylactic **heparin is abruptly discontinued** in patients to be started on Xigris [drotrecogin alfa (activated)] for severe sepsis. Patients who had low dose heparin treatment abruptly discontinued when starting **Xigris** treatment had increased mortality and risk of serious adverse, including cardiac, gastrointestinal and venous thrombotic events. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index_e.html
255. Hoppener MR, et al. Low incidence of deep vein thrombosis after **knee arthroscopy** without thromboprophylaxis: a prospective cohort study of 335 patients. Acta Orthop. 2006 Oct;77(5):767-71. (InfoPOEMs:In patients undergoing knee arthroscopy, approximately 6% will develop a deep vein thrombosis (**DVT**) or symptomatic pulmonary embolism (PE). If these data are translatable to other settings, thromboprophylaxis would appear to be unnecessary. (LOE = 1b-))
256. Clarke P, et al. **Vitamin K prophylaxis for preterm** infants: a randomized, controlled trial of 3 regimens. Pediatrics. 2006 Dec;118(6):e1657-66. Epub 2006 Nov 13.
257. Bazzano LA, Reynolds K, Holder KN, He J. Effect of **folic acid** supplementation on risk of **cardiovascular diseases**: a meta-analysis of randomized controlled trials. JAMA. 2006 Dec 13;296(22):2720-6. Folic acid supplementation has not been shown to reduce risk of cardiovascular diseases or all-cause mortality among participants with prior history of vascular disease.
258. Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HG, Williamson IJ. Anticoagulation for **three** versus six months in patients with **deep vein thrombosis or pulmonary embolism**, or both: randomised trial. BMJ. 2007 Feb 8; [Epub ahead of print] For patients in the UK with deep vein thrombosis or pulmonary embolism and no known risk factors for recurrence, there seems to be little, if any, advantage in increasing the duration of anticoagulation from three to six months. Any possible advantage would be small and would need to be judged against the increased risk of haemorrhage associated with the longer duration of treatment with warfarin.
259. Qaseem A, Snow V, Barry P, et al.; Joint American Academy of Family Physicians/American College of Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Current **diagnosis of venous thromboembolism** in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. Ann Fam Med. 2007 Jan-Feb;5(1):57-62.
260. King CS, Holley AB, Jackson JL, Shorr AF, Moores LK. **Twice vs three times daily heparin** dosing for thromboembolism prophylaxis in the general medical population: A metaanalysis. Chest. 2007 Feb;131(2):507-16. BID heparin dosing causes fewer major bleeding episodes, while TID dosing appears to offer somewhat better efficacy in preventing clinically relevant VTE events. (InfoPOEMs: Until a direct comparison study is performed, the best information available suggests that although 3-times-daily dosing of 5000 units unfractionated heparin (UH) is more effective then twice-daily dosing (approximately 1 fewer pulmonary embolism (PE) and 2 fewer deep vein thromboses (DVTs) per 1000 patient days), it is associated with more major bleeds (1 per 2500 patient days). Remember that both regimens are better than doing nothing for high-risk hospitalized medical patients. (LOE = 1a-))
261. Eshaghian S, Kaul S, Amin S, Shah PK, Diamond GA. **Role of clopidogrel in managing atherothrombotic cardiovascular disease**. Ann Intern Med. 2007 Mar 20;146(6):434-41.
262. Francis CW. Clinical practice. **Prophylaxis for thromboembolism in hospitalized medical patients**. N Engl J Med. 2007 Apr 5;356(14):1438-44.
263. Adams HP Jr, Del Zoppo G, et al. Guidelines for the **Early Management of Adults With Ischemic Stroke**. A Guideline From the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007 Apr 12; [Epub ahead of print]
264. Segal JB, Streiff MB, Hoffman LV, Thornton K, Bass EB. **Management of venous thromboembolism: a systematic review** for a practice guideline. Ann Intern Med. 2007 Feb 6;146(3):211-22. Epub 2007 Jan 29. Review. Summary for patients in: Ann Intern Med. 2007 Feb 6;146(3):I43. (InfoPOEMs: Low-molecular-weight heparin (**LMWH**) is superior to unfractionated heparin (UFH) for deep venous thrombosis (DVT) and as effective as UFH for pulmonary embolism (PE). Outpatient DVT treatment is safe and cost effective for selected patients. Compression stockings should be provided to patients with DVT at discharge. (LOE = 1a))
Snow V, Qaseem A, Barry P, et al; American College of Physicians;American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. **Management** of venous thromboembolism: a clinical practice **guideline** from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2007 Feb 6;146(3):204-10. Epub 2007 Jan 29.
Douketis James, Tosetto Alberto, Marcucci Maura, et al. Patient-Level Meta-analysis: Effect of Measurement Timing, Threshold, and Patient Age on Ability of **D-Dimer Testing** to Assess Recurrence Risk After Unprovoked Venous Thromboembolism. *Ann Intern Med* October 19, 2010 153:523-531.
van der Velde EF, Toll DB, Ten Cate-Hoek AJ, et al. Comparing the diagnostic performance of 2 clinical decision rules (**Well's or Primary care**) to rule out deep vein thrombosis in primary care patients. Ann Fam Med. 2011 Jan-Feb;9(1):31-6.
265. McFadden EP, et al. **Late thrombosis** in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004 Oct 23-29;364(9444):1519-21.
266. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with **off-label** and **untested** use of **drug-eluting stents**. JAMA 2007; 297:1992-2000. In contemporary US practice, off-label and untested use of drug-eluting stents is common. Compared with standard use, relative early safety is lower with off-label use, and the long-term effectiveness is lower with both off-label and untested use. However, the absolute event rates remain low.
267. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following **off-label** use of **drug-eluting stents**. Event Registry. JAMA 2007; 297:2001-2009. Compared with on-label use, off-label use of drug-eluting stents is associated with a higher rate of adverse outcomes during the index admission and at 1 year. Stent thrombosis occurred predominantly in patients who underwent off-label drug-eluting stent implantation. Clinicians should be cautious about extrapolating the benefits of drug-eluting stents over bare-metal stents observed in randomized clinical trials to higher-risk clinical settings that have not been assessed.
268. Harrington RA, Ohman EM. The enigma of **drug-eluting stents**: Hope, hype, humility, and advancing patient care. JAMA 2007; 297:2028-2030.
269 Deeugenio D, Kolman L, Decaro M, et al. Risk of major bleeding with concomitant **dual antiplatelet** therapy after percutaneous coronary intervention in patients receiving long-term **warfarin** therapy. Pharmacotherapy. 2007 May;27(5):691-6. There were 14/97 (14 %) major bleeds in the active group (including 1 death) and 3/97 (3 %) major bleeds in the control group during the study period. Mean international normalized ratio at the time of bleeding was 3.4. **Hazard ratio for major bleeding was 5.0** in patients receiving warfarin therapy (95% confidence interval 1.4-17.8, p=0.012). Warfarin was an independent predictor of major bleeding after PCI in patients receiving dual antiplatelet therapy. Prospective data to further characterize the safety of concomitant warfarin and dual antiplatelet therapy after PCI are needed.
270 **NICE** April 2007: **Venous thromboembolism**: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in **inpatients** undergoing surgery http://guidance.nice.org.uk/CG46
271 Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007 Jan 27;369(9558):283-92. Existing prognostic scores for stroke risk after TIA validate well on multiple independent cohorts, but the unified **ABCD(2) score** is likely to be most predictive. Patients at high risk need immediate evaluation to optimise stroke prevention.
ABCD2 score http://www.ganfyd.org/index.php?title=ABCD2_score
272. **NICE Guidelines May 2007** Secondary prevention in primary and secondary care for patients following a **myocardial infarction.** http://guidance.nice.org.uk/CG48
273. Pharmacists Letter. Does a cranberry juice-warfarin interaction really exist? June 2007.
274. Campbell CL, Smyth S, Montalescot G, and Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease. A systematic review. JAMA 2007; 297:2018-2024. Currently available clinical data do not support the routine, long-term use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher dosages, which may be commonly prescribed, do not better prevent events but are associated with increased risks of gastrointestinal bleeding.
275 Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. **Major hemorrhage** and tolerability of **warfarin** in the first year of therapy among **elderly** patients with atrial fibrillation. Circulation. 2007 May 29;115(21):2689-96. Epub 2007 May 21. {InfoPOEMs: The risk of major hemorrhage among older patients taking warfarin is higher than commonly reported (13.7% during the first year for patients aged 80 and older) and particularly in the first 3 months of treatment. If the decision is made to use anticoagulation, patients should be aware of the risks, the early warning signs of bleeding, and should be followed up closely during the first 3 months in particular to assure that the international normalized ratio (INR) does not exceed 3.0. (LOE = 2b)}
276. Aguilar M, Hart R, Pearce L. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2007 Jul 18;3:CD006186. Adjusted-dose warfarin and related oral anticoagulants reduce stroke, disabling stroke and other major vascular events for those with non-valvular AF by about one third when compared with antiplatelet therapy.
277. Spencer FA, Lessard D, Emery C, et al. **Venous thromboembolism in the outpatient setting**. Arch Intern Med. 2007 Jul 23;167(14):1471-5. In all, 73.7% of patients developed VTE in the outpatient setting; a substantial proportion of these patients had undergone surgery (23.1%) or hospitalization (36.8%) in the preceding 3 months. More VTEs were diagnosed in the 3 months following hospitalization than during hospitalization. Efforts to improve in-hospital use of VTE prophylaxis may help decrease the incidence of outpatient VTE.
278. Wein L, Wein S, Haas SJ, Shaw J, et al. Pharmacological Venous **Thromboembolism Prophylaxis** in **Hospitalized Medical Patients**: A **Meta-analysis** of Randomized Controlled Trials. Arch Intern Med. 2007 Jul 23;167(14):1476-1486. A UFH dosage of 5000 U 3 times daily was more effective in preventing DVT than a UFH dosage of 5000 U twice daily when compared with the control (RR, 0.27; 95% CI, 0.20-0.36; vs RR, 0.52; 95% CI, 0.28-0.96). Both UFH and LMWH reduce venous thromboembolic risk in hospitalized medical patients, but neither agent alters mortality. When directly compared, LMWH is more effective in preventing DVT.
279. Warfarin Antiplatelet Vascular Evaluation Trial Investigators (**WAVE**), Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, Sussex B, Liu L, Guzman R, Cina C, Crowell R, Keltai M, Gosselin G. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007 Jul 19;357(3):217-27. In patients with **peripheral arterial disease**, the combination of an **oral anticoagulant** and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with an increase in life-threatening bleeding.
280. Philbrick JT, Shumate R, Siadaty MS, Becker DM. **Air travel** and venous thromboembolism: a systematic review. J Gen Intern Med. 2007 Jan;22(1):107-14. All travelers, regardless of VTE risk, should avoid dehydration and frequently exercise leg muscles. Travelers on a flight of less than 6 hours and those with no known risk factors for VTE, regardless of the duration of the flight, do not need DVT prophylaxis. Travelers with 1 or more risk factors for VTE should consider graduated compression stockings and/or LMWH for flights longer than 6 hours.
Chandra D, Parisini E, and Mozaffarian D. **Travel** and risk for venous thromboembolism. Ann Intern Med 2009.
281. Paciaroni M, et al. Efficacy and safety of anticoagulant treatment in **acute cardioembolic stroke**: a meta-analysis of randomized controlled trials. Stroke. 2007Feb;38(2):423-30. Epub 2007 Jan4. Our findings indicate that in patients with acute cardioembolic stroke, early anticoagulation is associated with a nonsignificant reduction in recurrence of ischemic stroke, no substantial reduction in death and disability, and an increased intracranial bleeding.
282. Arepally GM, Ortel TL. Clinical practice. **Heparin-induced thrombocytopenia**. N Engl J Med. 2006 Aug 24;355(8):809-17.
283. Aster RH, Bougie DW. **Drug-induced immune thrombocytopenia**. N Engl J Med. 2007 Aug 9;357(6):580-7.
284. Chen ZM, Sandercock P, Pan HC, Counsell C, et al. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of collaborative groups. Stroke. 2000 Jun;31(6):1240-9. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet. 1997 Jun 7;3

TOP

The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997 May 31;349(9065):1569-81.
van der Worp HB, van Gijn J. Clinical practice. **Acute ischemic stroke**. N Engl J Med. 2007 Aug 9;357(6):572-9.

285. Mant J, Hobbs FD, Fletcher K, et al. **Warfarin versus aspirin for stroke prevention in an elderly** community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, **BAFTA**): a randomised controlled trial. Lancet. 2007; 370:493-503.
286. Anderson JL, Adams CD, Antman EM, et al. **ACC/AHA 2007** guidelines for the management of patients with **unstable angina/non-ST-elevation myocardial infarction**. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2007; DOI:10.1016/j.jacc.2007.02.028. http://content.onlinejacc.org/cgi/content/full/50/7/e1. *Circulation* 2007; DOI:10.1161/CIRCULATIONAHA.107.185752. http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.185752.
American Academy of Family Physicians, American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, , Wright, R. Scott, Anderson, Jeffrey L., Adams, Cynthia D., et al. **2011 ACCF/AHA Focused Update** of the Guidelines for the Management of Patients With **Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. **J Am Coll Cardiol 2011 0: j.jacc.2011.02.009.** http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.02.009v1.pdf
287. Cayley WE Jr. **Preventing deep vein thrombosis in hospital inpatients**. BMJ. 2007 Jul 21;335(7611):147-51.
288. Keller T, et al. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005158. The available evidence demonstrates that the use of clopidogrel plus aspirin is associated with a reduction in the risk of cardiovascular events compared with aspirin alone in patients with acute non-ST coronary syndrome. In patients at high risk of cardiovascular disease but not presenting acutely, there is only weak evidence of benefit and hazards of treatment almost match any benefit obtained.
289. Delaney JA, Opatrny L, Brophy JM, & Suissa S. **Drug-drug interactions between antithrombotic** medications and the risk of gastrointestinal bleeding. Can Med Assoc J 2007; 177:347-351. The prescribing of acetylsalicylic acid with either clopidogrel (adjusted rate ratio [RR] 3.90, 95% confidence interval [CI] 2.78-5.47) or warfarin (adjusted RR 6.48, 95% CI 4.25-9.87) was associated with a greater risk of gastrointestinal bleeding than that observed with each drug alone. The same was true when a nonsteroidal anti-inflammatory drug was combined with either clopidogrel (adjusted RR 2.93, 95% CI 1.74-4.93) or warfarin (RR 4.60, 95% CI 2.77-7.64). Drug combinations involving antiplatelets and anticoagulants are associated with a high risk of gastrointestinal bleeding beyond that associated with each drug used alone.
Shehab Nadine; Sperling Laurence S.; Kegler Scott R.; et al. National Estimates of Emergency Department Visits for Hemorrhage-Related Adverse Events From Clopidogrel Plus Aspirin and From Warfarin. Arch Intern Med. 2010;170(21):1926-1933.
Rodríguez Luis A. García, Lin Kueiyu Joshua, Hernández-Díaz Sonia, et al. **Risk of Upper Gastrointestinal Bleeding** With Low-Dose Acetylsalicylic Acid Alone and in Combination With Clopidogrel and Other Medications. Circulation 123: 1108-1115; online doi:10.1161/CIRCULATIONAHA.110.973008
Labos C, Dasgupta K, Nedjar H, et al. Risk of bleeding associated with combined use of **selective serotonin reuptake inhibitors** and antiplatelet therapy following acute myocardial infarction. CMAJ 2011; DOI:10.1503/cmaj.100912.
290. Pharmacists Letter. Genetic testing to aid warfarin dosing. Oct 2007.
291. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, et al. ACC/AHA 2007 Guidelines on **Perioperative Cardiovascular Evaluation** and Care for **Noncardiac Surgery**. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation. 2007 Sep 27; [Epub ahead of print] http://content.onlinejacc.org/cgi/reprint/50/17/e159
292. De Schryver E, Algra A, van Gijn J. **Dipyridamole** for preventing stroke and other vascular events in patients with vascular disease. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001820. For patients who presented with arterial vascular disease, there was no evidence that dipyridamole, in the presence or absence of another antiplatelet drug reduced the risk of vascular death, though it reduces the risk of further vascular events. This benefit was found only in patients presenting after cerebral ischaemia. There was no evidence that dipyridamole alone was more efficacious than aspirin.
293. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; for the **FASTER** Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol. 2007 Oct 9; [Epub ahead of print] Immediately after TIA or minor stroke, patients are at high risk of stroke, were followed for 90 days, which might be reduced by using clopidogrel in addition to aspirin. The haemorrhagic risks of the combination of aspirin (162mg load then 81mg od) and clopidogrel (300mg load then 75mg od) do not seem to offset this potential benefit. We were unable to provide evidence of benefit of simvastatin (40mg od in evening) in this setting. This aggressive prevention approach merits further study.
294. Rothwell PM, Giles MF, Chandratheva A, et al; on behalf of the Early use of Existing Preventive Strategies for Stroke (**EXPRESS**) study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007 Oct 8; [Epub ahead of print] (Drugs used:ASA 300mg x1 then 75mg od, clopidogrel 300mg x1 then 75mg od x 30 days, simvastatin 40mg od, perindopril 4mg od +/- indapamide 1.25mg od) Early initiation of existing treatments after TIA or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke. Further follow-up is required to determine long-term outcome, but these results have immediate implications for service provision and public education about TIA and minor stroke.[300-mg loading dose and subsequent 75-mg daily dose of aspirin. This was combined with a 300-mg loading dose followed by a 75-mg daily dose of **clopidogrel for 30 days**.90-day stroke risk was 10.3% in phase 1 and 2.1% in phase 2 (adjusted hazard ratio, 0.20; P = .0001).]
295. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O, Mazighi M, Nifle C, Niclot P, Lapergue B, Klein IF, Brochet E, Steg PG, Leseche G, Labreuche J, Touboul PJ, Amarenco P. A transient ischaemic attack clinic with round-the-clock access (**SOS-TIA**): feasibility and effects. Lancet Neurol. 2007 Oct 8; [Epub ahead of print]
296. Wiviott SD, Braunwald E, McCabe CH, et al.; the **TRITON-TIMI 38** Investigators. **Prasugrel** versus Clopidogrel in atients with Acute Coronary Syndromes. N Engl J Med. 2007 Nov 4; [Epub ahead of print] In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups.
297. Anderson JL, Horne BD, Stevens SM, Grove AS, Barton S, Nicholas ZP, Kahn SF, May HT, Samuelson KM, Muhlestein JB, Carlquist JF; Couma-Gen Investigators. Randomized trial of **genotype-guided** versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation. 2007 Nov 27;116(22):2563-70. Epub 2007 Nov 7. An algorithm guided by pharmacogenetic and clinical factors improved the accuracy and efficiency of warfarin dose initiation. Despite this, the primary end point of a reduction in out-of-range INRs was not achieved. In subset analyses, pharmacogenetic guidance showed promise for wild-type and multiple variant genotypes.(**CYP2C9 *2 and CYP2C9 *3 and VKORC1C1173T**)
298. Ad2000 Collaborative Group. **Aspirin 75mg/d in Alzheimer's disease** (AD2000): a randomised open-label trial. Lancet Neurol. 2007 Dec 6; [Epub ahead of print] n=310. Although aspirin is commonly used in dementia, in patients with typical AD 2 years of treatment with low-dose aspirin has no worthwhile benefit and increases the risk of serious bleeds.
299. Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with **short-term interruption** of warfarin therapy. Arch Intern Med. 2008;168 63-69. Current guidelines from several European and US cardiology groups allow for the cessation of warfarin for up to 1 week in patients at risk for bleeding because of an invasive procedure such as dental surgery or colonoscopy. Although we still need more research to provide a definitive answer, this study does not refute these recommendations, finding that 0.59% of patients who stop treatment develop a thromboembolism within the subsequent 30 days. (LOE = 2b)
300. Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. **Aspirin "resistance**" and risk of cardiovascular morbidity: systematic review and meta-analysis. BMJ. 2008 Jan 17; [Epub ahead of print] Patients who are resistant to aspirin are at a greater risk of clinically important cardiovascular morbidity long term than patients who are sensitive to aspirin.
301. van Stralen KJ, Rosendaal FR, Doggen CJ. **Minor injuries** as a risk factor for venous thrombosis. Arch Intern Med. 2008 Jan 14;168(1):21-6.
302. Oliveira GBF, Crespo EM, Becker RC, et al. Incidence and prognostic significance of **thrombocytopenia** in patients treated with **prolonged heparin** therapy. Arch Intern Med. 2008;168:94-102.
303. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the **acute hospital care** setting (**ENDORSE** study): a multinational cross-sectional study. Lancet. 2008;371:387-394.
304. Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with **stopping clopidogrel after acute coronary syndrome**. JAMA. 2008 Feb 6;299(5):532-9.
305. Sconce E, Avery P, Wynne H, et al. **Vitamin K supplementation can improve stability** of anticoagulation for patients with unexplained variability in response to warfarin. Blood. 2007 Mar 15;109(6):2419-23. Epub 2006 Nov 16. Vitamin K supplementation can help achieve control of anticoagulation in adults with unexplained instability of response to warfarin. This may be a welcome relief to frustrated patients, clinicians, and staff. (LOE = 1b)
306. Schwarz UI, Ritchie MD, Bradford Y, Li C, Dudek SM, Frye-Anderson A, Kim RB, Roden DM, Stein CM. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med. 2008 Mar 6;358(10):999-1008. Initial variability in the INR response to warfarin was more strongly associated with genetic variability in the pharmacologic target of warfarin, **VKORC1**, than with CYP2C9.
307. Tapson VF. **Acute pulmonary embolism**. N Engl J Med. 2008 Mar 6;358(10):1037-52.
Douma Renée A., Mos Inge C.M., Erkens Petra M.G., et al. , for the Prometheus Study Group. Performance **of 4 Clinical Decision Rules in the Diagnostic Management of Acute Pulmonary Embolism**: A Prospective Cohort Study. Ann Intern Med June 7, 2011 154:709-718.
Lucassen W, Geersing GJ, Erkens PM, et al. **Clinical Decision Rules** for **Excluding Pulmonary Embolism**: A Meta-analysis. Ann Intern Med. 2011 Oct 4;155(7):448-60.
308. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant **erythropoietin and darbepoetin** administration for the treatment of cancer-associated anemia. JAMA. 2008 Feb 27;299(8):914-24.
309. L'Allier PL, et al. PREPAIR Study Investigators. **Clopidogrel 600-mg double loading** dose achieves stronger platelet inhibition than conventional regimens: results from the PREPAIR randomized study. J Am Coll Cardiol. 2008 Mar 18;51(11):1066-72.
310. Douketis JD, et al. The **risk for fatal pulmonary embolism after discontinuing anticoagulant** therapy for venous thromboembolism. Ann Intern Med. 2007 Dec 4;147(11):766-74. The risk for fatal PE is 0.19 to 0.49 events per 100 person-years for patients who have finished a course of anticoagulant therapy for a first episode of symptomatic VTE. The case-fatality rate for death from recurrent PE is 4% to 9%.
311. Thijs V, Lemmens R, Fieuws S. **Network meta-analysis**: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. Eur Heart J. 2008 Mar 17; [Epub ahead of print] In the network meta-analysis, all antiplatelet regimens (aspirin, aspirin plus dipyridamole, thienopyridines, and combination of aspirin and thienopyridines) were significantly more effective than placebo. The combination of aspirin and dipyridamole was more effective than thienopyridines (OR, 0.84; 95% CI, 0.73-0.97) and more effective than aspirin (OR, 0.78; 95% CI, 0.70-0.87). Our analysis suggests that the most powerful antiplatelet regimen in the prevention of serious vascular events after TIA or stroke is the **combination of aspirin and dipyridamole**.
312. O'Donnell MJ, Hankey GJ, Eikelboom JW. Antiplatelet Therapy for **Secondary Prevention** of Noncardioembolic Ischemic Stroke. A Critical Review. Stroke. 2008 Mar 27; [Epub ahead of print] For patients with ischemic stroke or transient ischemic attack caused by atherothromboembolism, immediate & long-term aspirin reduces the relative risk of recurrent stroke, MI, & death attributable to vascular causes. Oral anticoagulation is not more effective than aspirin. Long-term clopidogrel reduces the relative risk of stroke, MI, or vascular death by about 9% (0.3% to 16.5%) compared with aspirin. Any long-term benefits of clopidogrel combined with aspirin, compared with aspirin or clopidogrel alone, appear to be offset by increased major bleeding. The combination of aspirin and extended-release dipyridamole reduces the relative odds of stroke, MI, or vascular death by about 18% (odds ratio 0.82, 0.74 to 0.91) compared with aspirin alone without causing more bleeding. Cilostazole reduces the risk of stroke, MI, or vascular death by 39% compared to placebo. A large clinical trial comparing clopidogrel with the combination of aspirin and dipyridamole, in >20 000 patients with recent (<120 days) atherothrombotic ischemic stroke, is expected to report in 2008. Emerging antiplatelet therapies presently being evaluated for secondary prevention of atherothromboembolism include other P2Y12 ADP receptor antagonists (prasugrel, cangrelor, AZD 6140), thromboxane receptor antagonists (eg, S18886 - terutroban), and thrombin receptor (PAR-1) antagonists (eg, SCH530348).
313. Verro P, Gorelick PB, Nguyen D. **Aspirin plus dipyridamole** versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. Stroke. 2008 Apr;39(4):1358-63. Epub 2008 Mar 6. The combination of aspirin plus dipyridamole is more effective than aspirin alone in preventing stroke and other serious vascular events in patients with minor stroke and TIAs.
314. Perry DJ, Nokes TJ, Heliwell PS. Guidelines for the management of patients on **oral anticoagulants requiring dental surgery**. London (UK): British Committee for Standards in Haematology; 2007.

TOP

315. Dember LM, Beck GJ, Allon M, et al. Dialysis Access Consortium Study Group. Effect of **clopidogrel** on early failure of arteriovenous **fistulas for hemodialysis**: a randomized controlled trial. JAMA. 2008 May 14;299(18):2164-71. Clopidogrel reduces the frequency of early thrombosis of new arteriovenous fistulas but does not increase the proportion of fistulas that become suitable for dialysis.
316. Medical Letter. Treatment Guidelines: **Antiplatelet and Anticoagulant Drugs** May 2008 & **Antithrombotic Drugs Oct 2011**
317. Lubitz SA, Fischer A, Fuster V. **Catheter ablation** for atrial fibrillation. BMJ. 2008 Apr 12;336(7648):819-26.
318. Ovbiagele B, Cruz-Flores S, Lynn MJ, Chimowitz MI; Warfarin-Aspirin Symptomatic Intracranial Disease (**WASID**) Study Group. Early stroke risk after transient ischemic attack among individuals with symptomatic intracranial artery stenosis. Arch Neurol. 2008 Jun;65(6):733-7. Among individuals having intracranial atherosclerotic disease with TIA, most subsequent strokes in the territory of a stenotic intracranial artery occur early (ie, < or =90 days). Prompt management of TIA in patients having intracranial stenosis, particularly those demonstrating cerebral infarction on brain imaging, is indicated.
319. Rahme E, Dasgupta K, Burman M, et al. **Postdischarge thromboprophylaxis** and mortality risk after hip-or knee-replacement surgery. CMAJ. 2008 Jun 3;178(12):1545-54. Fewer than 1 in 5 elderly patients discharged home after a hip-or knee-replacement surgery received postdischarge thromboprophylaxis. Those prescribed these medications had a lower risk of short-term mortality.
320. Eriksson BI, Dahl OE, Rosencher N, et al..; RE-NOVATE Study Group. **Dabigatran** etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet. 2007 Sep 15;370(9591):949-56. Erratum in: Lancet. 2007 Dec 15;370(9604):2004. Oral dabigatran etexilate was as effective as enoxaparin in reducing the risk of venous thromboembolism after total hip replacement surgery, with a similar safety profile.
321. Eriksson BI, et al. **Rivaroxaban** versus enoxaparin for thromboprophylaxis after hip arthroplasty. **RECORD1** N Engl J Med. 2008 Jun 26;358(26):2765-75. A once-daily, 10-mg oral dose of rivaroxaban was significantly more effective for extended thromboprophylaxis than a once-daily, 40-mg subcutaneous dose of enoxaparin in patients undergoing elective total hip arthroplasty. The two drugs had similar safety profiles.
322. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S; the **RECORD2** Investigators. Extended duration **rivaroxaban** versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008 Jul 5;372(9632):31-39. Epub 2008 Jun 24.
323. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG; **RECORD3** Investigators. **Rivaroxaban** versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2776-86. **Rivaroxaban** was superior to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding.
Turpie AG, Lassen MR, Davidson BL, et al.; for the **RECORD4** Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009 May 1. Oral rivaroxaban 10 mg once daily for 10-14 days was significantly superior to subcutaneous enoxaparin 30 mg given every 12 h for the prevention of venous thromboembolism after total knee arthroplasty.
324. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (**CHADS2**) risk stratification scheme. Am Heart J. 2008 Jul;156(1):57-64. (Increased with age & in men)
325. Ebbing M, Bleie Ø, Ueland PM, Nordrehaug JE, Nilsen DW, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. (**WENBIT**) JAMA. 2008 Aug 20;300(7): 795-804. This trial did not find an effect of treatment with folic acid/vitamin B(12) or vitamin B(6) on total mortality or cardiovascular events. Our findings do not support the use of B vitamins as secondary prevention in patients with coronary artery disease.
326. Yusuf S, Diener HC, Sacco RL, et al. the **PRoFESS** Study Group. **Telmisartan** to Prevent Recurrent Stroke and Cardiovascular Events. N Engl J Med. 2008 Aug 27. [Epub ahead of print] Therapy with telmisartan initiated soon after an ischemic stroke & continued for 2.5 years did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes.
Diener HC, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. Lancet Neurol. 2008 Oct;7(10):875-84. Epub 2008 Aug 29. Disability due to recurrent stroke and cognitive decline in patients with ischaemic stroke were not different between the two antiplatelet regimens and were not affected by the preventive use of telmisartan.
327. Sacco RL, Diener HC, Yusuf S, et al. the PRoFESS Study Group. Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke. N Engl J Med. 2008 Aug 27. [Epub ahead of print] There were more major hemorrhagic events among ASA-ERDP recipients (419 [4.1%]) than among clopidogrel recipients (365 [3.6%]) (hazard ratio, 1.15; 95% CI, 1.00 to 1.32), including intracranial hemorrhage (hazard ratio, 1.42; 95% CI, 1.11 to 1.83). The trial did not meet the predefined criteria for noninferiority but showed similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke.
328. Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, Khatri P, Stettler B, Adeoye O, Moomaw CJ, Broderick JP, Woo D. **Warfarin** use leads to larger **intracerebral hematomas**. Neurology. 2008 Sep 30;71(14):1084-9.
329. Bhatt DL, Scheiman J, Abraham NS, et al. **ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID** use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol***.** 2008; *Circulation.* 2008; DOI: DOI: 10.1161/CIRCULATIONAHA.108.191087. Available at: http://circ.ahajournals.org
330. Verhovsek M, et al. Systematic review: **D-dimer** to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. Ann Intern Med. 2008 Oct 7;149(7):481-90, W94.
331. Belch J, MacCuish A, Campbell I, et al. Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (**POPADAD**) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008 Oct 16;337:a1840. doi: 10.1136/bmj.a1840. N=1276. (awaiting Ascend trial results)
This trial does not provide evidence to support the use of aspirin or antioxidants in primary prevention of cardiovascular events and mortality in the population with diabetes studied.
332. Aisen PS, Schneider LS, Sano M, et al. Alzheimer Disease Cooperative Study (ADCS). High-dose **B vitamin supplementation** and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA. 2008 Oct 15;300(15):1774-83.
This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.
333. Yeomans N, Lanas A, Labenz J, van Zanten SV, et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol. 2008 Oct;103(10):2465-73. Epub 2008 Jul 12. Twenty-seven patients (5.4%) in the placebo group developed a gastric or duodenal ulcer during 26 weeks' treatment compared with eight patients (1.6%) in the esomeprazole group (life-table estimates: 6.2%vs 1.8%; P= 0.0007).
Esomeprazole 20 mg once daily reduces the risk of developing gastric and/or duodenal ulcers and symptoms associated with the continuous use of low-dose aspirin in patients aged > or =60 yr without preexisting gastroduodenal ulcers.
334. Xarelto (**Rivaroxaban**). Pharmacist's Letter Nov,2008.
335. Jackevicius CA, Tu JV, Demers V, et al. Cardiovascular outcomes after a change in **prescription policy for clopidogrel**. N Engl J Med. 2008 Oct 23;359(17):1802-10. The removal of a prior-authorization program led to improvement in timely access to clopidogrel for coronary stenting and improved cardiovascular outcomes.
336. Kearon C, Julian JA, Kovacs MJ, et al. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: Results from a randomized trial. Blood. 2008 Sep 12. [Epub ahead of print]
We conclude that single or multiple thrombophilic defects are not associated with a higher risk of recurrent VTE during warfarin therapy.
337. Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ. 2008 Aug 26;179(5):417-26.
338. Ogawa H, Nakayama M, Morimoto T, et al. for the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (**JPAD**) Trial Investigators. Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes: A Randomized Controlled Trial. JAMA. 2008 Nov 9. [Epub ahead of print] In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.
339. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the **postthrombotic syndrome** after acute deep venous thrombosis. Ann Intern Med. 2008 Nov 18;149(10):698-707. The postthrombotic syndrome occurs frequently after DVT. Patients with extensive DVT and those with more severe postthrombotic manifestations 1 month after DVT have poorer long-term outcomes.
340. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. CMAJ. 2008 Jul 29;179(3):235-44. The risks of hemorrhage and thromboemboli are minimized at **international normalized ratios of 2-3**. Ratios that are moderately higher than this therapeutic range appear safe and more effective than subtherapeutic ratios.
341. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Sacco RL, Schwamm LH, American Heart Association, American Stroke Association. Update to the **AHA/ASA recommendations for the prevention of stroke** in patients with stroke and transient ischemic attack. Stroke 2008 May;39(5):1647-52. http://stroke.ahajournals.org/cgi/reprint/STROKEAHA.107.189063
342. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke [trunc]. Stroke 2006 Feb;37(2):577-617.
343. Surgical management of the primary care **dental patient on warfarin** NHS Mar 2007: http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q--A/Surgical-management-of-the-primary-care-dental-patient-on-warfarin/
Warfarin Therapy - Management During Invasive Procedures and Surgery Oct 2010. http://www.bcguidelines.ca/pdf/warfarin_invasive.pdf
Lillis T, Ziakas A, Koskinas K, et al. Safety of Dental Extractions During Uninterrupted Single or Dual Antiplatelet Treatment. Am J Cardiol. 2011 Jul 22.
Ahmed I, Gertner E. Safety of arthrocentesis and joint injection in patients receiving anticoagulation at therapeutic levels. Am J Med. 2012 Mar;125(3):265-9.
344. Marik PE, Plante LA. **Venous thromboembolic disease and pregnancy**. N Engl J Med. 2008 Nov 6;359(19):2025-33.
345. Roy P, Bonello L, Torguson R, et al. Impact of nuisance **bleeding on clopidogrel** compliance in patients undergoing intracoronary drug-eluting stent implantation. Am J Cardiol 2008; 102:1614-1617. Overall, 11.1% of patients with nuisance bleeding discontinued clopidogrel. Greater education and follow-up in this patient subset may lead to improved compliance with clopidogrel therapy
346. Claassen DO, Kazemi N, Zubkov AY, Wijdicks EF, Rabinstein AA. **Restarting anticoagulation** therapy after warfarin-associated **intracerebral hemorrhage**. Arch Neurol. 2008 Oct;65(10):1313-8. In patients who resume warfarin after an intracranial hemorrhage (ICH) associated with warfarin, 22% will have serious rebleeding. However, in those who don't resume warfarin, 20% will have venous thromboembolic events. This study demonstrates that it is not easy to care for patients who take warfarin. (LOE = 2b-)
347. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, Payot L, Brugier D, Cayla G, Beygui F, Bensimon G, Funck-Brentano C, Montalescot G. Cytochrome P450 2C19 polymorphism in young patients treated with **clopidogrel after myocardial infarction**: a cohort study. Lancet. 2008 Dec 22. [Epub ahead of print] The **CYP2C19*2** genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after myocardial infarction.
348. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L; the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic Determinants of Response to Clopidogrel and Cardiovascular Events. N Engl J Med. 2008 Dec 22. [Epub ahead of print] Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying **CYP2C19** loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention.
349. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. N Engl J Med. 2008 Dec 22. [Epub ahead of print] Among persons treated with clopidogrel, carriers of a reduced-function **CYP2C19 allele** had significantly lower level of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers.
350. Andersen LV, Vestergaard P, Deichgraeber P, Lindholt JS, Mortensen LS, Frost L. Warfarin for the prevention of systemic embolism in patients with **non-valvular atrial fibrillation**: a meta-analysis. Heart. 2008 Dec;94(12):1607-13. Epub 2008 Jan 20. **Warfarin** not only reduces the risk of stroke but is better than placebo and antiplatelet agents in prevention of systemic embolism in patients with non-valvular AF. Warfarin increases the risk of major bleeding compared with placebo but not compared with antiplatelet agents.
351. Pradhan AD, Cook NR, Manson JE, Ridker PM, Buring JE. A randomized trial (WHS) of low-dose **aspirin in the prevention of clinical type 2 diabetes** in women. Diabetes Care. 2009 Jan;32(1):3-8. Epub 2008 Oct 3. These data suggest that l
aspirin does not prevent the development of clinical type 2 diabetes in initially healthy women. These data suggest that long-term low-dose aspirin does not prevent the development of clinical type 2 diabetes in initially healthy women.

TOP

352. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are **not adequately anticoagulated**. Stroke. 2009 Jan;40(1):235-40. Epub 2008 Aug 28.
353. Lindsay P Bscn Phd, Bayley M Md, Hellings C Bsch, Hill M Msc Md, Woodbury E Bcom Mha, Phillips S Mbbs; (Canadian Stroke Strategy Best Practices and Standards Writing Group on behalf of the Canadian Stroke Strategy, a joint initiative of the Canadian Stroke Network and the Heart and Stroke Foundation of Canada*). **Canadian best practice recommendations for stroke care** (updated 2008). CMAJ. 2008 Dec 2;179(12):S1-S25. http://www.cmaj.ca/cgi/reprint/179/12/S1
354. Chassot PG, Delabays A, Spahn DR. **Perioperative** use of anti-platelet drugs. Best Pract Res Clin Anaesthesiol. 2007 Jun;21(2):241-56.
355. Juurlink DN, Gomes T, Ko D, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180(7). DOI:10.1503/cmaj.082001. (RxFiles Jan/09 PPIs May Reduce Effectiveness Of Clopidogrel)
356. Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. Ann Intern Med. 2009 Jan 20;150(2):73-83.
Warfarin-related **genotyping** is unlikely to be cost-effective for typical patients with nonvalvular atrial fibrillation, but may be cost-effective in patients at high risk for hemorrhage who are starting warfarin therapy.
357. Hacke W, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008 Sep 25;359(13):1317-29. As compared with placebo, intravenous **alteplase administered between 3 and 4.5 hours after** the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage.
358. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J 2009; DOIi:10.1093/eurheartj/ehp041. Available at: http://eurheartj.oxfordjournals.org.
359. Young AM, Billingham LJ, Begum G, et al. WARP Collaborative Group, UK. **Warfarin** thromboprophylaxis in cancer patients with central venous catheters (**WARP**): an open-label randomised trial. Lancet. 2009 Feb 14;373(9663):567-74. The findings show that prophylactic warfarin compared with no warfarin is not associated with a reduction in symptomatic catheter-related or other thromboses in patients with **cancer** and therefore we should consider newer treatments.
360. Crowther MA, Ageno W, Garcia D, et al. Oral **Vitamin K** Versus Placebo to Correct Excessive Anticoagulation in Patients Receiving Warfarin: A Randomized Trial. Ann Intern Med. 2009 Mar 3;150(5):293-300. Low-dose oral vitamin K did not reduce bleeding in warfarin recipients with INRs of 4.5 to 10.0.
361. **International Warfarin Pharmacogenetics Consortium**, Klein TE, Altman RB, Eriksson N, Gage BF, et al. Estimation of the **warfarin dose with clinical and pharmacogenetic data**. N Engl J Med. 2009 Feb 19;360(8):753-64.
362. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, et al. Development of a **risk score for atrial fibrillation** (Framingham Heart Study): a community-based cohort study. Lancet. 2009 Feb 28;373(9665):739-45. From clinical factors readily accessible in primary care, our risk score could help to identify risk of atrial fibrillation for individuals in the community, assess technologies or markers for improvement of risk prediction, and target high-risk individuals for preventive measures.
363. Berger JS, Brown DL, et al. **Aspirin use, dose**, and clinical outcomes in postmenopausal women with stable cardiovascular disease--the Women's Health Initiative Observational Study. (WHI Observational Study) *Circ Cardiovasc Qual Outcomes* 2009; 2:78-87.
364. US Preventive Services Task Force. **Aspirin for the prevention** of cardiovascular disease: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009; 150:396-404. http://www.ahrq.gov/clinic/uspstf/uspsasmi.htm
Wolff T, Miller T, Ko S. USPSTF. Aspirin for the primary prevention of cardiovascular events: an update of the **evidence** for the U.S. Preventive Services Task Force. Ann Intern Med. 2009 Mar 17;150(6):405-10.
365. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: Review and updated meta-analysis of **statins** for stroke prevention. Lancet Neurol 2009; 8:453-463.
366. van Walraven C, Hart RG, Connolly S, et al. Effect of **age** on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke. 2009 Apr;40(4):1410-6. Epub 2009 Jan 29.
367. Desai NR, Mega JL, Jiang S, et al. Interaction between cigarette **smoking** and clinical benefit of **clopidogrel**. J Am Coll Cardiol 2009; 53:1273-1278.
368. Chua D, Ignaszewski A. **Clopidogrel in acute coronary syndromes**. BMJ. 2009 Apr 14;338:b1180. doi: 10.1136/bmj.b1180.
369. Mahmoodi BK et al. **Microalbuminuria** and the risk of venous thromboembolism. JAMA 2009 May 6; 301:1790.
370. Sansing LH, Messe SR, Cucchiara BL, Cohen SN, Lyden PD, Kasner SE; CHANT Investigators. Prior antiplatelet use does not affect **hemorrhage growth** or outcome after **ICH**. Neurology. 2009 Apr 21;72(16):1397-402. Epub 2009 Jan 7.
371. Prandoni P, Prins MH, Lensing AW, et al. AESOPUS Investigators. Residual thrombosis on **ultrasonography to guide the duration** of anticoagulation in patients with deep venous thrombosis: a randomized trial. Ann Intern Med. 2009 May 5;150(9):577-85.
372. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. **Aspirin** for the prevention of cardiovascular events in patients with **peripheral artery disease (PAD)**: a meta-analysis of randomized trials. JAMA. 2009;301(18):1909-1919.
373. The ACTIVE Investigators. Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation. (**Active A**) N Engl J Med. 2009 Apr 3. [Epub ahead of print] In patients with atrial fibrillation for whom vitamin K-antagonist therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage. That in 1000 of AF patients treated for 3 years, 28 strokes would be prevented, 17 of which would be fatal or disabling, and 6 myocardial infarctions (MIs), at the cost of 20 nonstroke major bleeds, 3 of which would be fatal.
Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, et al; on behalf of the **ACTIVE** Steering Committee and Investigators. Net clinical benefit of adding **clopidogrel to aspirin** therapy in patients with atrial fibrillation for whom **vitamin K antagonists are unsuitable**. Ann Intern Med. 2011;155:579-86.
374. Toyoda K. Pharmacotherapy for the **secondary prevention of stroke**. Drugs. 2009;69(6):633-47. doi: 10.2165/00003495-200969060-00001.
375. Massie BM, Collins JF, Ammon SE, et al. **WATCH** Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation. 2009 Mar 31;119(12):1616-24. Epub 2009 Mar 16. n=1587. The primary outcome measure and the mortality data do not support the primary hypotheses that warfarin is superior to aspirin and that clopidogrel is superior to aspirin.
376. Dixon BS, Beck GJ, Vazquez MA, et al.; the DAC Study Group. Effect of **Dipyridamole plus Aspirin** on **Hemodialysis Graft Patency**. N Engl J Med. 2009 May 21;360(21):2191-2201. Treatment with dipyridamole plus aspirin had a significant but modest effect in reducing the risk of stenosis and improving the duration of primary unassisted patency of newly created grafts.
Haskal ZJ, Trerotola S, Dolmatch B, Schuman E, Altman S, Mietling S, Berman S, McLennan G, Trimmer C, Ross J, Vesely T. **Stent Graft** versus Balloon Angioplasty for Failing Dialysis-Access Grafts. N Engl J Med. 2010 Feb 11;362(6):494-503.
377. Adhiyaman V, Adhiyaman S. **Transient ischaemic attack**. BMJ. 2009 Mar 23;338:a2343. doi: 10.1136/bmj.a2343.
378. Friedland S, et al. **Colonoscopic polypectomy** in anticoagulated patients. World J Gastroenterol. 2009 Apr 28;15(16):1973-6. Polypectomy can be performed in therapeutically anticoagulated patients with lesions up to 1 cm in size with an acceptable bleeding rate.
379. Milionis HJ, Giannopoulos S, Kosmidou M, et al. **Statin therapy after first stroke** reduces 10-year stroke recurrence and improves survival. Neurology 2009; 72:1816-1822.
380. Collins R et al. for the Antithrombotic Trialists' (ATT) Collaboration. **Aspirin in the primary and secondary prevention** of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009 May 30; 373:1849.
381. Montalescot G et al. **Prasugrel** compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): Double-blind, randomised controlled trial. Lancet 2009 Feb 28; 373:723.
382. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, et al.; PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation. 2007 Dec 18;116(25):2923-32. Epub 2007 Dec 3.
383. Chandratheva A, Mehta Z, Geraghty OC, et al. Oxford Vascular Study. Population-based study of risk and predictors of **stroke in the first few hours after a TIA**. Neurology. 2009 Jun 2;72(22):1941-7. 384. Bousser MG. Antithrombotic agents in the prevention of ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl 3:12-9. Epub 2009 May 14.
384. Usman MH, Notaro LA, Nagarakanti R, et al. Combination antiplatelet therapy for secondary stroke prevention: enhanced efficacy or double trouble?. Am J Cardiol. 2009 Apr 15;103(8):1107-12. Epub 2009 Mar 4. In conclusion, the combination of aspirin and clopidogrel is associated with significantly **greater bleeding than** either aspirin (< or =325 mg/day) or clopidogrel alone. Aspirin plus ER-DP has a greater bleeding rate than clopidogrel but a lower rate than aspirin (< or =325 mg/day) alone.
385. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the **CRUSADE** (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines) **Bleeding Score**. Circulation. 2009 Apr 14;119(14):1873-82. Epub 2009 Mar 30.
386. Cohen M. Expanding the recognition and assessment of **bleeding events** associated with antiplatelet therapy in primary care. Mayo Clin Proc. 2009 Feb;84(2):149-60.
387. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; on behalf of the American Heart Association Stroke Council. Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous **Tissue Plasminogen Activator**. A Science Advisory From the American Heart Association/American Stroke Association. Stroke. 2009 May 28. [Epub ahead of print]
388. Holmes DR, Kereiakes DJ, Kleiman NS, et al. **Combining antiplatelet and anticoagulant therapies**. J Am Coll Cardiol 2009; 54:95-109.
389. Mega JL, Braunwald E, et al.; **ATLAS ACS-TIMI 46** study group. **Rivaroxaban** versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009 Jul 4;374(9683):29-38. Epub 2009 Jun 17.
390. CLOTS Trials Collaboration, Dennis M, Sandercock PA, et al. Effectiveness of thigh-length graduated **compression stockings** to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet. 2009 Jun 6;373(9679):1958-65. Epub 2009 May 26. These data do not lend support to the use of thigh-length GCS in patients admitted to hospital with **acute stroke**. National guidelines for stroke might need to be revised on the basis of these results.
391. Lind M, Boman K, Johansson L, et al. **Thrombomodulin** as a marker for bleeding complications during warfarin treatment. Arch Intern Med. 2009 Jul 13;169(13):1210-5.
392. Tischenko A, Gula LJ, Yee R, et al. **Implantation of cardiac rhythm devices** without interruption of oral anticoagulation compared with perioperative bridging with low-molecular weight heparin. Am Heart J 2009; 158:252-256.
393. Hermida RC, Ayala DE, Mojón A, Fernández JR. Ambulatory blood pressure control with **bedtime aspirin** administration in subjects with prehypertension. Am J Hypertens. 2009 Aug;22(8):896-903. Epub 2009 Apr 30.
394. Geersing GJ, Janssen KJ, Oudega R, Bax L, Hoes AW, Reitsma JB, Moons KG. Excluding venous thromboembolism using point of care **D-dimer** tests in outpatients: a diagnostic meta-analysis. BMJ. 2009 Aug 14;339:b2990.
395. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of **colorectal cancer**. JAMA. 2009 Aug 12;302(6):649-58. Regular aspirin use after the diagnosis of colorectal cancer is associated with lower risk of colorectal cancer-specific and overall mortality, especially among individuals with tumors that overexpress COX-2.
396. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy (**PAPI**). JAMA 2009; 302: 849-858.
397. O'Donoghue ML, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: An analysis of two randomised trials. (**TRITON-TIMI 38 & PRINCIPLE-TIMI 44)** Lancet 2009; DOI:10.1016/S0140-6736(09)61525-7.
398. Connolly, Stuart J., Ezekowitz, Michael D., Yusuf, Salim, et al., the **RE-LY** Steering Committee and Investigators, Dabigatran versus Warfarin in Patients with Atrial Fibrillation**.** N Engl J Med 2009 0: NEJMoa0905561. In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.
Wallentin L et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. Lancet 2010 Aug 29; [e-pub ahead of print].
Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010 Nov 6.
Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY trial. Circulation 2012.
399. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Anticoagulant and antiplatelet usage associates with mortality among **hemodialysis** patients. J Am Soc Nephrol. 2009 Apr;20(4):872-81. Epub 2009 Mar 18.
400. Wallentin L, Becker RC, Budaj A, et al. **PLATO** Investigators. **Ticagrelor** versus Clopidogrel in Patients with **Acute Coronary Syndromes**. N Engl J Med. 2009 Aug 30. (1° NNT=53/1yr, Major bleed [non-CABG:including fatal intracranial] NNH=143/1yr)
401. Holmes DR Jr, Kereiakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. **Combining antiplatelet and anticoagulant** therapies. J Am Coll Cardiol. 2009 Jul 7;54(2):95-109.

TOP

402. Singer DE, Chang Y, Fang MC, et al. The **net clinical benefit of warfarin** anticoagulation in atrial fibrillation. Ann Intern Med 2009; 151: 297-305.
403. Bezemer ID, van der Meer FJ, Eikenboom JC, et al. The value of **family history** as a risk indicator for venous thrombosis. Arch Intern Med. 2009 Mar 23;169(6):610-5.
404. Oake N, van Walraven C, Rodger MA, Forster AJ. Effect of an **interactive voice** response system on oral **anticoagulant management**. CMAJ. 2009 Apr 28;180(9):927-33.
405. De Berardis G, Sacco M, Strippoli GF, et al. **Aspirin for primary prevention** of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009 Nov 6;339:b4531. doi: 10.1136/bmj.b4531.
Calvin AD, Aggarwal NR, Murad MH, et al. **Aspirin** for the Primary Prevention of Cardiovascular Events: A systematic review and meta-analysis comparing patients with and without **diabetes**. Diabetes Care December 2009 32:2300-2306; doi:10.2337/dc09-1297.
Canadian 2008 Guidelines (Sept 2008): http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
ADA- American Diabetes Association. Standards of Medical Care in Diabetes—**2011 Diabetes Care.** January 2011 34:S11-S61; doi:10.2337/dc11-S011. http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html
406. Berger JS, Bhatt DL, Cannon CP, et al. The relative efficacy and safety of **clopidogrel in women and men**. A sex-specific collaborative meta-analysis. J Am Coll Cardiol 2009; 54:1935-1945.
407. Tanzilli G, Greco C, et al. Effectiveness of two-year clopidogrel + aspirin in abolishing the risk of very late thrombosis after drug-eluting stent implantation (from the **TYCOON** [two-year ClOpidOgrel need] study). Am J Cardiol. 2009 Nov 15;104(10):1357-61.
408. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the **left atrial appendage** versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomised non-inferiority trial. Lancet 2009; 374:534-542.
409. Yinon Y, Siu SC, Warshafsky C, et al. Use of **low molecular weight Heparin in pregnant** women with mechanical heart valves. Am J Cardiol. 2009 Nov 1;104(9):1259-63. Epub 2009 Sep 16.
410. Strazzullo Pasquale, D'Elia Lanfranco, et al. **Salt** intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567, doi: 10.1136/bmj.b4567 (24 November 2009).
411. Sweetland Siân, Green Jane, Liu Bette, et al., on behalf of the **Million Women Study** collaborators. Duration and magnitude of the **postoperative risk** of venous thromboembolism in middle aged women: prospective cohort study. BMJ 2009;339:b4583, doi: 10.1136/bmj.b4583 (Published 3 December 2009)
412. **Thrombophillia testing**: may consider if neonatal thrombosis, recurrent thrombosis, first episode <40yr, family history esp if young first degree relative; Unusual presentation: cerebral, hepatic, mesenteric, or renal; or if warfarin skin necrosis; unexplained high PTT; or recurrent fetal loss, ITP, or SLE. Test may include: Antithrombin III measurement, Protein C antigen, Protein C activity, Protein S, Activated protein C resistance, antiphospholipid antibodies & lupus anticoagulant.
(Said JM et al. Inherited thrombophilia polymorphisms and pregnancy outcomes in nulliparous women. Obstet Gynecol 2010 Jan; 115:5.)
Shaheen K, Alraies MC, Alraiyes AH, et al. Factor V Leiden: How great is the risk of venous thromboembolism? Cleve Clin J Med. 2012 Apr;79(4):265-72.
413. Schulman, Sam, Kearon, Clive, Kakkar, Ajay K., et al. the **RE-COVER** Study Group, Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. N Engl J Med 2009 0: NEJMoa0906598 (Online Dec/09)
414. Sung JJ, Lau JY, Ching JY, et al. **Continuation of Low-Dose Aspirin in Peptic Ulcer Bleeding**: A Randomized Trial. Ann Intern Med. 2009 Nov 30. [Epub ahead of print]
415. Ay, H., Gungor, L., Arsava, E. M., et al. A **score** to predict **early risk of recurrence after ischemic stroke**. Neurology 2009 0: WNL.0b013e3181ca9cff.
A new tool to assess 90-day risk for ischemic stroke recurrence, the RRE-90 might help clinicians identify patients most in need of prompt follow-up. **RRE-90** (http://www.nmr.mgh.harvard.edu/RRE/
Tsivgoulis G et al. Multicenter external validation of the **ABCD2** score in triaging TIA patients. Neurology 2010 Apr 27; 74:1351.
Sheehan OC, Kyne L, Kelly LA, et al. Population-based study of **ABCD2** score, carotid stenosis, and atrial fibrillation for early stroke prediction after transient ischemic attack: the North Dublin TIA study. Stroke. 2010 May;41(5):844-50. Epub 2010 Mar 18.
Chandratheva A, Geraghty OC, Luengo-Fernandez R, et al. **ABCD2** score predicts severity rather than risk of early recurrent events after transient ischemic attack. Stroke. 2010 May;41(5):851-6.
Wijnhoud AD, Maasland L, Lingsma HF, et al. Prediction of major vascular events in patients with transient ischemic attack or ischemic stroke: a **comparison of 7 models**. Stroke. 2010 Oct;41(10):2178-85.
Merwick A, Albers GW, Amarenco P, et al. Addition of **brain and carotid imaging to the ABCD² score** to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. Lancet Neurol. 2010 Nov;9(11):1060-9.
Saposnik G, Kapral MK, Liu Y, et al; on behalf of the Investigators of the Registry of the Canadian Stroke Network and the Stroke Outcomes Research Canada (SORCan) Working Group. **IScore**: A Risk Score to Predict Death Early After Hospitalization for an Acute Ischemic Stroke. Circulation. 2011 Feb 22;123(7):739-749.
Perry JJ, Sharma M, Sivilotti ML, et al. Prospective validation of the **ABCD2 score** for patients in the emergency department with transient ischemic attack. CMAJ. 2011 Jul 12;183(10):1137-45.
Galvin R, Geraghty C, Motterlini N, et al. Prognostic value of the **ABCD(2)** clinical prediction rule: a systematic review and meta-analysis. Fam Pract. 2011 Aug;28(4):366-76.
Giles MF, Albers GW, Amarenco P, et al. Early stroke risk and **ABCD2 score** performance in tissue- vs time-defined TIA: A multicenter study. Neurology. 2011 Sep 27;77(13):1222-8.
Cancelli I, Janes F, Gigli GL, et al. Incidence of transient ischemic attack and early stroke risk: validation of the **ABCD2 score** in an Italian population-based study. Stroke. 2011 Oct;42(10):2751-7.
416. Banerjee S, Brown A, Hutton B, McGahan L, Asakawa K, Clark M, Severn M, Cox JL, Sharma M. Clopidogrel versus Other Antiplatelet Agents in the Secondary Prevention of Vascular Events in Adults with Cerebrovascular Disease: Clinical and Cost-Effectiveness Analyses. [Technology report number 123]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
417. Wardlaw JM, Murray V, Berge E, et al. **Thrombolysis** for acute ischaemic stroke. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD000213.
418. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of **bleeding** in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet. 2009 Dec 12;374(9706):1967-74.
Hansen Morten L.; Sorensen Rikke; Clausen Mette T.; et al. Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation. Arch Intern Med. 2010;170(16):1433-1441. In patients with AF, all combinations of warfarin, aspirin, and clopidogrel are associated with increased risk of nonfatal and fatal bleeding. Dual warfarin and clopidogrel therapy and triple therapy carried a more than 3-fold higher risk than did warfarin monotherapy. In patients with atrial fibrillation, adding multiple-drug therapy to prevent thromboembolism can greatly increase the risk for major bleeding, according to an *Archives of Internal Medicine* study. Investigators used Danish national databases to follow bleeding outcomes in some 80,000 patients with a discharge diagnosis of first-time atrial fibrillation. All patients had at least one postdischarge prescription for warfarin, aspirin, or clopidogrel. After a follow-up averaging 3.3 years, the relative risks associated with various regimens for fatal and nonfatal bleeding, relative to warfarin monotherapy, were as follows: Aspirin, 0.96 , Clopidogrel, 1.45, Clopidogrel + aspirin, 1.91, Warfarin + aspirin= 1.75, Warfarin + clopidogrel= 3.57, Warfarin + clopidogrel + aspirin= 4.03.
419. Cheetham TC, Levy G, Niu F, Bixler F. Gastrointestinal safety of nonsteroidal antiinflammatory drugs and selective **cyclooxygenase-2** inhibitors in patients on warfarin. Ann Pharmacother. 2009 Nov;43(11):1765-73. Epub 2009 Oct 6.
420. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of **aspirin** against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1983 Aug 18;309(7):396-403.
421. Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. **Pulmonary embolism in pregnancy**. Lancet. 2009 Nov 2. [Epub ahead of print]
422. Barkun AN, Bardou M, Kuipers EJ, et al. and for the **International Consensus** Upper Gastrointestinal Bleeding Conference Group. Management of Patients With **Nonvariceal Upper Gastrointestinal Bleeding**. Ann Intern Med January 19, 2010 152:101-113.
423. Glader EL, Sjölander M, Eriksson M, Lundberg M. Persistent use of **secondary preventive drugs declines** rapidly during the first 2 years after stroke. Stroke 2010; DOI: 10.1161/STROKEAHA.109.566950.
424. Madhwal S, Lincoff AM, Rolston DDK. Should patients on long-term **warfarin take aspirin** for heart disease? Cleveland Clin J Med 2008;75:206-08.
425. National Institute for Health and Clinical Excellence (NICE). **Rivaroxaban** for the prevention of venous thromboembolism after total hip or total knee replacement in adults. London (UK): NICE; 2009 Apr. 23 p. (Technology appraisal guidance; no. 170).
426. Johnson Stacy A.; Stevens Scott M.; Woller Scott C.; et al. Risk of Deep Vein Thrombosis Following a Single Negative **Whole-Leg Compression Ultrasound**: A Systematic Review and Meta-analysis. JAMA. 2010;303(5):438-445.
427. Pai M, Douketis JD. **Preventing venous thromboembolism in long-term** care residents: Cautious advice based on limited data. Cleve Clin J Med. 2010 Feb;77(2):123-30.
428. Holmes, Michelle D., Chen, Wendy Y., Li, Lisa, et al. **Aspirin** Intake and Survival **After Breast Cancer**. J Clin Oncol 2010 0: JCO.2009.22.7918.
429. Breet NJ, van Werkum JW, Bouman HJ et al. Comparison of **platelet function tests** in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010; 303:754-762.
430. Hill J, Treasure T; National Clinical Guideline Centre for Acute and Chronic Conditions. **Reducing the risk of venous thromboembolism in patients admitted to hospital**: summary of **NICE** guidance. BMJ. 2010 Jan 27;340:c95. doi: 10.1136/bmj.c95.
NICE Jan 2010: Venous thromboembolism: reducing the risk Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. http://www.nice.org.uk/nicemedia/live/12695/47195/47195.pdf
431. Cannon CP, Harrington RA, James S, et al. Comparison of **ticagrelor** with clopidogrel in patients with a planned **invasive strategy** for acute coronary syndromes (PLATO): A randomised double-blind study Lancet 2009; DOI:10.1016/S0140-6736(09)62191-7.
432. Decousus H, Quéré I, Presles E, et al; POST (Prospective Observational Superficial Thrombophlebitis) Study Group. **Superficial** venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. Ann Intern Med. 2010Feb16;152(4):218-24.
433. Fowkes FGR, Price JF, Steward MCW, et al. **Aspirin** for prevention of cardiovascular events in a general population screened for a low **ankle brachial index**. A randomized controlled trial. (**AAA**) JAMA 2010; 303:841-848.
434. Prabhakaran Shyam; Rivolta Juan; Vieira Julio R.; et al. Symptomatic **Intracerebral Hemorrhage** Among Eligible **Warfarin**-Treated Patients Receiving Intravenous **Tissue Plasminogen Activator** for Acute Ischemic Stroke. Arch Neurol. 2010;0(2010):2010.25.
435. Mak A, Cheung MW, Cheak AA, Ho RC. Combination of **heparin and aspirin** is superior to aspirin alone in enhancing live births in patients with **recurrent pregnancy loss and positive anti-phospholipid antibodies**: a meta-analysis of randomized controlled trials and meta-regression. Rheumatology (Oxford). 2010 Feb;49(2):281-8. Epub 2009 Dec 4.
436. Gurbel PA, Bliden KP, Butler K, et al. Response to **Ticagrelor in Clopidogrel** Nonresponders and Responders and Effect of Switching Therapies. The **RESPOND** Study. Circulation. 2010 Mar 1.
437. Würtz M, Grove EL, Kristensen SD, Hvas AM. The antiplatelet effect of **aspirin is reduced by proton pump inhibitors** in patients with coronary artery disease. Heart. 2010 Mar;96(5):368-71. Epub 2009 Nov 11.
438. Snoep JD, Hovens MM, Pasha SM, Frölich M, Pijl H, Tamsma JT, Huisman MV. **Time-dependent** effects of low-dose **aspirin** on plasma renin activity, aldosterone, cortisol, and catecholamines. Hypertension. 2009 Nov;54(5):1136-42.
439. Sawhney MS, McDougall H, Nelson DB, Bond JH. Fecal **Occult Blood Test** in Patients on Low-Dose Aspirin, Warfarin, Clopidogrel, or Non-steroidal Anti-inflammatory Drugs. Dig Dis Sci. 2010 Mar 3. [Epub ahead of print] Anticoagulants and antiplatelet medications lower the positive-predictive-value of FOBT for advance colonic neoplasia and should be stopped if clinically feasible prior to stool collection.
440. Park SJ, Park DW, Kim YH, et al. Duration of **Dual Antiplatelet** Therapy after Implantation of Drug-Eluting Stents. (**Real-Late, Zest-Late-RCT**) N Engl J Med. 2010 Mar 15. n=2701, 19.2 months, Primary: clopidogrel + ASA 1.8% vs ASA 1.2% NS.
441. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of **drug-eluting and bare metal stents**: comprehensive meta-analysis of randomized trials and observational studies. Circulation. 2009 Jun 30;119(25):3198-206.
442. Hankey GJ, Eikelboom JW. **Antithrombotic** drugs for patients with **ischaemic stroke and transient ischaemic attack** to prevent recurrent major vascular events. Lancet Neurol. 2010 Mar;9(3):273-84.
443. International Carotid Stenting Study. Carotid artery **stenting** compared with **endarterectomy** in patients with symptomatic carotid stenosis (International Carotid Stenting Study-**ICSS**): an interim analysis of a randomised controlled trial. Lancet. 2010 Feb 25.
444. Diedler J, Ahmed N, Sykora M, et al. Safety of intravenous **thrombolysis for acute ischemic stroke** in patients receiving antiplatelet therapy at stroke onset. Stroke. 2010 Feb;41(2):288-94. Epub 2010 Jan 7.
445. Kaandorp, Stef P., Goddijn, Mariette, van der Post, Joris A.M., et al. Aspirin plus Heparin or Aspirin Alone in Women with **Recurrent Miscarriage**. N Engl J Med 2010 0: NEJMoa1000641.
Neither aspirin combined with nadroparin nor aspirin alone improved the live-birth rate, as compared with **placebo**, among women with unexplained recurrent miscarriage.
446. Chan, Wee-Shian, Spencer, Frederick A, Ginsberg, Jeffrey S. **Anatomic distribution of deep vein thrombosis in pregnancy**. CMAJ 2010 0: cmaj.091692.
447. Seshadri S, Beiser A, Pikula A, et al. **Parental occurrence of stroke** and risk of stroke in their **children**: the Framingham study. Circulation 2010; 121:1304-1312.
448. Fischer HD, Juurlink DN, Mamdani MM, et al. **Hemorrhage during warfarin therapy associated with cotrimoxazole** and other urinary tract anti-infective agents: A population-based study. Arch Intern Med 2010; 170:617-621.
449. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 111: **Inherited thrombophilias in pregnancy**. Obstet Gynecol. 2010 Apr;115(4):877-87. (& **2011 Sep**.)
450. Stockl Karen M.; Le Lisa; Zakharyan Armen; et al. Risk of Rehospitalization for Patients Using **Clopidogrel With a Proton Pump Inhibitor**. Arch Intern Med. 2010;170(8):704-710.

TOP

451. Ho PM, Tsai TT, Maddox TM, et al. **Delays in filling clopidogrel** prescription after hospital discharge and adverse outcomes after drug-eluting stent implantation. Implications for transitions of care. Circ Cardiovasc Qual Outcomes 2010.
452. Schelleman H, Bilker WB, Brensinger CM, et al. **Fibrate/statin initiation in warfarin** users and gastrointestinal bleeding risk. Am J Med. 2010 Feb;123(2):151-7.
453. Di Sciascio G, Patti G, Pasceri V, et al. **Clopidogrel** reloading in patients undergoing percutaneous coronary intervention on chronic clopidogrel therapy: results of the **ARMYDA-4 RELOAD** (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty) randomized trial. Eur Heart J 2010
454. Salazar CA, Malaga G, Malasquez G. **Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins** for prevention of venous thromboembolism following total hip or knee replacement. Cochrane Database Syst Rev. 2010 Apr 14;4:CD005981.
455. Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of **venous thromboembolism in patients with liver disease**: a nationwide population-based case-control study. Am J Gastroenterol. 2009 Jan;104(1):96-101.
456. Garcia-Alamino JM, Ward AM, Alonso-Coello P, et al. **Self-monitoring** and self-management of oral anticoagulation. Cochrane Database Syst Rev. 2010 Apr 14;4:CD003839.
457. Meyer G, Roy PM, Gilberg S, Perrier A. **Pulmonary embolism**. BMJ. 2010 Apr 13;340:c1421. doi: 10.1136/bmj.c1421.
Agnelli, Giancarlo, Becattini, Cecilia. **Acute Pulmonary Embolism**. N Engl J Med 2010 363: 266-274.
458. Brott, Thomas G., Hobson, Robert W., II, Howard, George, et al. the **CREST** Investigators, **Stenting versus Endarterectomy** for Treatment of Carotid-Artery Stenosis. N Engl J Med 2010 0: NEJMoa0912321.
459. Cohen Danielle, Berger Stefan P, Steup-Beekman Gerda M et al., Diagnosis and management of the **antiphospholipid syndrome**. BMJ 2010;340
460. Lovelock CE, Cordonnier C, Naka H, et al. Antithrombotic Drug Use, **Cerebral Microbleeds**, and **Intracerebral Hemorrhage**: A Systematic Review of Published and Unpublished Studies. Stroke. 2010 Jun;41(6):1222-1228. Epub 2010 Apr 29
461. Gutierrez A, Rao SV. Incidence, outcomes, and management of **bleeding** in non-ST-elevation acute coronary syndromes Cleveland Clinic Journal of Medicine 2010; 77(6):369-379; doi:10.3949/ccjm.77a.09142.
462. ASGE Standards of Practice Committee, Anderson MA, Ben-Menachem T, Gan SI, et al. Management of antithrombotic agents for **endoscopic procedures**. Gastrointest Endosc 2009 Dec;70(6):1060-70.
463. Paikin Jeremy S., Wright Douglas S., Crowther Mark A. et al; **Triple Antithrombotic Therapy in Patients With Atrial Fibrillation and Coronary Artery Stents** Circulation 121: 2067-2070, doi:10.1161/CIRCULATIONAHA.109.924944
464. Varis J, Kuusniemi K, Järveläinen H. **Cholesterol microembolization syndrome**: a complication of anticoagulant therapy. CMAJ. 2010 Jun 15;182(9):931-3.
465. O'Donnell MJ, Xavier D, Liu Lisheng, et al; and on behalf of the **INTERSTROKE** investigators, Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study, The Lancet, Online 17 June 2010
466. Mehran R, Pocock SJ, Nikolsky E et al. A **risk score to predict bleeding** in patients with acute coronary syndromes (**ACS**). J Am Coll Cardiol. 2010 Jun 8;55(23):2556-66.
Ducrocq G, Wallace JS, Baron G, et al; REACH Investigators. **Risk score to predict serious bleeding** in stable outpatients with or at risk of atherothrombosis. Eur Heart J. 2010;31:1257-65.
Pisters R, Lane DA, Nieuwlaat R, et al. A novel userfriendly score (**HAS-BLED**) to assess one-year risk of major bleeding in atrial fi brillation patients: The Euro Heart Survey. Chest 2010; published online March 18. DOI:10.1378/chest.10-013 4.
467. Runchey S, McGee S. Does this patient have a hemorrhagic stroke?: clinical findings distinguishing **hemorrhagic stroke from ischemic stroke**. JAMA. 2010 Jun 9;303(22):2280-6.
468. Crowther MA, Garcia D, Ageno W, et al. **Oral vitamin K** effectively treats international normalised ratio (**INR**) values in **excess of 10**. Results of a prospective cohort study. Thromb Haemost. 2010 May 10;104(1).
469. Garcia D, Crowther MA, Ageno W. **Practical management of coagulopathy associated with warfarin**. BMJ. 2010 Apr 19;340:c1813. doi: 10.1136/bmj.c1813.
470. Collins L, Seraj S. Diagnosis and treatment of **venous ulcers**. Am Fam Physician. 2010 Apr 15;81(8):989-96.
471. Floyd JS, Serebruany VL. **Prasugrel as a potential cancer** promoter: Review of unpublished data. Arch Intern Med 2010; 170:1078-1080.
472. Dodd JM, McLeod A, Windrim RC, et al. Antithrombotic therapy for improving maternal or infant health outcomes in women considered at **risk of placental dysfunction**. Cochrane Database Syst Rev. 2010 Jun 16;6:CD006780.
473. Hull Russell D., Schellong, Sebastian M. Tapson, Victor F. Et al.and for the EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study. **Extended-Duration Venous Thromboembolism** Prophylaxis in Acutely Ill Medical Patients With Recently Reduced Mobility: A Randomized Trial. Ann Intern Med July 6, 2010 153:8-18. (see also ACPJC AnnIntMed Nov,2010)
474. Hulot JS, Collet JP, Silvain J, et al. Cardiovascular risk in **clopidogrel**-treated patients according to cytochrome **P450 2C19*2** loss-of-function allele or proton pump inhibitor co-administration. A systematic meta-analysis. J Am Coll Cardiol 2010; 56:134-143.
475. Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: **case-fatality rates of recurrent venous thromboembolism and major bleeding events** among patients treated for venous thromboembolism. Ann Intern Med. 2010 May 4;152(9):578-89.
476. Iorio A, Basileo M, Marcucci M, et al. **Influenza vaccination and vitamin K antagonist** treatment: a placebo-controlled, randomized, double-blind crossover study. Arch Intern Med. 2010 Apr 12;170(7):609-16.
477. Lee M, Hong KS, Chang SC, et al. Efficacy of homocysteine-lowering therapy with **folic Acid in stroke prevention**: a meta-analysis. Stroke. 2010 Jun;41(6):1205-12. Epub 2010 Apr 22.
478. Bushnell CD.; Zimmer LO.; Pan W; et al. for the **Adherence** Evaluation After Ischemic Stroke-Longitudinal Investigators. Persistence With Stroke Prevention Medications 3 Months After Hospitalization. Arch Neurol. 2010;0(2010):archneurol.2010.190.
479. Holmes David R., Jr, Dehmer Gregory J., Kaul Sanjay, et al. **ACCF/AHA Clopidogrel** Clinical Alert: Approaches to the FDA "Boxed Warning" **Genetic variability**: A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. Circulation 122: 537-557.
480. Iles-Shih L, Collins JF, Holub JL, Lieberman DA. Prevalence of Significant **Neoplasia in FOBT-Positive Patients** on Warfarin Compared With Those Not on Warfarin. Am J Gastroenterol. 2010 Aug 3.
481. Kobayashi H. Evaluation of the need to discontinue antiplatelet and anticoagulant medications before **cataract surgery**. J Cataract Refract Surg. 2010. Jul;36(7):1115-9.
482. Bujold E, Roberge S, Lacasse Y, et al. Prevention of **preeclampsia and intrauterine growth restriction with aspirin** started in early pregnancy: a meta-analysis. Obstet Gynecol. 2010 Aug;116(2 Pt 1):402-14. Low-dose aspirin initiated in early pregnancy is an efficient method of reducing the incidence of preeclampsia and IUGR.
483. Sachdeva A, Dalton M, Amaragiri SV, et al. **Elastic compression stockings** for prevention of deep vein thrombosis. Cochrane Database Syst Rev. 2010 Jul 7;7:CD001484. GCS are effective in diminishing the risk of DVT in hospitalised patients. Data examination also suggests that GCS on a background of another method of prophylaxis is more effective than GCS on its own.
484. Wallentin L et al. Efficacy and safety of **dabigatran** compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. Lancet 2010 Aug 29; [e-pub ahead of print].
485. Bellemain-Appaix A, Brieger D, Beygui F. **New P2Y12 inhibitors versus clopidogrel** in percutaneous coronary intervention. J Am Coll Cardiol 2010; DOI:10.1016/j.jacc.2010.07.012.
486. Paré G, Mehta SR, Yusuf S, et al. Effects of **CYP2C19 genotype** on clopidogrel treatment in CURE and ACTIVE. N Eng J Med 2010; DOI: 10.1056/NEJMoal008410.
487. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. **Early anticoagulation** is associated with reduced mortality for acute pulmonary embolism. Chest. 2010 Jun;137(6):1382-90.
488. **CURRENT–OASIS 7** Investigators. 1. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010;363:930-42.
489. Cooper K, Squires H, Carroll C, et al. **Chemoprevention of colorectal cancer**: systematic review and economic evaluation. Health Technol Assess. 2010 Jun;14(32):1-206. (Especially aspirin & celecoxib reviewed)
490. Medical Letter- Treatment Guidelines. **Treatment of Atrial Fibrillation**. Sept 2010.
491. Din FVN et al. Effect of **aspirin and NSAIDs on risk and survival from colorectal cancer**. Gut 2010 Sep 15; [e-pub ahead of print].
492. Routine **Aspirin or Nonsteroidal Anti-inflammatory Drugs for the Primary Prevention of Colorectal Cancer**, Topic Page. March 2007. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspsasco.htm
USPSTF recommends against the routine use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent colorectal cancer in individuals at average risk for colorectal cancer.
493. Bushnell CD, Zimmer LO, Pan W, et al.; for the **Adherence** Evaluation After Ischemic Stroke–Longitudinal Investigators. Persistence With Stroke Prevention Medications 3 Months After Hospitalization. Arch Neurol. 2010 Aug 9.
494. **CLOTS** (Clots in Legs Or sTockings after Stroke) Trial Collaboration. **Thigh-Length** Versus Below-Knee **Stockings** for Deep Venous Thrombosis Prophylaxis After Stroke: A Randomized Trial. *Ann Intern Med* ahead of print Sept 20, 2010.
495. Parker Chris, Coupland Carol, Hippisley-Cox Julia. **Antipsychotic drugs and risk of venous thromboembolism**: nested case-control study. BMJ 341:doi:10.1136/bmj.c4245 (especially if new user or atypical antipsychotic)
496. Bhatt DL et al. for the **COGENT** Investigators. **Clopidogrel with or without omeprazole** in coronary artery disease. N Engl J Med 2010 Oct 6; [e-pub ahead of print]. (http://www.nejm.org/doi/full/10.1056/NEJMoa1007964)
497. Smith EE, Shobha N, Dai D, et al. **Risk Score** for In-Hospital Ischemic Stroke Mortality Derived and Validated Within the Get With The Guidelines-Stroke Program. Circulation. 2010 Sep 27.
498. Clarke R. Halsey J, Lewington S, et al. Effects of lowering **homocystein levels with B vitamins** on cardiovascular disease, cancer, and cause-specific mortality. Meta-analysis of 8 randomized trials involving 37 485. Arch Intern Med 2010; 170:1622-1631.
499. Coutinho JM., Ferro JM., Canhão P, et al., and for the ISCVT Investigators. **Unfractionated or Low–Molecular** Weight Heparin for the Treatment of **Cerebral Venous Thrombosis**. Stroke published October 7, 2010, doi:10.1161/STROKEAHA.110.588822
500. Schellinger PD et al. Evidence-based guideline: Role of diffusion & perfusion **MRI** for the diagnosis of acute ischemic stroke. Report of the Therapeutics & Technology Assessment Subcommittee of American Academy of Neurology. Neurology 2010Jul 13; 75:177.
501. Furie Karen L., Kasner Scott E., Adams Robert J., et al., and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the **Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack** (Secondary Prevention). A Guideline for Healthcare Professionals From the American Heart Association (**AHA**) /American Stroke Association (**ASA**).
Stroke published October 21, 2010, doi:10.1161/STR.0b013e3181f7d043 http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181f7d043v1
502. Iorio Alfonso; Kearon Clive; Filippucci Esmeralda; et al. **Risk of Recurrence** After a First Episode of Symptomatic **Venous Thromboembolism** Provoked by a Transient Risk Factor: A Systematic Review. Arch Intern Med. 2010;170(19):1710-1716.
503. Ruiz-Irastorza Guillermo, Crowther Mark, Branch Ware, et al. **Antiphospholipid syndrome**, The Lancet, In Press, Corrected Proof, Available online 6 September 2010, ISSN 0140-6736, DOI: 10.1016/S0140-6736(10)60709-X.
504. Shinohara Yukito, Katayama Yasuo, Uchiyama Shinichiro, et al. and for the CSPS 2 group, **Cilostazol** for prevention of secondary stroke (**CSPS 2**): an aspirin-controlled, double-blind, randomised non-inferiority trial, The Lancet Neurology, Volume 9, Issue 10, October 2010, Pages 959-968, ISSN 1474-4422
505. Wiviott SD, Antman EM, Braunwald E. **Prasugrel**. Circulation. 2010 Jul 27;122(4):394-403.
506. Mega JL, Simon T, Collet JP, et al. **Reduced-function CYP2C19 genotype** and risk of adverse clinical outcomes among patients treated with **clopidogrel** predominantly for PCI. (Meta-analysis) JAMA 2010; 304:1821-1830.
507. Branch DW, Gibson M, Silver RM. Clinical practice. **Recurrent miscarriage**. N Engl J Med. 2010 Oct 28;363(18):1740-7.
508. Goldstein JN, Greenberg SM. **Should anticoagulation be resumed after intracerebral hemorrhage**? Cleveland Clinic Journal of Medicine 2010; 77(11):791-799; doi:10.3949/ccjm.77a.10018
509. Institute for Clinical Systems Improvement (**ICSI**). **Venous thromboembolism diagnosis and treatment**. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 Feb. 81 p.
510. Kong, Jae Cheol, Lee, Myeong Soo, Shin, Byung-Cheul, et al. **Acupuncture** for functional recovery after stroke: a systematic review of sham-controlled randomized clinical trials. CMAJ 2010 182: 1723-1729.
511. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of **aspirin on colorectal cancer** incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010 Oct 21.
Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily **aspirin on long-term risk of death due to cancer**: analysis of individual patient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41.
512. Kahn, Susan R., Shrier, Ian, Shapiro, Stan, et al. Six-month **exercise training** program to treat **post-thrombotic syndrome**: a randomized controlled two-centre trial. CMAJ 2010 0: cmaj.100248
Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional **catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis** (the **CaVenT** study): a randomized controlled trial. Lancet 2011
Prandoni P, Noventa F, Quintavalla R, et al. Thigh-length versus **below-knee** compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. Blood. 2012 Feb 9;119
513. Nishant K Mishra, Niaz Ahmed, Grethe Andersen, et al. , for the VISTA and SITS collaborators. **Thrombolysis in very elderly** people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke

TOP

BMJ 341:doi:10.1136/bmj.c6046 (Published 23 November 2010)
514. Toyoda K, Yasaka M, Uchiyama S, et al .; Bleeding with Antithrombotic Therapy (BAT) Study Group. **Blood pressure levels and bleeding** events during antithrombotic therapy: the Bleeding with Antithrombotic Therapy (BAT) Study. Stroke 2010;41:1440–4.
515. Carotid Stenting Trialists' Collaboration, Bonati LH, Dobson J, Algra A; et al. Short-term outcome after **stenting versus endarterectomy** for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data.Lancet.2010Sep 25;376(9746):1062-73.
516. Alshekhlee A, Mohammadi A, Mehta S, et al. Is **thrombolysis safe in the elderly**?: analysis of a national database. Stroke. 2010 Oct;41(10):2259-64. Epub 2010 Sep 9.
517. **EINSTEIN** investigators. Oral **rivaroxaban** for symptomatic venous thromboembolism. N Engl J Med 2010; DOI:10.1056/NEJMoa1007903.
518. Kyrle Paul Alexander, Rosendaal Frits R, Eichinger Sabine. **Risk assessment for recurrent venous thrombosis**. The Lancet 04 December 2010(Article in Press DOI: 10.1016/S0140-6736(10)60962-2)
519. Brenner Hermann, Tao Sha, Haug Ulrike. Low-Dose **Aspirin Use** and Performance of Immunochemical **Fecal Occult Blood Tests**. JAMA. 2010;304(22):2513-2520.doi:10.1001/jama.2010.1773.
520. Thompson BB, Béjot Y, Caso V, et al. **Prior antiplatelet therapy** and outcome following **intracerebral hemorrhage**: a systematic review. Neurology. 2010 Oct 12;75(15):1333-42.
521. **ACCF- AHA-HRS Atrial Fibrillation 2011 Focused Update**. Circulation 2011. http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181fa3cf4v1
522. Banerjee S, Brown A, McGahan L, et al. **Clopidogrel** versus other antiplatelet agents for secondary prevention of vascular events in adults with **acute coronary syndrome or peripheral vascular disease**: clinical and cost-effectiveness analyses. Canadian Agency for Drugs and Technologies in Health. 2010 Nov;133:1-213.
523. Nahab F, Le A, Judd S, Frankel MR, Ard J, Newby PK, Howard VJ. Racial and geographic differences in fish consumption: The REGARDS Study. Neurology. 2010 Dec 22.
524. Sattelmair JR, Kurth T, Buring JE, et al. **Physical activity** and risk of stroke in women. Stroke 2010; 41:1243-1250.
525. Smith EE, Shobha N, Dai D, et al. **Risk score** for **in-hospital ischemic stroke mortality** derived and validated within the Get With the Guidelines-Stroke Program. Circulation 2010; 122:1496-1504.
526. Cucchiara Brett, Kasner Scott E.. **In the Clinic: Transient Ischemic Attack**. *Ann Intern Med* Jan 4, 2011 154:ITC1-1; doi:10.1059/0003-4819-154-1-201101040-01001.
527. Freeman JV, Zhu RP, Owens DK., et al. **Cost-Effectiveness of Dabigatran Compared With Warfarin** for Stroke Prevention in Atrial Fibrillation. *Ann Intern Med* January 4, 2011 154:1-11; ahead of print Nov 1, 2010, doi:10.1059/0003-4819-154-1-201101040-00289.
528. Miesner Andrew R, Sullivan Timothy S. Elevated International Normalized Ratio from **Vitamin K Supplement Discontinuation**. Articles Ahead of Print published on 1 January 2011, DOI 10.1345/aph.1P461. Ann Pharmacother ;45:e2.
529. Dossett LA, Riesel JN, Griffin MR, Cotton BA. Prevalence and Implications of **Preinjury Warfarin Use**: An Analysis of the National **Trauma** Databank. Arch Surg. 2011 Jan 17.
530. Limdi NA, Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, Allon M, Beasley TM. **Warfarin** dosing in patients with **impaired kidney function**. Am J Kdney Dis. 2010 Nov;56(5):823-31.
531. Ying Xian, Robert G. Holloway, Paul S. Chan, et al. Association Between **Stroke Center Hospitalization** for Acute Ischemic Stroke and Mortality. *JAMA*. 2011;305(4):373-380.doi:10.1001/jama.2011.22.
532. Olesen JB, Lip G, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:doi:10.1136/bmj.d124 (31 Jan 11). CHADS2 vs **CHA2DS2-VASc**
533. Chassot PG, Marcucci C, Delabays A, Spahn DR. **Perioperative** antiplatelet therapy. Am Fam Physician. 2010 Dec 15;82(12):1484-9.
534. Gutierrez C. Blanchard DG. **Atrial Fibrillation**: Diagnosis and Treatment. Am Fam Physician. 2011 Jan 1;83(1):61-68.
535. Brott TG, Halperin JL, Abbara S, et al. JASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with **extracranial carotid and vertebral artery disease**: Executive summary. Circulation 2011: DOI:10.1161/CIR.0b013e31820d8d78. http://content.onlinejacc.org/cgi/reprint/j.jacc.2010.11.006v1.pdf
536. Chollet F et al. **Fluoxetine for motor recovery after acute ischaemic stroke (FLAME)**: A randomised placebo-controlled trial. Lancet Neurol 2011 Feb; 10:123.
537. Kulik A, Le May MR, Voisine P, et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting (CABG): the clopidogrel after surgery for coronary artery disease (**CASCADE**) Trial. Circulation. 2010 Dec 21;122(25):2680-7.
538. Baerlocher, Mark O., Myers, Andy, Asch, Murray. Managing **anticoagulation and antiplatelet therapy before interventional radiology procedures**. CMAJ 2011 183: 223.
539. Bungard TJ, Yakiwchuk E, Foisy M. **Drug interactions involving warfarin**: Practice tool and practical management tips. CJP. Jan/Feb Vol 144. No 1. 2011.
540. Connolly SJ., Eikelboom J, Joyner C, et al. **AVERROES** Steering Committee & Investigators. **Apixaban in Patients with Atrial Fibrillation**. February 10, 2011. (n=5599 over 1.1yr; apixaban 5mg bid vs ASA 81-324mg od; Stroke or systemic embolism 1.6 vs 3.7% NNT= 48/year)
541. Eikelboom JW, Weitz JI. New oral anticoagulants (**dabigatran, rivaroxaban**) for **thromboprophylaxis in patients having hip or knee arthroplasty**. BMJ. 2011 Jan 18;342:c7270. doi: 10.1136/bmj.c7270.
542. Chollet F, Tardy J, Albucher J-F, et al. **Fluoxetine** for motor recovery after acute ischaemic stroke (**FLAME**): a randomised placebo-controlled trial, The Lancet Neurology, Vol 10, Issue 2, Feb 2011, Pages 123-130, ISSN 1474-4422.
543. Baker William L., Colby Jennifer A., Tongbram Vanita, et al. **Neurothrombectomy** Devices for the Treatment of Acute Ischemic Stroke: State of the Evidence. *Ann Intern Med* E-306published ahead of print January 17, 2011.
544. Galioto NJ, Danley DL, Van Maanen RJ. **Recurrent venous thromboembolism**. Am Fam Physician. 2011 Feb 1;83(3):293-300.
545. Earnshaw Stephanie R.; Scheiman James; Fendrick A. Mark; et al. **Cost-Utility of Aspirin and Proton Pump Inhibitors for Primary Prevention**. Arch Intern Med. 2011;171(3):218-225.
546. Balami Joyce S, Chen Ruo-Li, Grunwald Iris Q, et al. **Neurological complications of acute ischaemic stroke**, The Lancet Neurology, In Press, Corrected Proof, Available online 17 January 2011, ISSN 1474-4422, DOI: 10.1016/S1474-4422(10)70313-6.
547. Sandset EC, Bath PMW, Boysen G et al. The angiotensin-receptor blocker **candesartan for treatment of acute stroke (SCAST):** A randomised, placebo-controlled, double-blind trial. *Lancet* 2011;DOI:10.1016/S0140-6736(11)60104-9.
548. Bartholomew JR, Schaffer JL, McCormick GF. **Air travel and venous thromboembolism**: Minimizing the risk *Cleveland Clinic Journal of Medicine* 2011; 78(2):111-120; doi:10.3949/ccjm.78a.10138
549. Lin, Yulia, Callum, Jeannie. **Emergency reversal of warfarin** anticoagulation. CMAJ 2010 182: 2004
550. Douketis J, Tosetto A, Marcucci M, et al. **Risk of recurrence after venous thromboembolism in men** and women: patient level meta-analysis. BMJ. 2011 Feb 24;342:d813. doi: 10.1136/bmj.d813.
551. Devos H, Akinwuntan AE, Nieuwboer A, et al. Screening for fitness to **drive after stroke**: A systematic review and meta-analysis. Neurology. 2011 Feb 22;76(8):747-56.
552. García Rodríguez LA, Cea Soriano L, Hill C, et al. Increased risk of **stroke after discontinuation of acetylsalicylic acid**: A UK primary care study. Neurology. 2011 Feb 22;76(8):740-6.
553. Rodríguez Luis A. García, Lin Kueiyu Joshua, Hernández-Díaz Sonia, et al. **Risk of Upper Gastrointestinal Bleeding** With Low-Dose Acetylsalicylic Acid Alone and in Combination With Clopidogrel and Other Medications. Circulation 123: 1108-1115; online doi:10.1161/CIRCULATIONAHA.110.973008
554. Cairns JA, Connolly S, McMurtry S, et al. CCS Atrial Fibrillation Guidelines Committee. **Canadian cardiovascular society atrial fibrillation guidelines 2010**: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol. 2011 Jan-Feb;27(1):74-90.
555. Zhao HJ, Zheng ZT, Wang ZH, et al. ``**Triple therapy**`` rather than ``triple threat``: a meta-analysis of the two antithrombotic regimens **after stent implantation** in patients receiving long-term oral anticoagulant treatment. Chest. 2011 Feb;139(2):260-70.
556. AHA Writing Group Members, Roger VL, Go AS, Lloyd-Jones DM, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Roger VL, Turner MB; On behalf of the American Heart Association Heart Disease and Stroke Statistics Writing Group. Executive Summary: **Heart Disease and Stroke Statistics**—2011 Update: A Report From the American Heart Association. Circulation. 2011 Feb 1;123(4):459-463.
557. Jacob M, Smedira N, Blackstone E, Williams S, Cho L. Effect of timing of chronic preoperative **aspirin discontinuation** on morbidity and mortality in **coronary artery bypass surgery**. Circulation. 2011 Feb 15;123(6):577-83.
558. Saposnik G, Kapral MK, Liu Y, et al; on behalf of the Investigators of the Registry of the Canadian Stroke Network and the Stroke Outcomes Research Canada (SORCan) Working Group. **IScore**: A Risk Score to Predict Death Early After Hospitalization for an Acute Ischemic Stroke. Circulation. 2011 Feb 22;123(7):739-749.
559. Kamal AK, Naqvi I, Husain MR, et al. **Cilostazol versus aspirin** for secondary prevention of vascular events after stroke of arterial origin. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008076. DOI: 10.1002/14651858.CD008076.pub2.
560. Hamann Gale L, Campbell Jennifer D, George Christa M. **Warfarin-Cranberry Juice** Interaction. Articles Ahead of Print published on 1 March 2011, DOI 10.1345/aph.1P451. Ann Pharmacother ;45:e17.
561. Price MJ, Berger PB, Teirstein PS, et al. **Standard- vs high-dose clopidogrel** based on platelet function testing after percutaneous coronary intervention: The **GRAVITAS** randomized trial. JAMA 2011; 305:1097-1105. (high dose not reduce 1^0 events vs std dose)
562. **PROTECT** Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. **Dalteparin versus Unfractionated Heparin in Critically Ill Patients**. Mar 22, 11 (10.1056/NEJMoa1014475)
563. Leizorovicz A, Cohen AT, Turpie AGG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, Placebo-Controlled Trial of **Dalteparin** for the Prevention of Venous Thromboembolism in **Acutely Ill Medical Patients (PREVENT)**. Circulation 2004; 110:874-9.
564. Samama MM, Cohen AT, Darmon JY, Desjardins L, et al. A comparison of **enoxaparin** with placebo for the prevention of venous thromboembolism in **acutely ill medical patients (MEDENOX)**. N Engl J Med 1999; 341:793-800.
565. Jaff Michael R., McMurtry M. Sean, Archer Stephen L., et al. and on behalf of the American Heart Association (AHA) Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of **Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension:** A Scientific Statement From the American Heart Association. Circulation published March 21, 2011, doi:10.1161/CIR.0b013e318214914f
566. Rodriguez LAG et al. **Increased risk for stroke after discontinuation of acetylsalicylic acid**: a UK primary care study. Neurology. 2011;76:740.
567. Nils Kucher. **Deep-Vein Thrombosis of the Upper Extremities**. N Engl J Med 2011; 364:861-869.
568. Larsson SC et al. **Coffee consumption** and risk of stroke in women. Stroke 2011 Mar 10.
569. Silber S, Windecker S, Vranckx P, Serruys PW, on behalf of the **RESOLUTE All Comers** investigators. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Lancet 2011; published online Arpil 3. DOI:10.1016/S0140-6736(11)60395-4. (2yr data; Dual antiplate therapy was @ 1yr=~84%, 2yr= ~18% but >1yr stent thrombosis was only ~0.3%)
570. Bauer Kenneth A. **Long-term Management of Venous Thromboembolism**: A 61-Year-Old Woman With Unprovoked Venous Thromboembolism. JAMA. 2011;305(13):1336-1345.Published online March 8, 2011. doi:10.1001/jama.2011.361
571. McArthur K S, Quinn T J, Dawson J, et al. **Diagnosis and management of transient ischaemic attack and ischaemic stroke in the acute phase.** BMJ 2011;342:doi:10.1136/bmj.d1938 (Published 31 March 2011)
571. McArthur K S, Quinn T J, Higgins P, et al. **Post-acute care and secondary prevention** after ischaemic stroke. BMJ 2011;342:doi:10.1136/bmj.d2083 (Published 8 April 2011)
572. Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, et al. Meta-analysis: effect of patient **self-testing and self-management of longterm anticoagulation** on major clinical outcomes. Ann Intern Med. 2011;154: 472-82.
573. Callahan T, Baranowski B. Managing newly diagnosed atrial fibrillation: Rate, rhythm, and risk. Cleve Clin J Med. 2011 Apr;78(4):258-64.
574. Varbo A, Nordestgaard BG, Tybjaerg-Hansen A, et al. Nonfasting **triglycerides, cholesterol**, and ischemic stroke in the general population. Ann Neurol. 2011 Feb 18. doi: 10.1002/ana.22384.
575. Bigi S, Fischer U, Wehrli E, et al. Acute Ischemic **Stroke In Children Versus Young Adults**. Annals of Neurology. Accepted manuscript online: 21 MAR 2011: 1-30.
576. Akl EA, Vasireddi SR, Gunukula S, Barba M, Sperati F, Terrenato I, Muti P, Schünemann H. Anticoagulation for the initial treatment of venous **thromboembolism in patients with cancer**. Cochrane Database Syst Rev. 2011 Feb 16;2:CD006649
577. Morgenstern LB, Hemphill JC III, Anderson C, on behalf of the American Heart Association Stroke Council and endorsed by the American Academy of Neurology, American Association of Neurological Surgeons, and the Congress of Neurological Surgeons. Guidelines for the management of **spontaneous intracerebral hemorrhage**: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010; 41: 2108–29. http://stroke.ahajournals.org/cgi/reprint/41/9/2108
578. Hankey GJ, Eikelboom JW. **Dabigatran** etexilate: a new oral thrombin inhibitor. Circulation. 2011 Apr 5;123(13):1436-50.
579. Murad MH, Shahrour A, Shah ND, et al. A systematic review and meta-analysis of randomized trials of **carotid endarterectomy vs stenting**. J Vasc Surg. 2011 Mar;53(3):792-7.
580. Bartolucci AA, Tendera M, and Howard G. Meta-analysis of multiple **primary prevention** trials of cardiovascular events using **aspirin**. Am J Cardiol 2011; DOI:10.1016/j.amjcard.2011.02.325.

TOP

581. Nathisuwan S, Dilokthornsakul P, Chaiyakunapruk N, et al. Assessing Evidence of **Interaction Between Smoking and Warfarin**: A Systematic Review and Meta-analysis. Chest. 2011 May;139(5):1130-9.
582. Hong Keun-Sik, Yegiaian Sharon, Lee Meng, et al. **Declining Stroke and Vascular Event Recurrence Rates in Secondary Prevention Trials Over the Past 50 Years** and Consequences for Current Trial Design. Circulation 123: 2111-2119.
583. Langhorne P, Bernhardt J, Kwakkel G. **Stroke rehabilitation**. Lancet. 2011 May 14;377(9778):1693-702.
584. McArthur KS, Quinn TJ, Higgins P, Langhorne P. **Post-acute care and secondary prevention** after ischaemic stroke. BMJ. 2011 Apr 8;342:d2083. doi:10.1136/bmj.d2083.
585. Rothwell PM, Algra A, Amarenco P. **Medical treatment** in **acute and long-term secondary prevention** after transient ischaemic attack and ischaemic stroke. Lancet. 2011 May 14;377(9778):1681-92.
586. Saposnik G, Levin M; for the Stroke Outcome Research Canada (SORCan) Working Group. **Virtual Reality in Stroke Rehabilitation**: A Meta-Analysis and Implications for Clinicians. Stroke. 2011 May;42(5):1380-1386.
587. The Stroke Prevention in Reversible Ischemia Trial (**SPIRIT**) Study Group. A randomized trial of **anticoagulants versus aspirin** after cerebral ischemia of presumed arterial origin. Ann Neurol 1997;42: 857–65.
Mohr JP, Thompson JL, Lazar RM, et al. A comparison of **warfarin and aspirin** for the prevention of recurrent ischemic stroke. N Engl J Med 2001; 345: 1444–51.
The ESPRIT Study Group. Medium intensity oral **anticoagulants versus aspirin** after cerebral ischaemia of arterial origin (**ESPRIT**): a randomised controlled trial. Lancet Neurol 2007; 6: 115–24.
588. Martinsson L, Hårdemark H, Eksborg S. **Amphetamines** for improving recovery after stroke. Cochrane Database Syst Rev 2007; 1: CD002090.
589. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding **length of anticoagulant treatmen**t and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ 2011;342:d3036.
590. Yingying Tang, Barbara Sampson, Stephanie Pack, et al. **Ethnic Differences** in Out-of-Hospital Fatal Pulmonary Embolism. Circulation 123: 2219-2225; published online before print as doi:10.1161/CIRCULATIONAHA.110.976134.
591. Cook-Norris RH et al. **Complications of cutaneous surgery in patients taking clopidogrel**-containing anticoagulation. J Am Acad Dermatol 2011 Apr 22.
592. Hoffman JT, Hartig C, Sonbol E, Lang M. Probable interaction between **warfarin and rifaximin** in a patient treated for small intestine bacterial overgrowth. Ann Pharmacother. 2011 May;45(5):e25.
593. Bovio JA, Smith SM, Gums JG. **Dabigatran** etexilate: a novel oral thrombin inhibitor for thromboembolic disease. Ann Pharmacother. 2011 May;45(5):603-14.
594. Rubboli A, Kovacic JC, Mehran R, Lip GY. **Coronary Stent Implantation** in Patients Committed to Long-term Oral Anticoagulation Therapy: Successfully Navigating the Treatment Options. Chest. 2011 May;139(5):981-7. (Triple therapy)
595. Charlot M, Grove EL, Hansen PR, et al. **Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients** with first time myocardial infarction: nationwide propensity score matched study. BMJ. 2011 May 11;342:d2690. doi: 10.1136/bmj.d2690.
596. Bousser M-G, Amarenco P, Chamorro A, et al, the **PERFORM** Study Investigators. **Terutroban versus aspirin** in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. Lancet 2011; online May 25. DOI:10.1016/S0140-6736(11)60600-4.
597. PILL Collaborative Group (2011) An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill (''**Polypill''**) in People with Raised Cardiovascular Risk. PLoS ONE 6(5): e19857. doi:10.1371/journal.pone.0019857.
598. Wechsler Lawrence R. Intravenous **Thrombolytic Therapy (rt-PA)** for Acute Ischemic Stroke. N Engl J Med 2011; 364:2138-2146.
599. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of **bleeding with 2 doses of dabigatran** compared with warfarin in older and younger patients with atrial fibrillation. Circulation 2011; 123:2363-2372.
600. Douma Renée A., Mos Inge C.M., Erkens Petra M.G., et al. , for the Prometheus Study Group. Performance **of 4 Clinical Decision Rules in the Diagnostic Management of Acute Pulmonary Embolism**: A Prospective Cohort Study. Ann Intern Med June 7, 2011 154:709-718.
601. Avorn Jerry. The Relative **Cost-Effectiveness of Anticoagulants**: Obvious, Except for the Cost and the Effectiveness. Circulation 123: 2519-2521; published online before print as doi:10.1161/CIRCULATIONAHA.111.030148
602. Shah Shimoli V., Gage Brian F.. **Cost-Effectiveness of Dabigatran** for Stroke Prophylaxis in Atrial Fibrillation. Circulation 123: 2562-2570; published online before print as doi:10.1161/CIRCULATIONAHA.110.985655
603. Callahan Alfred; Amarenco Pierre; Goldstein Larry B.; et al. for the **SPARCL** Investigators. Risk of Stroke and Cardiovascular Events After Ischemic Stroke or Transient Ischemic Attack in Patients With **Type 2 Diabetes or Metabolic Syndrome**: Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial Arch Neurol. 2011;0(2011):archneurol.2011.146.
604. Ghate Sameer R, Biskupiak JE, Ye X, et al. Hemorrhagic and Thrombotic Events Associated with **Generic Substitution of Warfarin** in Patients with Atrial Fibrillation: A Retrospective Analysis. Ahead of Print on 1 June 2011, DOI 10.1345/aph.1P593. Ann Pharmacother ;45:701-712.
605. James SK, Roe MT, Cannon CP, et al. **Ticagrelor versus clopidogrel** in patients with **acute coronary syndromes intended for non-invasive management**: substudy from the Prospective Randomised PLATelet inhibition and patient Outcomes (**PLATO**) trial. BMJ 2011;342:d3527.
606. Callahan A, Amarenco P, Goldstein LB, et al. for the **SPARCL** Investigators. Risk of Stroke and Cardiovascular Events After Ischemic Stroke or Transient Ischemic Attack in Patients With **Type 2 Diabetes or Metabolic Syndrome**: Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Arch Neurol. 2011 Jun 13.
607. Passacquale Gabriella, Ferro Albert. Therapeutics: Oral antiplatelet agents **clopidogrel and prasugrel** for the prevention of cardiovascular events. BMJ 2011;342:doi:10.1136/bmj.d3488 (Published 17 June 2011)
608. Aujesky D, Roy P-M, Verschuren F, et al. **Outpatient versus inpatient treatment for patients with acute pulmonary embolism**: an international, open-label, randomised, non-inferiority trial. Lancet 2011; published online June 23. DOI:10.1016/S0140-6736(11)60824-6.
609. Hobbs F D R, Roalfe A K, Lip G Y H, et al. on behalf of the Birmingham Atrial Fibrillation in the Aged (**BAFTA**) investigators and Midland Research Practices Consortium (MidReC) network. **Performance of stroke risk scores** in older people with atrial fibrillation not taking warfarin: comparative cohort study from BAFTA trial. BMJ 2011;342:doi:10.1136/bmj.d3653 (23 June 2011)
610. Geraghty AJ, Welch K. Antithrombotic agents for preventing thrombosis after **infrainguinal arterial bypass surgery**. Cochrane Database Syst Rev. 2011 Jun 15;6:CD000536. Patients undergoing infrainguinal venous graft are more likely to benefit from treatment with VKA than platelet inhibitors. Patients receiving an artificial graft benefit from platelet inhibitors (aspirin). However, the evidence is not conclusive.
611. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation. 2011 Jun 14;123(23):2736-47.
Hicks KA, Stockbridge NL, Targum SL, Temple RJ. Bleeding academic research consortium (**BARC**) consensus report: the food and drug administration perspective. Circulation. 2011 Jun 14;123(23):2664-5.
612. Hochholzer W, Wiviott SD, Antman EM, et al. **Predictors of Bleeding** and Time Dependence of Association of Bleeding With Mortality: Insights From the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel--Thrombolysis in Myocardial Infarction 38 (**TRITON-TIMI 38**). Circulation. 2011 Jun 14;123(23):2681-9. Conclusions— The major predictors of serious bleeding were a combination of patient and procedural characteristics and antiplatelet therapies. Although serious bleeding was strongly associated with mortality within the first month of the bleeding event, this association was not significant beyond 40 days.
613. Kawut SM, Bagiella E, Lederer DJ, et al; on behalf of the **ASA-STAT Study** Group. Randomized Clinical Trial of **Aspirin and Simvastatin for Pulmonary Arterial Hypertension**: ASA-STAT. Circulation. 2011 Jun 28;123(25):2985-2993.
614. García Rodriguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. **Discontinuation of low dose aspirin and risk of myocardial infarction**: case-control study in UK primary care. BMJ 2011;343:d4094.
615. Raju N, Sobieraj-Teague M, Hirsh J, et al. Effect of **aspirin on mortality in the primary prevention** of cardiovascular disease. Am J Med. 2011 Jul;124(7):621-9.
616. Stanley AJ, Dalton HR, Blatchford O, et al. Multicentre comparison of the **Glasgow Blatchford and Rockall scores** in the prediction of clinical end-points after upper gastrointestinal haemorrhage. Aliment Pharmacol Ther. 2011 Aug;34(4):470-5. doi: 10.1111/j.1365-2036.2011.04747.x.
617. Marmo R, Koch M, Cipolletta L, et al. Italian registry on upper gastrointestinal bleeding (Progetto Nazionale Emorragie Digestive--**PNED 2**). Predicting mortality in non-variceal upper gastrointestinal bleeders: validation of the Italian PNED Score and Prospective Comparison with the **Rockall Score**. Am J Gastroenterol. 2010 Jun;105(6):1284-91.
618. Bhala Neeraj, Taggar Jaspal S, Rajasekhar Praveen, et al. Anticipating and **managing bleeding complications in patients with coronary stents** who are receiving dual antiplatelet treatment. BMJ 2011;343:doi:10.1136/bmj.d4264 (21 July 2011)
619. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome (**Appraise-2**). N Engl J Med 2011 (5mg po bid: increased the number of **major bleeding** events without a significant reduction in recurrent ischemic events)
620. Hughes GJ, Patel PN, Saxena N.. Effect of **acetaminophen on international normalized ratio** in patients receiving warfarin therapy. Pharmacotherapy 2011 June;31(6):591–597.
621. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (**QThrombosis**) to estimate **future risk of venous thromboembolism**: prospective cohort study. BMJ. 2011 Aug 16;343:d4656. doi: 10.1136/bmj.d4656.
622. Luo J-C et al. Randomised clinical trial: **Rabeprazole plus aspirin is not inferior to rabeprazole plus clopidogrel** for the healing of aspirin-related peptic ulcer. Aliment Pharmacol Ther 2011 Sep; 34:519.
623. Patel MR, Mahaffey KW, Garg J, et al. **Rivaroxaban** versus warfarin in nonvalvular atrial fibrillation. (**Rocket-AF**) N Engl J Med 2011.
Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with **rivaroxaban** compared with warfarin in patients with non-valvular atrial fibrillation and moderate **renal impairment**. Eur Heart J. 2011 Aug 28.
624. Kuklina EV, Tong X, Bansil P, et al. Trends in **pregnancy hospitalizations that included a stroke** in the United States from 1994 to 2007. Stroke 2011; DOI: 10.1161/STROKEAHA.110.610592.
625. Faxon D, Eikelboom J, Berger P, et al. **Consensus document: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting**. Thromb Haemost 2011: DOI:10.1160/TH11-04-0262. (North American consensus)
626. Huhtakangas J, Tetri S, Juvela S, et al. Effect of Increased Warfarin Use on **Warfarin-Related Cerebral Hemorrhage**: A Longitudinal Population-Based Study. Stroke. 2011 Jul 28.
627. Rose AJ, Ozonoff A, Berlowitz DR, et al. Reexamining the Recommended **Follow-up Interval After Obtaining an In-Range International Normalized Ratio** Value: Results from the Veterans Affairs Study to Improve Anticoagulation. Chest. 2011 Aug;140(2):359-65.
628. Schultz Karen T, Bungard Tammy J, Dosing Options for **Decreasing the Time to Achieve Therapeutic Anticoagulation When Reinitiating Warfarin**:A Case Series. Pharmacotherapy 2011;31(8):793–805). In select patients, the option of administering a warfarin loading dose of approximately 40% greater than the previous daily maintenance dose for 2 or 3 days shortens the time to achieving therapeutic anticoagulation.
629. Jowett S, Bryan S, Mant J, et al. Cost effectiveness of **warfarin versus aspirin in patients older than 75 years** with atrial fibrillation. Stroke. 2011 Jun;42(6):1717-21
630. Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation (**ARISTOTLE**). N Engl J Med . 2011 Aug 28.
Easton JD, Lopes RD, Bahit MC, et al, for ARISTOTLE Committees and Investigators. Apixaban compared with warfarin in patients with atrial fibrillation and **previous stroke or transient ischaemic attack**: subgroup analysis of ARISTOTLE trial. Lancet Neurol 2012; online May 8.
631. Fang MC, Go AS, Chang Y, et al. A New Risk Scheme to **Predict Warfarin-Associated Hemorrhage The ATRIA** (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011 Jul 19;58(4):395-401.
632. Engelter ST, Soinne L, Ringleb P, et al. **IV thrombolysis and statins**. Neurology. 2011 Aug 17.
633. Zöller B, Li X, Sundquist J, Sundquist K. **Age- and Gender-Specific Familial Risks** for Venous Thromboembolism: A Nationwide Epidemiological Study Based on Hospitalizations in Sweden. Circulation. 2011 Aug 8.
634. Mahaffey KW, Wojdyla DM, Carroll K, et al. **Ticagrelor compared with clopidogrel** by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Circulation 2011
635. Hill MD, Coutts SB. **Preventing stroke** after transient ischemic attack. CMAJ. 2011 Jul 12;183(10):1127-8.
636. Lillis T, Ziakas A, Koskinas K, et al. Safety of **Dental Extractions** During Uninterrupted Single or Dual Antiplatelet Treatment. Am J Cardiol. 2011 Jul 22.
637. Siristatidis CS, Dodd SR, Drakeley AJ. **Aspirin for in vitro fertilisation**. Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD004832. DOI: 10.1002/14651858.CD004832.pub3
638. Broderick JP, Bonomo JB, Kissela BM, et al. **Withdrawal of antithrombotic agents** and its impact on ischemic stroke occurrence.Stroke 2011.
639. Fjaertoft H, Rohweder G, Indredavik B. Stroke unit care combined with early supported discharge improves 5-year outcome: a randomized controlled trial. Stroke. 2011 Jun;42(6):1707-11.
640. Institute for Clinical Systems Improvement (**ICSI**). Venous thromboembolism diagnosis and treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Mar.
641. Boggon R, van Staa TP, Timmis A, et al. **Clopidogrel discontinuation** after acute coronary syndromes: frequency, predictors and associations with death and myocardial infarction--a hospital registry-primary care linked cohort (MINAP-GPRD). Eur Heart J. 2011 Aug 29.
642. Samieri C., Féart C., Proust-Lima C., et al. **Olive oil consumption**, plasma oleic acid, and stroke incidence: The Three-City Study Neurology June 15, 2011
643. Grunau BE, Wiens MO, Harder KK. Patient **self-management of warfarin** therapy: Pragmatic feasibility study in Canadian primary care. Can Fam Physician. 2011 Aug;57(8):e292-8.
644. Alberts MJ, Latchaw RE, Jagoda A, et al. Revised and updated recommendations for the **establishment of primary stroke centers**: A summary statement from the Brain Attack Coalition. Stroke 2011; 42:2651-2665.
645. Davies R, Galloway JB, Watson KD, Lunt M, Symmons DP, Hyrich KL; ; BSRBR Control Centre Consortium, British Society for Rheumatology Biologics Register. Venous thrombotic events are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Jul 22.
646. Laver KE, George S, Thomas S, Deutsch JE, Crotty M. **Virtual reality for stroke rehabilitation**. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD008349. DOI: 10.1002/14651858.CD008349.pub2. We found limited evidence that the use of virtual reality and interactive video gaming may be beneficial in improving arm function and ADL function when compared with the same dose of conventional therapy.
647. Spyropoulos AC, Anderson FA Jr, et al. for the IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) Investigators. Predictive and Associative Models to Identify Hospitalized Medical Patients at Risk for Venous Thromboembolism. Chest. 2011 Mar 24.
648. Hackam DG, Austin PC, Huang A, et al. **Statins and intracerebral hemorrhage**: a retrospective cohort study. Arch Neurol. doi:10.1001/archneurol.2011.228.
649. Griep LMO, Verschuren WM, Kromhout D, Ocke MC, Geleijnse JM. Colors of **fruit and vegetables** and 10-year incidence of stroke. Stroke. 2011.
650. Larsson SC, Orsini N. **Fish Consumption** and the Risk of Stroke: A Dose-Response Meta-Analysis. Stroke. 2011 Sep 8.
651. McKinney JS, Deng Y, Kasner SE, Kostis JB; for the Myocardial Infarction Data Acquisition System (MIDAS 15) Study Group. **Comprehensive Stroke Centers** Overcome the Weekend Versus Weekday Gap in Stroke Treatment and Mortality. Stroke. 2011 Sep;

TOP

652. Rerkasem K, Rothwell PM. **Carotid endarterectomy for symptomatic carotid stenosis**. Cochrane Database Syst Rev. 2011 Apr 13;(4):CD001081.
653. Zhang Y, Tuomilehto J, Jousilahti P, et al. **Lifestyle Factors on the Risks** of Ischemic and Hemorrhagic Stroke. Arch Intern Med. 2011 Sep 12.
654. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. **Stenting versus aggressive medical therapy** for intracranial arterial stenosis. (**Sammpris**) N Engl J Med 2011. DOI: 10.1056/NEJMoa1105335.
655. Bushnell CD, Olson DM, Zhao X, et al. For the AVAIL Investigators. Secondary preventive medication **persistence and adherence** 1 year after stroke. Neurology. 2011 Sep 7.
656. Kaatz S, Qureshi W, Lavender RC. **Venous thromboembolism**: What to do after anticoagulation is started. Cleve Clin J Med. 2011 Sep;78(9):609-18.
657. Parodi G, Marcucci R, Valenti R, et al. **High residual platelet reactivity after clopidogrel** loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI (**RECLOSE-2 ACS**). JAMA. 2011;306(11):1215-1223.
658. Caritis S, Sibai B, Hauth J, et al. Lowdose **aspirin to prevent preeclampsia** in women at high risk. N Engl J Med 1998; 338:701-5.
659. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. **Antiplatelet agents for prevention of pre-eclampsia**: a meta-analysis of individual patient data. Lancet 2007;369:1791-8.
660. Health Canada Sep/11 is informing health professionals and patients of updated recommendations involving the use of Plavix (**clopidogrel**) in combination with a class of drugs known as proton pump inhibitors (PPIs). New evidence has shown that while **PPIs** do interact with Plavix, not all reduce the effectiveness of Plavix to the same degree. (Omeprazole interacts, but pantoprazole not interact as strongly)
661. Pluta RM, Lynm C, Golub RM. JAMA **patient page**. **Stroke imaging**. JAMA. 2011 Sep 21;306(11):1277.
662. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. **Depression and risk of stroke** morbidity and mortality: a meta-analysis and systematic review. JAMA. 2011 Sep 21;306(11):1241-9.
663. Spinler SA, Willey VJ. A **Patient's Guide** to Taking **Dabigatran** Etexilate. Circulation. 2011 Aug 23;124(8):e209-11.
664. Chen YL, Chang CL, et al. **Major Adverse Upper Gastrointestinal Events** in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Coronary Intervention and **Dual Antiplatelet Therapy**. Am J Cardiol. 2011 Sep 14. (Major GI 10.4% over 4yrs)
665. Squizzato A, Romualdi E, Dentali F, et al. **Statins for acute ischemic stroke**. Cochrane Database Syst Rev. 2011 Aug 10;(8):CD007551. **Insufficient data** were available from randomized trials to establish if statins are safe and effective in cases of acute ischemic stroke and TIA.
666. Albaladejo P, Marret E, Samama CM, et al. **Non-cardiac surgery in patients with coronary stents**: the RECO study. Heart. 2011 Oct;97(19):1566-72. **Interruption** of antiplatelet therapy **more than 5days prior** to invasive procedure is a key player for major CV events.
667. Holmes MV, Newcombe P, Hubacek JA, et al. Effect modification by population **dietary folate on the association between MTHFR genotype**, **homocysteine**, and stroke risk: a meta-analysis of genetic studies and randomised trials. Lancet 2011; published online Aug 1.
668. Poli D, Antonucci E, Testa S, et al. for the Italian Federation of Anticoagulation Clinics (FCSA). **Bleeding Risk in Very Old Patients on Vitamin K Antagonist** Treatment: Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation. Circulation. 2011 Aug 16;124(7):824-829.
669. Patti G, Bárczi G, Orlic D, et al. Outcome comparison of **600- and 300-mg loading doses of clopidogrel** in patients undergoing primary PCI for STEMI. Results from the **ARMYDA-6 MI** (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty—Myocardial Infarction) randomized study. J Am Coll Cardiol 2011; 58:1592-1599.
670. Labos C, Dasgupta K, Nedjar H, et al. Risk of **bleeding** associated with combined use of **selective serotonin reuptake inhibitors** and antiplatelet therapy following acute myocardial infarction. CMAJ 2011; DOI:10.1503/cmaj.100912.
671. Nallamothu BK, Gurm HS, Ting HH, et al . **Operator exper** ience and **carotid stenting outcomes (CAS)** in Medicare beneficiaries. JAMA. 2011;306(12): 1338-1343.
672. Jacob M, Smedira N, Blackstone E, et al. Effect of timing of chronic **preoperative aspirin discontinuation** on morbidity and mortality in **coronary artery bypass surgery**. Circulation 2011;DOI:10.1161/CIRCULATIONAHA.110.957373.
It is therefore acceptable to continue aspirin to within 3 days to 5 days of surgery for patients at higher risk of cardiovascular events preoperatively, while discontinuing aspirin a bit earlier for those who may be at higher risk of bleeding complications.
673. Cheema AN, Mohammad A, Hong T, et al. Characterization of **clopidogrel hypersensitivity** reactions and management with oral steroids (**prednisone** x 3 weeks) without clopidogrel discontinuation. J Am Coll Cardiol 2011; 58:1445-1454.
674. Jung S-Y, Choi N-K, Kim J-Y, et al. **Short-acting nifedipine and risk of stroke** in elderly hypertensive patients. Neurology 2011;77:1229 –1234.
675. Giles MF, Albers GW, Amarenco P, et al. Early stroke risk and **ABCD2 score** performance in tissue- vs time-defined TIA: A multicenter study. Neurology. 2011 Sep 27;77(13):1222-8.
676. Easton JD, Saver JL, Albers GW, et al. **Definition and evaluation of transient ischemic attack**: a scientific statement for healthcare professionals from the American Heart Association (AHA)/American Stroke Association (ASA) Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease: the American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40: 2276–2293.
677. Rooke TW, Hirsch AT, Misra S, et al. 2011 **ACCF/AHA** focused update of the guideline for the management of patients with **peripheral artery disease** (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124.
678. Lee M, Saver JL, Chang B, Chang K-H, Hao Q, Ovbiagele B. Presence of baseline **prehypertension and risk of incident stroke**: a meta-analysis. Neurology 2011;77:1330 –1337.
679. Wiviott SD, Desai N, Murphy SA, et al. Efficacy and Safety of Intensive Antiplatelet Therapy With **Prasugrel** from **TRITON-TIMI 38** in a Core Clinical Cohort Defined by Worldwide Regulatory Agencies. Am J Cardiol. 2011 Oct 1;108(7):905-11.
680. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in **stroke hospitalizations** and associated risk factors among **children and young adults**, 1995-2008. Ann Neurol. 2011 Sep 2. doi: 10.1002/ana.22539.
681. Amin AN, Lin J, Thompson S, Wiederkehr D. Inpatient and outpatient occurrence of deep vein thrombosis and pulmonary embolism and thromboprophylaxis following **selected at-risk surgeries**. Ann Pharmacother. 2011 Sep;45(9):1045-52.
682. Crouch MA, Colucci VJ, Howard PA, Spinler SA. P2Y12 Receptor Inhibitors: Integrating **Ticagrelor** into the Management of Acute Coronary Syndrome. Ann Pharmacother. 2011 Sep;45(9):1151-6.
683. Koennecke HC, Belz W, Berfelde D, et al. For the Berlin Stroke Register Investigators. Factors influencing in-hospital **mortality** and morbidity in patients treated on a **stroke unit**. Neurology. 2011 Sep 6;77(10):965-972.
684. Ussia GP, Scarabelli M, Mulè M, et al. **Dual Antiplatelet Therapy Versus Aspirin** Alone in Patients Undergoing **Transcatheter Aortic Valve Implantation**. Am J Cardiol. 2011 Sep 10.
685. Holmes MV, Newcombe P, Hubacek JA, et al. Effect modification by population **dietary folate** on the association between MTHFR genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials. Lancet. 2011 Aug 13;378(9791):584-94.
686. Moores LK, King CS, Holley AB. Current approach to the diagnosis of acute nonmassive pulmonary embolism. Chest. 2011 Aug;140(2):509-18.
687. Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of **CYP2C19 variant genotypes** on clinical efficacy of antiplatelet treatment with **clopidogrel**: systematic review and meta-analysis. BMJ. 2011 Aug 4;343:d4588.
688. Cuisset T, Quilici J, Cohen W, et al. Usefulness of **High Clopidogrel Maintenance Dose** According to **CYP2C19 Genotypes** in Clopidogrel Low Responders Undergoing Coronary Stenting for Non ST Elevation Acute Coronary Syndrome. Am J Cardiol. 2011Sep5;108(6):760-5.
689. Vargas-Hitos JA, Ateka-Barrutia O, Sangle S, Khamashta MA. Efficacy and safety of long-term **low molecular weight heparin in patients with antiphospholipid syndrome**. Ann Rheum Dis. 2011 Sep;70(9):1652-4.
690. Lucassen W, Geersing GJ, Erkens PM, et al. **Clinical Decision Rules** for **Excluding Pulmonary Embolism**: A Meta-analysis. Ann Intern Med. 2011 Oct 4;155(7):448-60.
691. Olesen JB, Lip GYH, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with **atrial fibrillation**: A net clinical benefit analysis using a 'real world' nationwide cohort study. Thromb Haemost 2011; 106: 739-749. (**not ASA**)
692. Hamm CW, Bassand JP, Agewall S, et al. **ESC** Guidelines for the management of **acute coronary syndromes** in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Sep 21.
693. Warkentin TE, Davidson BL, Büller HR, et al. Prevalence and risk of pre-existing **heparin-induced thrombocytopenia antibodies** in patients with acute VTE. Chest. 2011 Aug;140(2):366-73.
694. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. **Dabigatran** versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing **cardioversion**. Circulation. 2011;123:131–136.
695. Greenhalgh J, Bagust A, Boland A, et al. Clopidogrel and modified-release dipyridamole for the prevention of **occlusive vascular events** (review of Technology Appraisal No. 90): systematic review and economic analysis. Health Technol Assess. 2011 Sep;15(31):1-178. The evidence suggests that the most cost-effective treatment for patients with ischaemic stroke/TIA is clopidogrel followed by MRD + ASA followed by ASA; for patients with MI, ASA followed by clopidogrel; and for patients with established peripheral arterial disease or multivascular disease, clopidogrel followed by ASA.
696. Rodríguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. **Discontinuation of low dose aspirin and risk** of **myocardial infarction**: case-control study in UK primary care. BMJ. 2011 Jul 19;343:d4094.
697. Thomalla G, Cheng B, Ebinger M, et al. **DWI-FLAIR mismatch** for the identifi cation of patients with acute ischaemic stroke within 4·5 h of symptom onset (**PRE-FLAIR**): a multicentre observational study. Lancet Neurol 2011. DOI:10.1016/S1474-4422(11)70192-2.
698. Kim ES, Park N, Peterson C. Dispositional **optimism** protects older adults from stroke: the health and retirement study. Stroke. 2011 Oct;42(10):2855-9.
699. Cadavid JC, DiVietro ML, Torres EA, et al. **Warfarin-induced pulmonary metastatic calcification** and calciphylaxis in a patient with end-stage renal disease. Chest. 2011 Jun;139(6):1503-6.
700. Tarnutzer AA, Berkowitz AL, Robinson KA, et al. Does my **dizzy patient have a stroke**? A systematic review of bedside diagnosis in acute vestibular syndrome. CMAJ. 2011 Jun 14;183(9):E571-92.
701. Kabrhel C, Varraso R, Goldhaber SZ, et al. **Physical inactivity** and idiopathic pulmonary embolism in women: prospective study. BMJ. 2011 Jul 4;343:d3867.
702. Anthony CJ, Karim S, Ackroyd-Stolarz S, et al. **Intensity of anticoagulation** with warfarin and risk of **adverse events** in patients presenting to the emergency department. Ann Pharmacother. 2011 Jul;45(7-8):881-7.
703. Patanwala AE, Acquisto NM, Erstad BL. **Prothrombin complex concentrate** for critical bleeding. Ann Pharmacother. 2011 Jul;45(7-8):990-9.
704. Broderick JP, Bonomo JB, Kissela BM, et al. **Withdrawal of antithrombotic agents** and its impact on ischemic stroke occurrence. Stroke. 2011 Sep;42(9):2509-14.
705. Lillis T, Ziakas A, Koskinas K, et al. Safety of **dental extractions** during uninterrupted single or dual antiplatelet treatment. Am J Cardiol. 2011 Oct 1;108(7):964-7.
706. Loewen P, Dahri K. **Risk of bleeding** with oral anticoagulants: an updated systematic review and performance analysis of clinical prediction rules. Ann Hematol. 2011 Oct;90(10):1191-200.
707. Burn J, Gerdes A-M, Macrae F, et al, on behalf of the **CAPP2** Investigators. Long-term effect of **aspirin on cancer risk** (Lynch syndrome) in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011.
708. Strijkers R H W, Cate-Hoek A J ten, Bukkems S F F W, et al. Management of **deep vein thrombosis and prevention of post-thrombotic syndrome**. BMJ 2011;343:doi:10.1136/bmj.d5916 (Published 31 October 2011)
709. Pink J, Lane S, Pirmohamed M, Hughes DA. **Dabigatran** etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses. BMJ 2011;343:d6333.
710. Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. **Heart disease and stroke statistics**—2011 update: a report from the American Heart Association. Circulation. 2011;123:e18 – e209.
711. Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, et al; on behalf of the **ACTIVE** Steering Committee and Investigators. Net clinical benefit of adding **clopidogrel to aspirin** therapy in patients with atrial fibrillation for whom **vitamin K antagonists are unsuitable**. Ann Intern Med. 2011;155:579-86.
712. Powers WP, Clarke WR, Grubb RL, Videen TO, Adams HP, Derdeyn CP; Carotid Occlusion Surgery Study (**COSS**) Investigators. **Extracranial-intracranial bypass surgery** for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study Randomized trial. JAMA 2011; 306 (18) : 1983-1992.
713. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. **Apixaban versus enoxaparin** for thromboprophylaxis in medically ill patients. (**ADOPT**) NewEngl J Med 2011; DOI:10.1056/NEJM0a1110899.
714. Mega JL et al. for the **ATLAS ACS 2–TIMI 51** Investigators. **Rivaroxaban** in patients with a recent acute coronary syndrome.N Engl J Med 2011 Nov 13. (but at baseline only 66% on BB, & 39% on ACEI)
715. American College of Obstetricians and Gynecologists (**ACOG**). **Thromboembolism in pregnancy**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2011 Sep. 12 p. (ACOG practice bulletin; no. 123).
716. Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian JA, Levine M. **Warfarin dose assessment every 4 weeks versus every 12 weeks** in patients with stable international normalized ratios. A randomized trial. Ann Intern Med. 2011;155:653-9.
717. Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the **RE-LY** trial. Ann Intern Med. 2011;155:660-7.
718. Lederle FA, Zylla D, Macdonald R, Wilt TJ. **Venous thromboembolism prophylaxis** in **hospitalized medical patients** and those with stroke: a background review for an american college of physicians clinical practice guideline. Ann Intern Med. 2011 Nov 1;155(9):602-15.
719. Qaseem A, Chou R, Humphrey LL, et al. for the Clinical Guidelines Committee of the American College of Physicians. **Venous Thromboembolism Prophylaxis in Hospitalized Patients**: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2011 Nov 1;155(9):625-632.
720. Wong PF, Chong LY, Mikhailidis DP, et al. **Antiplatelet agents for intermittent claudication**. Cochrane Database Syst Rev. 2011 Nov 9;11:CD001272. Antiplatelet agents have a beneficial effect in reducing all cause mortality and fatal cardiovascular events in patients with IC. Treatment with antiplatelet agents in this patient group however is associated with an increase in adverse effects, including GI symptoms, and healthcare professionals and patients need to be aware of the potential harm as well as the benefit of therapy; more data are required on the effect of antiplatelets on major bleeding.
721. Biffi A, Battey TW, Ayres AM, et al. **Warfarin-related intraventricular hemorrhage**: Imaging and outcome. Neurology. 2011 Nov 15;77(20):1840-6.
722. Canadian Agency for Drugs and Technologies in Health (**CADTH**). **Optimal warfarin** management for the prevention of thromboembolic events in patients with atrial fibrillation: review of Canadian **economic studies** [Internet]. Ottawa: The Agency; 2011 Nov [

TOP

(Optimal use report; vol. 1 iss. 2b). Available from http://www.cadth.ca/media/pdf/OP0508_warfarin_science-report-2_cost_e.pdf
Canadian Agency for Drugs and Technologies in Health (**CADTH**). **Optimal warfarin** management for the prevention of thromboembolic events in patients with atrial fibrillation: a **systematic review** of the clinical evidence [Internet]. Ottawa: The Agency; 2011 Nov [2011 Nov 21].
(Optimal use report; vol. 1 iss. 2a). Available from http://www.cadth.ca/media/pdf/OP0508_warfarin-science-report-1_clinical_e.pdf
Canadian Agency for Drugs and Technologies in Health (**CADTH**). Recommendations for **Optimal Warfarin** Management for Prevention of Thromboembolic Events in Patients with Atrial Fibrillation.
http://www.cadth.ca/media/pdf/OP0508_warfarin_rec-report_e.pdf
CERC recommends that patients with NVAF requiring **warfarin** be managed by a **well-coordinated**, **structured approach** dedicated to their anticoagulation therapy. CERC does **not recommend self-management** for most patients with NVAF requiring warfarin.

723. Stone DH, Goodney PP, Schanzer A, et al. Vascular Study Group of New England. **Clopidogrel is not associated with major bleeding** complications during peripheral arterial surgery. J Vasc Surg. 2011 Sep;54(3):779-84.
724. Berger JS, Lala A, Krantz MJ, et al. **Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease**: a meta-analysis of randomized trials. Am Heart J. 2011 Jul;162(1):115-24.e2.
725. Zöller B, Li X, Sundquist J, Sundquist K. Risk of **pulmonary embolism in patients with autoimmune disorders**: a nationwide follow-up study from Sweden. Lancet 2011; published online Nov 26. DOI:10.1016/S0140-6736(11)61306-8.
726. Chapman SA, Irwin ED, Beal AL, et al. **Prothrombin complex concentrate** versus standard therapies for INR reversal in trauma patients receiving **warfarin**. Ann Pharmacother. 2011 Jul;45(7-8):869-75.
727. Teichert M, Visser LE, Uitterlinden AG, et al. **Selective serotonin re-uptake inhibiting antidepressants** and the risk of **overanticoagulation** during acenocoumarol maintenance treatment. Br J Clin Pharmacol. 2011 Nov;72(5):798-805.
728. Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptorantagonists **clopidogrel and ticagrelor** in the PLATelet inhibition and patient Outcomes (**PLATO**) trial. Eur Heart J. 2011 Nov 16.
729. Büller HR, Gallus AS, Pillion G, et al. on behalf of the Cassiopea Investigators. Enoxaparin followed by once-weekly **idrabiotaparinux** versus enoxaparin plus warfarin for patients with acute symptomatic pulmonary embolism: a randomised, double-blind, double-dummy, non-inferiority trial. Lancet 2011; published online Nov 28.
730. Rautiainen S, Larsson S, Virtamo J, Wolk A. **Total antioxidant capacity of diet and risk of stroke**: A population-based prospective cohort of women. Stroke 2012; DOI:10.1161/STROKEAHA.111.635557.
731. Heneghan C, Ward, A, Perera R, and The Self-Monitoring Trialist Collaboration. **Self-monitoring of oral anticoagulation**: systematic review and meta-analysis of individual patient data. Lancet 2011; published online Dec 1.
732. Simpson SH, Gamble JM, Mereu L, et al. Effect of **aspirin** dose on mortality and cardiovascular events in people with **diabetes**: a meta-analysis. J Gen Intern Med. 2011 Nov;26(11):1336-44.
733. Ho KM, Chavan S, Pilcher D. **Omission of early thromboprophylaxis and mortality in critically ill patients**: a multicenter registry study. Chest. 2011;140(6):1436-1446.
734. Lip GYH, Andreotti F, Fauchier L, et al. **Bleeding risk assessment and management in atrial fibrillation** patients. Executive summary of a position document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [**ESC**] Working Group on Thrombosis. Thromb Haemost 2011; 106:997-1011.
735. Biondi-Zoccai G, Landoni G. **Discontinuation of aspirin** for secondary prevention. BMJ. 2011 Jul 19;343:d3942. doi: 10.1136/bmj.d3942.
736. Douketis JD, Iorio A. The association between **venous thromboembolism and physical inactivity** in everyday life. BMJ. 2011 Jul 4;343:d3865.
737. Sipahi I, Swaminathan A, Natesan V, et al. Effect of antihypertensive therapy on incident **stroke in cohorts with prehypertensive** blood pressure levels: A meta-analysis of randomized controlled trials. Stroke 2011
738. Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional **catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis** (the **CaVenT** study): a randomized controlled trial. Lancet 2011
739. Canadian Agency for Drugs and Technologies in Health. Optimal **warfarin management** for the prevention of thromboembolic events in patients with atrial fibrillation: review of Canadian economic studies. (CADTH). 2011 Nov; 1: 1-27.
740. Kakkar AK, Cimminiello C, Goldhaber SZ, et al. Low-molecular-weight heparin (**enoxaparin**) and mortality in acutely ill medical patients (**LIFENOX**). N Engl J Med 2011; 365: 2463-2472.
Kakkar VV, Corrigan TP, Fossard DP, et al. Prevention of **fatal postoperative pulmonary embolism by low doses of heparin**. An international multicentre trial. Lancet 1975; 2:45-51.
741. Holmes MV, Perel P, Shah T, et al. **CYP2C19 genotype, clopidogrel** metabolism, platelet function and cardiovascular events. A systematic review and meta-analysis. JAMA 2011; 306:2704-2714.
742. Uchino K, Hernandez AV. **Dabigatran** association with **higher risk of acute coronary events**: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. doi:10.1001/archinternmed.2011.1666.
743. Seshasai SRK, Wijesuriya S, Sivakumaran R, et al. Effect of **aspirin** on **vascular and nonvascular outcomes**: meta-analysis of randomized controlled trials [online Jan 9, 2012]. Archives Intern Med. doi:10.1001/archinternmed.2011.628.
744. Flinterman LE, van Hylckama Vlieg A, Cannegieter S, Rosendaal FR. **Long-term survival** in a large cohort of patients with venous thrombosis: Incidence and predictors. PLoS Med 2012; DOI:10.1371/journal.pmed.1001155.
745. Lip GY, Felmeden DC, Dwivedi G. **Antiplatelet agents and anticoagulants** for hypertension. Cochrane Database Syst Rev. 2011 Dec 7;12:CD003186. Antiplatelet therapy with ASA for primary prevention in patients with elevated blood pressure provides a benefit, reduction in myocardial infarction, which is negated by a harm of similar magnitude, increase in major haemorrhage.The benefit of antiplatelet therapy for secondary prevention in patients with elevated blood pressure is many times greater than the harm.Benefit has not been demonstrated for warfarin therapy alone or in combination with aspirin in patients with elevated blood pressure.
746. Leung AN, Bull TM, Jaeschke R, et al. **ATS/STR** Committee on Pulmonary Embolism in Pregnancy. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: **evaluation of suspected pulmonary embolism in pregnancy**. Am J Respir Crit Care Med. 2011 Nov 15;184(10):1200-8.
747. Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with **cangrelor** in patients undergoing cardiac surgery. A randomized controlled trial. (**BRIDGE**) JAMA 2012; 307:265-274.
748. Januel J-M, Chen G, Ruffieux C, et al. Symptomatic **in-hospital deep vein thrombus and pulmonary embolism** following **hip and knee arthroplasty** among patients receiving recommended prophylaxis. A systematic review. JAMA 2012; 307:294-303.
749. Roy B et al. Effect of **Warfarin on Outcomes in Septuagenarian** Patients With Atrial Fibrillation. (**AFFIRM**) Am J Cardiol. 2011 Nov 23.
750. Gwon HC, Hahn JY, et al. **Six-month versus 12-month dual antiplatelet** therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (**EXCELLENT**) randomized, multicenter study.Circulation. 2012;125:505–513.
751. Menditto VG, Lucci M, Polonara S et al. Management of **Minor Head Injury in Patients Receiving Oral Anticoagulant Therapy (warfarin)**: A Prospective Study of a 24-Hour Observation Protocol. Ann Emerg Med. 2012 Jan 13. (Second CT scan to detect delayed bleeding)
752. Kappelman MD, Horvath-Puho E, Sandler RS, et al. **Thromboembolic risk among Danish children and adults with inflammatory bowel diseases**: a populationbased nationwide study. Gut 2011;60:937–943.
753. Cayla G, Hulot JS, O'Connor SA et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. JAMA. 2011 Oct 26;306(16):1765-74. (3 genes and 2 clopidogrel related factors-loading dose & PPIs))
754. Carlquist JF, Anderson JL. Using **pharmacogenetics in real time to guide warfarin** initiation: a clinician update. Circulation. 2011 Dec 6;124(23):2554-9.
755. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of **dabigatran versus warfarin** for periprocedural anticoagulation in patients undergoing **radiofrequency ablation** for atrial fibrillation. J Am Coll Cardiol 2012.
756. Diener HC, Eikelboom J, Connolly SJ, et al. **Apixaban versus aspirin** in patients with atrial fibrillation and **previous stroke** or transient ischaemic attack: a predefined subgroup analysis from **AVERROES**, a randomised trial. Lancet Neurol 2012.
757. Seshasai SRK, Wijesuriya S, Sivakumaran R, et al. Effect of **aspirin** on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials [online January 9, 2012]. Arch Intern Med. 2012;172(3):209-216.
758. Wellenius GA, Burger MR, Coull BA, et al. Ambient **air pollution** and the risk of acute ischemic stroke. Arch Intern Med. 2012;172(3):229-23.
759. Agnelli G, George DJ, Kakkar AK, et al. **Semuloparin** for thromboprophylaxis in patients receiving chemotherapy for cancer. (**SAVE-ONCO**) N Engl J Med 2012;366:601-9.
760. Jaturapatporn D, Isaac MG, McCleery J, et al. **Aspirin, steroidal and non-steroidal anti-inflammatory drugs** for the treatment of **Alzheimer`s disease**. Cochrane Database Syst Rev. 2012 Feb 15;2:CD006378. Based on the studies carried out so far, the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven. Therefore, these drugs cannot be recommended for the treatment of AD.
761. Prandoni P, Noventa F, Quintavalla R, et al. Thigh-length versus below-knee compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. Blood. 2012 Feb 9;119(6):1561-1565
762. Cohen JM, Akl EA, Kahn SR. Pharmacologic and compression therapies for **postthrombotic syndrome** (PTS): a systematic review of randomized controlled trials. Chest. 2012 Feb;141(2):308-20. (supports **intermittent compression**)
763. Poli D, Antonucci E, Testa S, et al. Italian Federation of Anticoagulation Clinics. Bleeding risk in **very old patients** on vitamin K antagonist (**warfarin**) treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. Circulation. 2011 Aug 16;124(7):824-9.
764. Paikin J, Eikelboom, J. **Aspirin (patient page).** Circulation. 2012;125:e439-e442.
765. Furlan AJ, Reisman M, Massaro J, et al. **Closure** or medical therapy for cryptogenic stroke with **patent foramen ovale**. **(Closure I)** N Engl J Med 2012;366:991-9. (closure with a device did not benefit)
766. **Aspirin for cancer**: Rothwell PM, Price JF, Fowkes FGR, et al. Short-term eff ects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefi ts in 51 randomised controlled trials. Lancet 2012; online March 21.
Rothwell PM, Wilson M, Price JF, Belch JFF, Meade TW, Mehta Z. Eff ect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012; online March 21. DOI:10.1016/S0140-6736(12)60209-8.
Algra AM, Rothwell PM. Eff ects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncology 2012; online March 21. DOI:10.1016/S1470-2045(12)70112-2.
Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of **aspirin on colorectal cancer** incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010 Oct 21.
Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily **aspirin on long-term risk of death due to cancer**: analysis of individualpatient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41.
Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study (**WHS**): a randomized controlled trial. JAMA 2005; 294: 47–55. (no effect)
Sturmer T, Glynn RJ, Lee IM, Manson JE, Buring JE, Hennekens CH. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study (**PHS**). Ann Intern Med 1998; 128: 713–20. (no effect)
767. Health Canada Mar/12 The Pradax (**dabigatran** etexilate) product monograph has been updated to include in elderly to assess **renal function** initially & at least once a year.
Use of Pradax® in patients with hemodynamically significant rheumatic valvular heart disease, especially mitral stenosis, or in patients with prosthetic heart valves is not recommended.
768. Palmer SC, Micco LD, Razavian M, et al. Effects of **antiplatelet therapy** on mortality and cardiovascular and bleeding outcomes in persons with **chronic kidney disease**. A systematic review and meta-analysis. Ann Intern Med 2012; 156:445-459.
769. Skanes AC, Healey JS, Cairns JA, et al. Focused **2012 update of the Canadian Cardiovascular Society (CCS) atrial fibrillation guidelines**: Recommendations for stroke prevention and rate/rhythm control. Can J Cardiol 2012; 28:125-136.
770. Schulman S. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: no. Stroke. 2011 Dec;42(12):3663-4.
Steiner T. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: yes. Stroke. 2011 Dec;42(12):3661-2.
771. Büller HR et al. for the **EINSTEIN–PE** Investigators. Oral **rivaroxaban** (15mg po bid x 3 wk, then 20mg od) for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012 Mar 26.
772. Agarwal S, Hachamovitch R, Menon V. Current **trial-associated outcomes with warfarin** in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis [published online March 26, 2012]. Arch Intern Med. doi10.1001/archinternmed.2012.121
773. Morrow DA et al. for the **TRA 2P–TIMI 50** Steering Committee and Investigators. **Vorapaxar** in the secondary prevention of atherothrombotic events. N Engl J Med 2012 Mar 24.
774. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (**RAPID GENE**): a prospective, randomised, proof-of-concept trial. Lancet 2012; online March 29. (clopidogrel or prasugrel given)
775. Walter S, Kostopoulos P, Haass A, et al. Diagnosis and treatment of patients with stroke in a **mobile stroke unit** versus in hospital: A randomised controlled trial. Lancet Neurol 2012.
776. Ahmed I, Gertner E. Safety of **arthrocentesis and joint injection in patients receiving anticoagulation** at therapeutic levels. Am J Med. 2012 Mar;125(3):265-9.
777. Kasiman K, Lundholm C, Sandin S, et al. **Familial Effects on Ischemic Stroke**: The Role of Sibling Kinship, Sex and Age of Onset. Circ Cardiovasc Genet. 2012 Mar 9.
778. Piazza G. **Cerebral venous thrombosis**. Circulation. 2012 Apr 3;125(13):1704-9.
779. Shaheen K, Alraies MC, Alraiyes AH, et al. **Factor V Leiden**: How great is the risk of venous thromboembolism? Cleve Clin J Med. 2012 Apr;79(4):265-72.
780. Voore NK, Rahman A, Sanna S, Bahrain H. **Purpuric lesion** on the elbow. Cleve Clin J Med. 2012 Apr;79(4):253-4. (**warfarin induced necrosis**)
781. De Caterina R, Husted S, Wallentin L, et al. **New oral anticoagulants** in **atrial fibrillation** and acute coronary syndromes. **ESC** Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease position paper. J Am Coll Cardiol 2012; 59:1413-25.
782. Liu CP, Chen WC, Lai KH, et al. **Esomeprazole Alone Compared with Esomeprazole Plus Aspirin** for the Treatment of Aspirin-Related Peptic Ulcers. Am J Gastroenterol. 2012 Apr 17.
783. Hsu PI, Lai KH, Liu CP. **Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone**, in patients with atherosclerosis. Gastroenterology. 2011 Mar;140(3):791-8.
784. Lin KJ, Hernández-Díaz S, García Rodríguez LA. **Acid suppressants reduce risk of gastrointestinal bleeding in patients on antithrombotic** or anti-inflammatory therapy. Gastroenterology. 2011 Jul;141(1):71-9.
785. Anderson JL, Horne BD, Stevens SM, et al. A randomized and clinical effectiveness trial comparing two **pharmacogenetic algorithms** and standard care for individualizing warfarin dosing (**Coumagen-II**). Circulation. 2012;125:1997–2005.

TOP

786. Valgimigli M, Campo G, Monti M, et al. **Short- versus long-term duration (6 vs 24 months)** of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial (**Prodigy**). Circulation. 2012;125:2015–2026.
787. Bastiaannet E, Sampieri K, Dekkers OM, et al. Use of **Aspirin** postdiagnosis improves survival for **colon cancer** patients. Br J Cancer. 2012 Mar 27.
788. Hart RG, Diener HC, Yang S, et al. **Intracranial hemorrhage** in atrial fibrillation patients during anticoagulation with warfarin or **dabigatran**: The **RE-LY** trial. Stroke 2012.
789. Baillargeon J, Holmes HM, Lin YL, et al. Concurrent use of **warfarin and antibiotics** (eg azoles, macrolides, quinolones etc..) and the risk of **bleeding** in older adults. Am J Med. 2012 Feb;125(2):183-9.
790. Olesen JB, Torp-Pedersen C, Hansen ML, and Lip GYH. The value of the **CHA2DS2-VASc score** for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: A nationwide cohort study. Thromb Haemost 2012.
791. Homma S, Thompson JLP, Pullicino PM, et al. **Warfarin and aspirin** in patients with **heart failure** and sinus rhythm. (**WARCEF**) N Engl J Med 2012. DOI: 10.1056/NEJMoa1202299.
792. Rogers MAM, Levine DA, Blumberg N, et al. **Triggers of hospitalization for venous thromboembolism**. Circulation. 2012;125:2092–2099.
793. Prasad V, Rho J, Cifu A. The Diagnosis and **Treatment of Pulmonary Embolism**: A Metaphor for Medicine in the Evidence-Based Medicine Era. Arch Intern Med. 2012 Apr 2.
794. Tsai J, Grosse SD, Grant AM, et al. Trends in In-Hospital **Deaths** Among Hospitalizations With **Pulmonary Embolism**. Arch Intern Med. 2012 Apr 2.
795. Goldhaber SZ, Bounameaux H. **Pulmonary embolism and deep vein thrombosis**. Lancet. 2012 Apr 5.
796. Larsson SC, Virtamo J, Wolk A. **Dairy** Consumption and Risk of **Stroke** in Swedish Women and Men. Stroke. 2012 Apr 19.
797. Lee SJ, Shin DH, Hwang HJ et al. **Bleeding Risk** and Major Adverse Events in Patients With **Previous Ulcer on Oral Anticoagulation** Therapy. Am J Cardiol. 2012 Apr 18.
798. Rubboli A, Magnavacchi P, Guastaroba P, et al.Antithrombotic Management and 1-Year Outcome of Patients on **Oral Anticoagulation Undergoing Coronary Stent** Implantation (from the Registro Regionale Angioplastiche Emilia-Romagna Registry). Am J Cardiol. 2012 Feb 17.
799. Di Nisio M, Wichers IM, Middeldorp S. **Treatment for superficial thrombophlebitis of the leg.** Cochrane Database Syst Rev. 2012 Mar 14;3:CD004982. Prophylactic dose fondaparinux given for six weeks appears to be a valid therapeutic option for ST of the legs. Further research is needed to assess the role of new oral direct thrombin and activated factor-X inhibitors, LMWH, NSAIDs; the optimal doses and duration of treatment; and whether a combination therapy may be more effective than single treatment. Adequately designed and conducted studies are required to clarify the role of topical and surgical treatments.
800. Frelinger AL 3rd, Lee RD, Mulford DJ, et al. A randomized, 2-period, crossover design study to assess the effects of **dexlansoprazole, lansoprazole, esomeprazole, and omeprazole** on the steady-state pharmacokinetics and pharmacodynamics of **clopidogrel** in healthy volunteers. J Am Coll Cardiol. 2012 Apr 3;59(14):1304-11.
801. Ng FH, Tunggal P, Chu WM, et al. **Esomeprazole compared with famotidine** in the prevention of upper gastrointestinal bleeding in patients with acute coronary syndrome or myocardial infarction. Am J Gastroenterol. 2012 Mar;107(3):389-96.
802. Derry S, Moore RA. Single dose oral **aspirin for acute postoperative pain** in adults. Cochrane Database Syst Rev. 2012 Apr 18;4:CD002067. Aspirin is an effective analgesic for acute pain of moderate to severe intensity. High doses are more effective, but are associated with increased adverse events, including drowsiness and gastric irritation. The pain relief achieved with aspirin was very similar milligram for milligram to that seen with paracetamol.
803. Perk J, De Backer G, Gohlke H, et al. **European guidelines (ESC) on cardiovascular disease** in clinical practice (version 2012). Eur Heart J2012; DOI:10.1093/eurheartj/ehs092.
804. Sobieraj DM, Lee S, Coleman CI et al. **Prolonged versus standard-duration** venous thromboprophylaxis in major orthopedic surgery. A systematic review. Ann Intern Med. 2012;156:720-7.
805. Neumann I, Rada G, Claro JC et al. **Oral direct factor Xa inhibitors versus low-molecular-weight heparin** to prevent thromboembolism in patients undergoing total hip or knee replacement. A systematic review and meta-analysis. Ann Intern Med. 2012;156:710-9.
806. Del Río Solá ML, Antonio J, Fajardo G, Vaquero Puerta C. Influence of **Aspirin** Therapy in the Ulcer Associated With **Chronic Venous Insufficiency**. Ann Vasc Surg. 2012 Mar 19.
807. Davis SM, Donnan GA. **Secondary Prevention after Ischemic Stroke or Transient Ischemic Attack**. N Engl J Med 2012; 366:1914-1922.
808. Maletis GB, Inacio MC, Reynolds S, Funahashi TT. Incidence of symptomatic **venous thromboembolism** after **elective knee arthroscopy**. J Bone Joint Surg Am. 2012 Apr 18;94(8):714-20. The ninety-day incidence of symptomatic venous thromboembolism after elective knee arthroscopy was relatively low, with a 0.25% incidence of deep venous thrombosis and a 0.17% incidence of pulmonary embolism.
809. Parkin L, Sweetland S, Balkwill A, et al. the **Million Women Study Collaborators**. **Body Mass Index, Surgery, and Risk of Venous Thromboembolism** in Middle-Aged Women: A Cohort Study. Circulation. 2012 Apr 17;125(15):1897-1904.
810. IST-3 collaborative group. The benefits and harms of **intravenous thrombolysis** with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet 2012; online May 23.
811. Wardlaw J, Murray V, Berge E, et al. **Recombinant tissue plasminogen activator** for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 2012; published online May 23.
812. Becattini C, Agnelli G, Schenone A, et al. **Aspirin for preventing the recurrence of venous thromboembolism**. (**WARFASA**) N Engl J Med 2012;366:1959-67.
813. Park Y, Jeong YH, Tantry US, et al. Accelerated platelet inhibition (with **clopidogrel**) by switching from **atorvastatin to a non-CYP3A4-metabolized statin** in patients with high platelet reactivity (ACCEL-STATIN) study. Eur Heart J 2012.
814. Medical Letter. Choice of drugs for **Heparin-Induced Thrombocytopenia** (HIT). May 28, 2012. (argatroban, fondaparinux, danaparoid)
815. Lackland DT, Elkind MSV, D'Agostino R, et al. Inclusion of **stroke in cardiovascular risk prediction** instruments: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012;
816. Feske SK. **Thrombolytic therapy of acute stroke**. Circulation. 2012 May 29;125(21):2662-6.
817. Schindewolf M, Lindhoff-Last E, Ludwig RJ, Boehncke WH. **Heparin-induced skin lesions**. Lancet. 2012 May 25.
818. Cappuccio FP, Ji C. **Less salt** and less risk of stroke: further support to action. Stroke. 2012 May;43(5):1195-6.
819. Banerjee C, Moon YP, Paik MC, et al. Duration of **diabetes and risk of ischemic stroke**: the northern Manhattan study. Stroke. 2012 May;43(5):1212-7.
820. Mazighi M, Meseguer E, Labreuche J, Amarenco P. **Bridging therapy in acute ischemic stroke**: a systematic review and meta-analysis. Stroke. 2012 May;43(5):1302-8.
821. Lee M, Saver JL, Hong K-S, Song S, Chang K-H, Ovbiagele B. Effect of **pre-diabetes on future risk of stroke**: meta-analysis. BMJ 2012;344:e3564.
822. Schouten HJ, Koek HL, Oudega R, et al. **Validation of two age dependent D-dimer cut-off values** for exclusion of deep vein thrombosis in suspected elderly patients in primary care: retrospective, cross sectional, diagnostic analysis. BMJ. 2012 Jun 6;344:e2985.
823. Dávalos A, Alvarez-Sabín J, Castillo J, et al, International Citicoline Trial on acUte Stroke (**ICTUS**) trial investigators. **Citicoline** in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). Lancet 2012; online June 11.
824. Price MJ, Walder JS, Baker BA et al. Recovery of platelet function after **discontinuation of prasugrel or clopidogrel** maintenance dosing in aspirin-treated patients with stable coronary disease. The RECOVERY trial. J Am Coll Cardiol 2012.
825. Gómez-Outes A, et al. **Dabigatran, rivaroxaban, or apixaban versus enoxaparin** for thromboprophylaxis after total **hip or knee replacement**: systematic review, meta-analysis, and indirect treatment comparisons. BMJ 2012;344:e3675.
826. Garcia DA, Crowther MA. **Reversal of warfarin**: case-based practice recommendations. Circulation. 2012 Jun 12;125(23):2944-7.
827. Mills EJ, Wu P, Alberton M, et al. **Low-dose Aspirin** and **Cancer** Mortality: A Meta-analysis of Randomized Trials. Am J Med. 2012 Jun;125(6):560-7.
828. James SK, Storey RF, Khurmi NS, et al.. **Ticagrelor versus clopidogrel** in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. (**Plato**) *Circulation.* 2012;125:2914 –2921.
829. Jardine MJ, Kang A, Zoungas S, et al. The effect of **folic acid based homocysteine lowering** on cardiovascular events in people with **kidney disease**: systematic review and meta-analysis. BMJ 2012;344:e3533.
830. Kiviniemi T, Karjalainen P, Pietilä M, et al. Comparison of **Additional Versus No Additional Heparin During Therapeutic Oral Anticoagulation** (warfarin) in Patients Undergoing Percutaneous Coronary Intervention. Am J Cardiol. 2012 Mar 29.
831. Kumai Y, Kamouchi M, Hata J, et al; For the FSR Investigators. **Proteinuria and clinical outcomes after ischemic stroke**. Neurology. 2012 Jun 12;78(24):1909-1915.
832. **BRIDGE** Study Investigators. Bridging **anticoagulation**: is it needed when warfarin is interrupted around the time of a surgery or procedure? Circulation. 2012 Mar 27;125(12):e496-8.
833. Geeganage CM, Diener HC, Algra A, et al. **Dual or mono antiplatelet therapy for patients with acute ischemic stroke** or transient ischemic attack: systematic review and meta-analysis of randomized controlled trials. Stroke. 2012 Apr;43(4):1058-66.
834. Gurbel PA, Nolin TD, Tantry US. **Clopidogrel efficacy and cigarette smoking** status. JAMA 2012; 307:2495-2496.
835. Hamer M, Kivimaki M, Stamatakis E, Batty GD. **Psychological distress** as a risk factor for death from cerebrovascular disease. CMAJ. 2012 Jun 18.
836. Streiff MB, Carolan HT, Hobson DB, et al. Lessons from the Johns Hopkins Multi-Disciplinary **Venous Thromboembolism (VTE) Prevention Collaborative**. BMJ. 2012 Jun 19;344:e3935.
837. Costa GL, Lamego RM, Colosimo EA, et al. Identifying Potential Predictors of **High-Quality Oral Anticoagulation** Assessed by Time in Therapeutic International Normalized Ratio Range: A Prospective, Long-Term, Single-Center, Observational Study. Clin Ther. 2012 Jun 18.
838. Suh DC, Nelson WW, Choi JC, Choi I. Risk of **Hemorrhage and Treatment Costs Associated With Warfarin Drug Interactions** in Patients With Atrial Fibrillation. Clin Ther. 2012 Jun 19.
839. Ndrepepa G, Schuster T, Hadamitzky M et al. Validation of the bleeding academic research consortium definition of bleeding (**BARC**) in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation. 2012 Mar 20;125(11):1424-31.
840. Subherwal S, Peterson ED, Chen AY, et al. Admission International Normalized Ratio Levels, Early Treatment Strategies, and Major Bleeding Risk Among **Non-ST-Segment-Elevation Myocardial Infarction** Patients on Home **Warfarin** Therapy: Insights From the National Cardiovascular Data Registry. Circulation. 2012 Mar 20;125(11):1414-23.
841. Capodanno D, Angiolillo DJ. **Antithrombotic therapy in patients with chronic kidney disease**. Circulation. 2012 May 29;125(21):2649-61.
842. De Berardis G, Lucisano G, D'Ettorre A, et al. Association of **aspirin use** with major **bleeding** in patients with and without **diabetes**. JAMA. 2012;307(21): 2286-2294.
843. Reny JL, Berdagué P, Poncet A, et al. **Antiplatelet Drug Response Status Does Not** Predict Recurrent Ischemic Events in Stable Cardiovascular Patients: Results of the ADRIE Study. Circulation. 2012 May 21.

TOP

Acknowledgements: Contributors & Reviewers: Adrienne Lindblad, PharmD (Red Deer), Dr. Omar Sultan, MD, FRCPC (RQHR) & the RxFiles Advisory Committee. Prepared by: *M. Jin*$_{PharmD}$, *L.Kosar*$_{MSc}$, *B. Jensen* $_{BSP}$, *L. Regier* $_{BSP, BA}$

References: RxFiles Atrial Fibrillation

Additional references:

Adlan AM, Lip GY. Role of the **CHADS2 Score in Acute Coronary Syndromes**: With or Without Atrial Fibrillation. Chest. 2012 Jun;141(6):1375-6.

Agarwal S, Hachamovitch R, Menon V. Current **trial-associated outcomes with warfarin** in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis [published online March 26, 2012]. Arch Intern Med. doi10.1001/archinternmed.2012.121

Alberts MJ, Bernstein RA, Naccarelli GV, Garcia DA. Using Dabigatran in Patients With Stroke: A Practical Guide for Clinicians. Stroke. 2011 Dec 8. [Epub ahead of print]

Allan GM, Korownyk C, Kolber MR. Rate versus rhythm in atrial fibrillation: And how slow do you go? Can Fam Physician. 2011 Dec;57(12):1411.

Alonso A, Lopez FL, Matsushita K, et al. **Chronic Kidney Disease** Is Associated With the Incidence of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2011 Jun 28;123(25):2946-53.

Ansell J. New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. Circulation. 2012 Jan 3;125(1):165-70; discussion 170. Review.

Atrial Fibrillation Investigators. **Risk factors** for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from 5 randomized controlled trials. *Arch Intern Med.* 1994;154:1449–1457.

Bäck M, Yin L, Ingelsson E. **Cyclooxygenase-2 inhibitors** and cardiovascular risk in a nationwide cohort study after the withdrawal of rofecoxib. Eur Heart J 2011.

Boersma LV, Castella M, van Boven WJ, et al. Atrial fibrillation **catheter ablation versus surgical ablation treatment (FAST):** A two-year randomized clinical trial. Circulation 2012

Boriani G, Cervi E, Diemberger I, et al. Clinical management of atrial fibrillation: need for a comprehensive **patient-centered approach**. Chest. 2011 Oct;140(4):843-5.

Büller HR et al. for the **EINSTEIN–PE** Investigators. Oral **rivaroxaban** (15mg po bid x 3 wk, then 20mg od) for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012 Mar 26.

Bum Kim J, Suk Moon J, Yun SC, et al. Long-term outcomes of **mechanical valve replacement** in patients with atrial fibrillation: impact of the maze procedure. Circulation. 2012 May 1;125(17):2071-80.

Canadian Agency for Drugs and Technologies in Health (CADTH). Dabigatran for stroke prevention in atrial fibrillation: a review of the evidence on safety. March 6, 2012.

Capodanno D, Capranzano P, Giacchi G, et al. **Novel oral anticoagulants versus warfarin** in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients. Int J Cardiol. 2012 Apr 9.

Carlberg B, Samuelsson O, Lindholm LH. **Atenolol in hypertension**: is it a wise choice? Lancet. 2004 Nov 6;364(9446):1684-9.

Carlsson J, Miketic S, Windeler J, et al. for the **STAF** Investigators. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol.* 2003;41:1690–1696.

Chan PS, Maddox TM, Tang F, et al. **Practice-Level Variation in Warfarin** Use Among Outpatients With Atrial Fibrillation (from the NCDR PINNACLE Program). Am J Cardiol. 2011 Oct 15;108(8):1136-40.

Chan W et al. Melbourne Interventional Group Investigators. Impact of **Periprocedural Atrial Fibrillation** on Short-Term Clinical Outcomes Following Percutaneous Coronary Intervention. Am J Cardiol. 2011 Dec 15.

Chao TF, Tsao HM, Lin YJ, Tsai CF, et al. Clinical Outcome of **Catheter Ablation** in Patients with Non-Paroxysmal Atrial Fibrillation:The Results of 3-Year Follow Up. Circ Arrhythm Electrophysiol. 2012 May 1.

Chatterjee S, Ghosh J, Lichstein E, et al. Meta-Analysis of Cardiovascular Outcomes With **Dronedarone** in Patients With Atrial Fibrillation or Heart Failure. Am J Cardiol. 2012 May 18.

Conen D, Tedrow UB, Koplan BA, et al. Influence of **systolic and diastolic blood pressure** on the risk of incident atrial fibrillation in women. Circulation. 2009;119:2146 –2152.

Conen D, Chae CU, Glynn RJ, et al. Risk of death & cardiovascular events in initially **healthy women with new-onset atrial fibrillation**. (WHS) JAMA. 2011;305:2080-7.

Darby AE, Dimarco JP. Management of atrial fibrillation in patients **with structural heart disease**. Circulation. 2012 Feb 21;125(7):945-57.

Davis SM, Donnan GA. **Secondary Prevention after Ischemic Stroke or Transient Ischemic Attack**. N Engl J Med 2012; 366:1914-1922.

De Caterina Raffaele; Ruigomez Ana; Rodriguez Luis Alberto Garcia. Long-term Use of Anti-inflammatory Drugs (**NSAIDS**) and Risk of Atrial Fibrillation. Arch Intern Med. 2010;170(16):1450-1455.

Desmukh A, Pant S, Gagan K, et al. Comparison of outcomes of **weekend versus weekday admission** for atrial fibrillation. Am J Cardiol 2012.

Dublin S, Anderson ML, Haneuse SJ, et al. Atrial fibrillation and risk of **dementia**: a prospective cohort study. J Am Geriatr Soc. 2011 Aug;59(8):1369-75.

Easton JD, Lopes RD, Bahit MC, et al, for the **ARISTOTLE** Committees and Investigators. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol 2012; online May 8.

Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. **Reversal of Rivaroxaban** and Dabigatran by Prothrombin Complex Concentrate: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects. Circulation.2011 Sep 6.

El-Chami MF, Kilgo PD, Elfstrom KM, et al. Prediction of New Onset Atrial Fibrillation **After Cardiac Revascularization Surgery**. Am J Cardiol. 2012 May 21.

EMA: European Medicines Agency. European Medicines Agency recommends restricting use of dronedarone- Multaq [press release]. September 22, 2011.

Ezekowitz MD, Aikens TH, Nagarakanti R, Shapiro T. Atrial fibrillation: **outpatient presentation and management**. Circulation. 2011 Jul 5;124(1):95-9.

Fang WT, Li HJ, Zhang H et al. The Role of **Statin** Therapy in the Prevention of Atrial Fibrillation: A Meta-Analysis of Randomized Controlled Trials. Br J Clin Pharmacol. 2012 Feb 29.

Fauchier L, Pellegrin C, Bernard A, et al. Comparison of Frequency of Major Adverse Events in Patients With Atrial Fibrillation Receiving **Bare-Metal Versus Drug-Eluting Stents** in Their Coronary Arteries. Am J Cardiol. 2012 Mar 29.

Faxon DP, Eikelboom JW, Berger PB, et al. Consensus Document: Antithrombotic therapy in patients with atrial fibrillation undergoing **coronary stenting**. A North-American perspective. Thromb Haemost. 2011 Sep 27;106(4):572-84.

FDA Dec/11 Has revised the label of the antiarrhythmic drug **dronedarone** (Multaq) to caution against prescribing it to patients with permanent atrial fibrillation. Dronedarone doubles their risk for cardiovascular **death, stroke, and heart failure**, the agency announced after reviewing data from the **PALLAS** trial.

Fragakis N, Koskinas KC, Katritsis DG, et al. Comparison of Effectiveness of **Ranolazine Plus Amiodarone** Versus Amiodarone Alone for Conversion of Recent-Onset Atrial Fibrillation. Am J Cardiol. 2012 May 21.

Friberg Leif, Rosenqvist Mårten, Lip Gregory Y.H.. Evaluation of **risk stratification schemes** for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J first published online January 13, 2012 doi:10.1093/eurheartj/ehr488. (CHA2DS2-VASc, HAS-BLED)

Friberg L, Rosenqvist M, Lip GYH. **Net clinical benefit of warfar**in in patients with atrial fibrillation: a report from the Swedish Atrial Fibrillation Cohort Study. Circulation. 2012;125:2298 –2307.

Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of **female sex as a risk factor** in atrial fibrillation in Sweden: nationwide retrospective cohort study. BMJ. 2012 May 30;344:e3522.

Fuster V, Chinitz JS. Net clinical benefit of warfarin: extending the reach of antithrombotic therapy for atrial fibrillation. Circulation. 2012 May 15;125(19):2285-7. Epub 2012 Apr 18.

Fuster V, Ryde´n LE, Cannom DS, et al.**2011 ACCF/AHA/HRS** focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011;123:e269–e367.

Gao S, Juhaeri J, Schiappacasse HA, et al. Evaluation of **Dronedarone** Use in the US Patient Population Between 2009 and 2010: A Descriptive Study Using a Claims

Database. Clin Ther. 2011 Sep 27.
Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. **Validation of clinical classification schemes for predicting stroke**: results from the National Registry of Atrial Fibrillation. ($CHADS_2$) *JAMA*. 2001; 285:2864 –2870.
Ganesan AN, Brooks AG, Roberts-Thomson KC, et al. Role of **AV nodal ablation** in cardiac resynchronization therapy in patients with coexistent atrial fibrillation and **heart failure**: a systematic review. J Am Coll Cardiol 2012; 59:719-726.
Gorin L, Fauchier L, Nonin E, et al. Prognosis and Guideline-Adherent **Antithrombotic Treatment** in Patients With Atrial Fibrillation and Atrial Flutter: Implications of Undertreatment and Overtreatment in Real-life Clinical Practice; the Loire Valley Atrial Fibrillation Project. Chest. 2011 Oct;140(4):911-7.
Granger CB, Armaganijan LV. Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism. Circulation. 2012 Jan 3;125(1):159-64; discussion 164. Review.
Groenveld HF, Crijns HJGM, Van den Berg MP, et al., for the RACE II Investigators. The effect of **rate control on quality of life** in patients with permanent atrial fibrillation: data of the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation) study. J Am Coll Cardiol 2011;58:1795– 803.
Grundvold I, Skretteberg PT, Liestøl K, et al. **Upper normal blood pressures** predict incident atrial fibrillation in healthy middle-aged men: a 35-year follow-up study. Hypertension. 2012;59:198 –204.
Grundvold I, Skretteberg PT, Liestøl K, et al. Importance of **Physical Fitness** on Predictive Effect of Body Mass Index and Weight Gain on Incident Atrial Fibrillation in Healthy Middle-Age Men. Am J Cardiol. 2012 May 9.
Guyatt Gordon H., Akl Elie A., Crowther Mark. **Executive Summary**: Antithrombotic Therapy and Prevention of Thrombosis,**9th ed**: American College of Chest Physicians. (ACCP-AT9)Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2)(Suppl):7S–47S.
Hart RG, Diener HC, Yang S et al. Intracranial Hemorrhage in Atrial Fibrillation Patients During Anticoagulation With Warfarin or Dabigatran: The RE-LY Trial. Stroke. 2012 Jun;43(6):1511-7.
Healey JS, Connolly SJ, Gold MR, et al. **Subclinical atrial fibrillation** and the risk of stroke. N Engl J Med 2012; 366:120-129.
Health Canada Mar/12 The Pradax (**dabigatran** etexilate) product monograph has been updated to include in elderly to assess **renal function** initially & at least once a year**.** Use of Pradax® in patients with hemodynamically significant rheumatic valvular heart disease, especially mitral stenosis, or in patients with prosthetic heart valves is not recommended.
Heist EK, Mansour M, Ruskin JN. Rate control in atrial fibrillation: targets, methods, resynchronization considerations. Circulation. 2011 Dec13;124(24):2746-55.
Hendriks JM, de Wit R, Crijns HJ, et al. **Nurse-led care vs. usual care** for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. Eur Heart J. 2012 Mar 27.
Hermida J, Lopez FL, Montes R, et al. Usefulness of **High-Sensitivity C-Reactive Protein** to Predict Mortality in Patients With Atrial Fibrillation (from the Atherosclerosis Risk In Communities [**ARIC**] Study). Am J Cardiol. 2011 Sep 29.
Hijazi Z, Oldgren J, Andersson U, et al. **Cardiac Biomarkers** Are Associated With an Increased Risk of Stroke and Death in Patients With Atrial Fibrillation: A Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Substudy. Circulation. 2012 Apr 3;125(13):1605-16. (troponin I, NT-proBNP)
Hohnloser SH, Kuck KH, Lilienthal J for the PIAF Investigators. Rhythm or rate control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (**PIAF**): a randomised trial. *Lancet.* 2000;356:1789 –1794.
Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of **dronedarone** on cardiovascular events in atrial fibrillation. (**ATHENA**) N Engl J Med 2009;360:668-78.
Imazio M, Brucato A, Ferrazzi P, et al. **Colchicine** reduces postoperative atrial fibrillation. Results of the colchicine for the prevention of **postpericardiotomy symdrome** (**COPPS**) atrial fibrillation substudy. Circulation 2011; 124:2290-2295.
Ionescu-Ittu R, Abrahamowicz M, Jackevicius CA, et al. **Comparative effectiveness of rhythm control vs rate control** drug treatment effect on mortality in patients with atrial fibrillation [published online June 4, 2012]. *Arch Int Med*.
Iwasaki YK, Nishida K, Kato T, Nattel S. **Atrial fibrillation** pathophysiology: implications for management. Circulation. 2011 Nov 15;124(20):2264-74.
Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death **after myocardial infarction**: a community study. Circulation. 2011;123:2094-100.
Kirchhof P, Andresen D, Bosch R et al. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. Lancet. 2012 Jun 15.
Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after **dronedarone** therapy for severe heart failure. (**ANDROMEDA**) N Engl J Med 2008;358:2678-87.
Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of **dabigatran versus warfarin** for periprocedural anticoagulation in patients undergoing **radiofrequency ablation** for atrial fibrillation. J Am Coll Cardiol 2012.
Lansberg MG, et al. Antithrombotic and thrombolytic therapy for **ischemic stroke**: antithrombotic therapy & prevention of thrombosis, **9th ed:** American College of Chest Physicians (ACCP-AT9) evidence-based clinical practice guidelines. Chest. 2012;141(2)(supp):e601S-e636S.
Liakopoulos OJ, Kuhn EW, Slottosch I, et al. **Preoperative statin** therapy for patients undergoing cardiac surgery. Cochrane Database Syst Rev. 2012 Apr 18;4:CD008493.
Preoperative statin therapy reduces the odds of post-operative AF and shortens the stay on the ICU and in the hospital. Statin pretreatment had no influence on perioperative mortality, stroke, myocardial infarction or renal failure. Since analysed studies included mainly patients undergoing myocardial revascularizations the results cannot be extrapolated to patients undergoing other cardiac procedures such as heart valve or aortic surgery.
Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of atrial fibrillation and stroke **in rheumatoid arthritis**: Danish nationwide cohort study. BMJ. 2012 Mar 8;344:e1257.
Lip GYH et al. Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel **Risk Factor-Based Approach**: The Euro Heart Survey on Atrial Fibrillation. (**CHA_2DS_2VASc)** Chest 2010;137;263-272.
Lip GYH et al. **Comparative Validation** of a Novel Risk Score for Predicting Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation The **HAS-BLED** Score. J Am Coll Cardiol 2011;57:173?80.
Lip GYH, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive summary of a position document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. Thromb Haemost 2011; 106:997-1011.
Lip GY, Tse HF, Lane DA. Atrial fibrillation. Lancet. 2011 Dec 9. [Epub ahead of print]
Loewen P, Dahri K. Risk of **bleeding with oral anticoagulants**: an updated systematic review and performance analysis of clinical prediction rules. Ann Hematol. 2011 Oct;90(10):1191-200.
Mackenzie C, Syed J, Pollak PT, Koren G. Falling between the cracks: a case of **amiodarone toxicity**. CMAJ. 2011 Sep 6;183(12):1393-7.
Mandyam MC, Vedantham V, Scheinman MM, et al. **Alcohol and Vagal Tone as Triggers** for Paroxysmal Atrial Fibrillation. Am J Cardiol. 2012 Apr 20.
Marzona I, O'Donnell M, Teo K, et al. Increased risk of **cognitive and functional decline** in patients with atrial fibrillation: results of the **ONTARGET** and **TRANSCEND** studies. CMAJ 2012
Mason PK, Lake DE, Dimarco JP et al. Impact of the CHA(2)DS(2)-VASc Score on Anticoagulation Recommendations for Atrial Fibrillation. Am J Med. 2012 Jun;125(6):603.e1-6. Epub 2012 Apr 11.
Medical Letter- Treatment Guidelines. **Treatment of Atrial Fibrillation**. Sept 2010.
Medical Letter. Treatment Guidelines: **Antithrombotic Drugs**. Oct 2011.
Miller CS, Grandi SM, Shimony A, et al. Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (**Dabigatran, Rivaroxaban, Apixaban) Versus Warfarin** in Patients With Atrial Fibrillation. Am J Cardiol. 2012 Apr 24.
Monahan K, Brewster J, Wang L, et al. Relation of the **Severity of Obstructive Sleep Apnea** in Response to Anti-Arrhythmic Drugs in Patients With Atrial Fibrillation or Atrial Flutter. Am J Cardiol. 2012 Apr 18.
Naccarelli GV, Panaccio MP, Cummins G et al. **CHADS(2) and CHA(2)DS(2)-VASc** Risk Factors to Predict First Cardiovascular Hospitalization Among Atrial Fibrillation/Atrial Flutter Patients. Am J Cardiol. 2012 Feb 21.
Nagarakanti R, Ezekowitz MD, Oldgren J, et al. **Dabigatran** versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing **cardioversion**. *Circulation*. 2011;123:131–136.
Nedeltchev K. Critique of **apixaban versus warfarin** in patients with atrial fibrillation. Stroke. 2012 Mar;43(3):922-3.
Neumann I, Rada G, Claro JC et al. **Oral direct factor Xa inhibitors versus low-molecular-weight heparin** to prevent thromboembolism in patients undergoing total hip or knee replacement. A systematic review and meta-analysis. Ann Intern Med. 2012;156:710-9.
Olesen JB, Lip GYH, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with **atrial fibrillation**: A net clinical benefit analysis using a 'real world' nationwide cohort study. Thromb Haemost 2011; 106: 739-749. (**not ASA**)
Oleson BJ et al. **Validation** of **risk stratification schemes** for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study.

TOP

BMJ 2011;342:d124. **CHA_2DS_2-VASc performed better than $CHADS_2$** in predicting patients at high risk, and those categorised as low risk by CHA_2DS_2-VASc were truly at low risk for thromboembolism.
Olesen JB, Fauchier L, Lane DA, et al. **Risk factors for stroke and thromboembolism in relation to age** among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Chest. 2012 Jan;141(1):147-53.
Ogilvie IM, Weiner SA, Cowell W, Lip GY. Characterization of the proportion of **untreated** and antiplatelet therapy treated patients with atrial fibrillation. Am J Cardiol 2011;108:151–161.
Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. **Underuse** of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010;123:638 – 645.
Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving **dabigatran or warfarin** in relation to the **CHADS2** score: a subgroup analysis of the **RE-LY** trial. Ann Intern Med. 2011;155:660-7.
Olesen JB, Torp-Pedersen C, Hansen ML, and Lip GYH. The value of the **CHA2DS2-VASc score** for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: A nationwide cohort study. Thromb Haemost 2012.
Opolski G, Torbicki A, Kosior DA, et al. for the Investigators of the Polish HOT CAFÉ Trial. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (**HOT CAFE**) study. *Chest.* 2004;126:476–486.
Parikh MG et al. Usefulness of **Transesophageal Echocardiography** to Confirm Clinical Utility of **CHA(2)DS(2)-VASc and CHADS(2) Scores** in Atrial Flutter. Am J Cardiol. 2011 Nov 29.
Pena JM, Macfadyen J, Glynn RJ, et al. High-sensitivity C-reactive protein, **statin** therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. Eur Heart J. 2012 Feb;33(4):531-7.
Pisters R et al. A Novel User Friendly Score (**HAS-BLED**) to Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation: The Euro Heart Survey. Chest 2010;138;1093-1100.
Poçi D, Hartford M, Karlsson T, et al. Effect of **New Versus Known Versus No Atrial Fibrillation** on 30-Day and 10-Year Mortality in Patients With **Acute Coronary Syndrome**. Am J Cardiol. 2012 Apr 20. (especially AF with ACS)
Poçi D, Hartford M, Karlsson T, et al. Role of the **CHADS2 score in acute coronary syndromes** - risk of subsequent death or stroke in patients with and without atrial fibrillation. Chest. 2011 Oct 20.
Podolecki T, Lenarczyk R, et al. Effect of **Type of Atrial Fibrillation** on Prognosis in **Acute Myocardial Infarction** Treated Invasively. Am J Cardiol. 2012 Mar 20.
Pogge EK, Haber SL. Elevated international normalized ratio associated with use of **dronedarone and warfarin**. Ann Pharmacother. 2011 Sep;45(9):e46.
Poli D, Testa S, Antonucci E, et al. **Bleeding and Stroke Risk** in a Real-world Prospective Primary Prevention Cohort of Patients With Atrial Fibrillation. Chest. 2011 Oct;140(4):918-24.
Potpara TS , Vasiljevic ZM , Vujisic-Tesic BD , et al . **Mitral annular calcification** predicts cardiovascular morbidity and mortality in middle-aged patients with atrial fibrillation: the Belgrade Atrial Fibrillation Study. Chest . 2011 ; 140 (4): 902 - 910 .
Potpara TS, Stankovic GR, Beleslin BD, et al. A 12-year follow-up study of patients with newly-diagnosed **lone atrial fibrillation**: implications of arrhythmia progression on prognosis: The Belgrade Atrial Fibrillation Study. Chest. 2012;141(2):339-347.
Radecki RP. Dabigatran--Uncharted Waters and Potential Harms. Ann Intern Med. 2012 May 28.
Rahimi Kazem, Emberson Jonathan, McGale Paul, et al., PWM is acting on behalf of the PROSPER Executive. Effect of **statins** on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. BMJ 342:doi:10.1136/bmj.d1250
Rienstra M, Sun JX, Magnani JW, et al. **White Blood Cell Count** and Risk of Incident Atrial Fibrillation (From the Framingham Heart Study). Am J Cardiol. 2011 Nov 17.
Rienstra M, McManus DD, Benjamin EJ. **Novel risk factors** for atrial fibrillation: useful for risk prediction and clinical decision making? Circulation. 2012 May 22;125(20):e941-6.
Rienstra M, Lubitz SA, Mahida S, et al. **Symptoms and functional status** of patients with atrial fibrillation: state of the art and future research opportunities. Circulation. 2012 Jun 12;125(23):2933-43.
Roy D, Talajic M, Nattel S, et al. Atrial Fibrillation and Congestive Heart Failure Investigators. (**AF CHF**) Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–2677.
Roy B et al. Effect of **Warfarin on Outcomes in Septuagenarian** Patients With Atrial Fibrillation. (AFFIRM) Am J Cardiol. 2011 Nov 23.
Ruiz-Nodar JM, Marín F, Manzano-Fernández S, et al. An evaluation of the **CHADS2** stroke risk score in patients with atrial fibrillation who undergo **percutaneous coronary revascularization**. Chest. 2011 Jun;139(6):1402-9.
Sandhu RK, Kurth T, Conen D, et al. Relation of **Renal Function** to Risk for Incident Atrial Fibrillation in Women. Am J Cardiol. 2011 Nov 17.
Savelieva I, Kakouros N, Kourliouros A, Camm AJ. **Upstream therapies** for management of **atrial fibrillation**: review of clinical evidence and implications for **European** Society of Cardiology guidelines: II, secondary prevention. Europace. 2011; 13(5):610-625.
Schmidt M et al. **Non-Steroidal anti-inflammatory drug** (NSAID) use and risk of atrial fibrillation or flutter: population based case-control study. BMJ 2011;343:d3450 doi: 10.1136/bmj.d3450
Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian JA, Levine M. **Warfarin dose assessment every 4 weeks versus every 12 weeks** in patients with stable international normalized ratios. A randomized trial. Ann Intern Med. 2011;155:653-9.
Schulman S. Resumption of oral anticoagulation after warfarin-associated **intracerebral hemorrhage: no.** Stroke. 2011 Dec;42(12):3663-4.
Seet RC, Zhang Y, Wijdicks EF, et al. Relationship between chronic atrial fibrillation and **worse outcomes in stroke patients after intravenous thrombolysis**. Arch Neurol. 2011 Nov;68(11):1454-8.
Shah R, Freeman J, Shilane D, et al. Procedural complications, rehospitalizations, and repeat procedures **after catheter ablation** for atrial fibrillation. J Am Coll Cardiol 2012; 59:143-149.
Shibazaki K, Kimura K, Fujii S et al. **Brain Natriuretic Peptide** Levels as a Predictor for New Atrial Fibrillation During Hospitalization in Patients With Acute Ischemic Stroke. Am J Cardiol. 2012 Feb 14.
Siu CW, Wong MP, Ho CM, et al. **Fatal lung toxic effects related to dronedarone** use. Arch Intern Med. 2012 Mar 26;172(6):516-7.
Singer DE, Chang Y, Fang MC, Borowsky et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med. 2009 Sep 1;151(5):297-305.
Stangier J, Stähle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet. 2008;47(1):47-59. The effects of pantoprazole coadministration on the bioavailability of dabigatran were considered acceptable, and dose adjustment is not considered necessary.
Steiner T. Resumption of oral anticoagulation after warfarin-associated **intracerebral hemorrhage: yes**. Stroke. 2011 Dec;42(12):3661-2.
Strohecker J. Dabigatran for Prevention of Stroke in Atrial Fibrillation. Am Fam Physician. 2011 Dec 15;84(12):1397-1398.
Suzuki S, Sagara K, Otsuka T, et al. A New Scoring System for Evaluating the Risk of **Heart Failure** Events in Japanese Patients With Atrial Fibrillation (**H_2ARDD**). Am J Cardiol. 2012 May 21.
Takahashi Y et al. **Renal function** after catheter ablation of atrial fibrillation. Circulation. 2011 Nov 29;124(22):2380-7. (improves kidney function over 1yr)
Tsadok MA, Jackevicius CA, Rahme E, et al. **Sex differences** in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 2012; 307:1952-1958.
Turagam MK, Velagapudi P, Kocheril AG. **Atrial fibrillation in athletes**. Am J Cardiol. 2012 Jan 15;109(2):296-302.
Uchino K, Hernandez AV. **Dabigatran** association with **higher risk of acute coronary events**: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. doi:10.1001/archinternmed.2011.1666.
van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease **undergoing noncardiac surgery**: an analysis of 38 047 patients. Circulation. 2011 Jul 19;124(3):289-96.
Van Gelder IC, Hagens VE, Bosker HA, et al. for the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. (**RACE)** *N Engl J Med.* 2002; 347:1834 –1840.
Van Gelder IC, Groenveld HF, Crijns HJ, et al.; **RACE II** Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010 Apr 15;362(15):1363-73.
Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with **severe sepsis** [published online November 13, 2011]. JAMA. doi:10.1001 /jama.2011.1615.
Wallentin L, Yusuf S, Ezekowitz MD et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010 Sep18;376(9745):975-83.

TOP

Wang Z, Zhang Y, Gao M, et al. **Statin Therapy** for the Prevention of Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials. Pharmacotherapy. 2011 Nov;31(11):1051-62.

Wilkinson GS, Baillargeon J, Kuo YF, et al. **Atrial fibrillation** and stroke associated with intravenous bisphosphonate therapy in older patients with cancer. J Clin Oncol. 2010 Nov 20;28(33):4898-905.

Wiysonge C, et al. **Beta-blockers for hypertension**. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD002003.

Wu JH, Lemaitre RN, King IB, et al. Association of plasma phospholipid long-chain **omega-3 Fatty acids** with incident atrial fibrillation in older adults: the cardiovascular health study. Circulation. 2012 Mar 6;125(9):1084-93.

Wyse DG, Waldo AL, DiMarco JP, et al. Atrial Fibrillation Follow-up Investigation of Rhythm Management (**AFFIRM**) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825–1833.

You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e531S-e575S.

---

[1] Healey JS, Parkash R, Pollak, T. et al. Society Guidelines. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Etiology and Initial Investigations. Can J Cardiol 2011;27:31-7.
[2] Kannel WB, Wolf PA, Benjamin EJ. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N-9N
[3] Canadian Agency for Drugs and Technologies in Health. Therapeutic Review Report: Recommendations for New Oral Anticoagulants for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation. DRAFT April 9th, 2012.
[4] Dorian P, Guerra PG, Kerr CR, et al. Validation of a new simple scale to measure symptoms in atrial fibrillation: the Canadian Cardiovascular Society Severity in Atrial Fibrillation scale. Circ Arrhythm Electrophysiol 2009;2:213-4.
[5] Callahan T, Baranowski B. Managing newly diagnosed atrial fibrillation: Rate, rhythm, and risk. Cleveland Clinic Journal of Medicine. 2011;78(4):258-64.
[6] http://www.theheart.org/documents/sitestructure/en/content/programs/1230553/1230553.html, accessed July 25, 2011
[7] Alboni P, Tomasi C, Menozzi C, et al. Efficacy and safety of out-of-hospital self-administered single-dose oral drug treatment in the management of infrequent, well-tolerated paroxysmal supraventricular tachycardia. J Am Coll Cardiol 2001;37:548-53
[8] Capucci A, Villani GQ, Piepoli MF. Reproducible efficacy of loading oral propafenone in restoring sinus rhythm in patients with paroxysmal atrial fibrillation. Am J Cardiol 2003;92:1345-7
[9] Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. J Am Coll Cardiol 2001;37:542-7.
[10] Gillis AM, Verma A, Talajic M, Nattel S, et al. and the CCS Atrial Fibrillation Guidelines Committee. Society Guidelines Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Rate and Rhythm Management. Can J Cardio 2011;27:47-59.
[11] Wyse DG, Waldo AL, DiMarco JP, et al. Atrial fibrillation follow-up investigation of rhythm management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
[12] Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.
[13] Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patietns with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834-40.
[14] Testa L, Biondi-Zoccai GG, Dello Russo A, et al. Rate-control vs. rhythm-control in patients with atrial fibrillation: a meta-analysis. Eur Heart J 2005;26:2000-6.
[15] Ogawa S. Yamashita T, Yamazaki T, et al. Optimal treatment strategy for patients with paroxysmal atrial fibrillation. J-RHYTHM study. Circ J 2009;73:242-8.
[16] van der Hooft CS, Heeringa J, van Herpen G, et al. Drug-Induced Atrial Fibrillation. J Am Coll Cardiol 2004;44:2117-24
[17] Verma A, Macle L, Cox J, Skanes AC; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010:catheter ablation for atrial fibrillation/atrial flutter. Can J Cardiol. 2011 Jan-Feb;27(1):60-6.
[18] Wazni O, Wilkoff B, Saliba W. Catheter ablation for atrial fibrillation. N Engl J Med. 2011 Dec 15;365(24):2296-304.
[19] Rordorf R, Savastano S, Gandolfi E, Vicentini A, Petracci B, Landolina M. Pharmacological therapy following catheter ablation of atrial fibrillation. J Cardiovasc Med (Hagerstown). 2012 Jan;13(1):9-15.
[20] Cairns JA, Connolly S, McMurtry S, Stepenson M, Talajic M, and the CCS Atrial Fibrillation Guidelines Committee. Society Guidelines Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter. Can J Cardiol 2011;27:74-90.
[21] Skanes A, Healey J, Cairns J, et al. Focused 2012 Update of the CCS Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control. Can J Cardiol 2012; 28:125-136.
[22] You JJ, Singer DE, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians (ACCP-AT9)evidence -based clinical practice guidelines. Chest. 2012;141(2)(suppl):e531S-575S.
[23] Camm AJ, Kirchhof P, Lip GY, et al; European Heart Rhythm Association; European Association for Cario-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369-429.
[24] Fang MC, Go AS, Chang Y, et al. A New Risk Scheme to Predict Warfarin-Associated Hemorrhage. The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation Study). J Am Coll Cardiol 2011;58:395-401.
[25] Ruiz-Gimenez N, Suarez C, Gonzalez R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. Thrombos Haemostas 2008;100:26-31.
[26] Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006;151:713-9.
[27] De Caterina R, Husted S, Wallentin L, et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes. ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease position paper. J Am Coll Cardiol 2012; 59:1413-25.
[28] E-cps, accessed March 5, 2011
[29] Micromedex, accessed on-line March 5, 2011
[30] Giorgi MA, Arazi Hc, Gonzalez CD et al. Changing anticoagulant paradigms for atrial fibrillation: dabigatran, apixaban and rivaroxaban. Expert Opin. Pharmacother. 2001;12(4):567-77.
[31] Health Canada Endorsed Important Safety Information: Risk of potential patient harm associated with name confusion involving the prescription drugs Pradax® and Plavix®, November 8th, 2011. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/public/2011/plavix_2_pc-cp-eng.pdf. Accessed December 16, 2011.
[32] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom PJ, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009;361:1139-51. {RE-LY} RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf
[33] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. August 10, 2011. http://www.nejm.org/doi/full/10.1056/NEJMoa1009638 {ROCKET-AF} RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf
[34] FDA Advisory Committee Briefing Document: Rivaroxaban for the Prevention of Stroke and Non-Central Nervous System (CNS) Systemic Embolism in Patients With Atrial Fibrillation. August 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM270797.pdf
[35] Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. (ARISTOTLE) N Engl J Med August 28, 2011 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1107039
Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome (Appraise-2). N Engl J Med 2011 (5mg po bid: increased major bleeding without a significant reduction in recurrent ischemic events) {ARISTOTLE} (RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE-AF-Apixaban.pdf)
Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. (AVERROES) N Engl J Med 2011;364:806–17.
Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol 2012.
[36] e-cps, September 2011
[37] Micromedex, September 2011
[38] Dorian P, Connors P. Pharmacological and non pharmacological methods for rate control. Can J Cardiol 2005;21(suppl B):11B-14B.
[39] Borrello F, Beahan M, Klein L, et al. Reappraisal of beta-blocker therapy in the acute and chronic post-myocardial infarction period. Rev Cardiovasc Med. 2003;4 Suppl 3:S13-24.
[40] Vittorio TJ, Zolty R, Kasper ME, et al. Differential effects of carvedilol and metoprolol succinate on plasma norepinephrine release and peak exercise heart rate in subjects with chronic heart failure. J Cardiovasc Pharmacol Ther 2008;13:51-7
[41] Doyle JF, Ho KM. Benefits and risks of long-term amiodarone therapy for persistent atrial fibrillation: a meta-analysis. Mayo Clinic Proceedings 2009 84(3):234-242
[42] Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. (PALLAS) N Engl J Med 2011. DOI: 10.1056/NEJMoa1109867. http://www.theheart.org/article/1252319.do, Heartwire, July 12, 2011
[43] Permanent Atrial fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), http://clinicaltrials.gov/ct2/show/NCT01151137?term=pallas&rank=1, July 15, 2011
Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. (ATHENA) N Engl J Med 2009;360:668-78.
Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. (ANDROMEDA) N Engl J Med 2008;358:2678-87.
[44] Heuzey JY, De Ferrari GM, Radzik D, et al. A Short-Term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study. J Cardiovasc Electrophysiol 2010;21:597-605.
[45] Fetsch T, Bauer P, Engberding R, et al. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. Eur Heart J 2004;25:1385-94.
[46] Singh BN, Singh SN, Reda DJ et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352:1861-72.
[47] The Cardiac Arrhythmia Suppression Trial (CAST) Investigators, Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression after Myocardial Infarction. N Engl J Med 1989; 321:406-412
[48] Shireman T, Mahnken J, Howard P, et al. Development of a contemporary bleeding risk model for elderly warfarin recipients. Chest 2006;130:1390-6.
[49] Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003;349:631-9
[50] Kuijer P, Hutten B, Prins M et al. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med. 1999;159:457-60.
[51] Beyth R, Quinn L, Landefeld C. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998;105-91-9.
[52] Stiell IG, Macle L, and CCS Atrial Fibrillation Guidelines Committee. Society Guidelines Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Management of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Depeartment. Can J Cardiol 2011;27:38-46.

TOP

Brain Natriuretic Peptide (BNP) has diagnostic value for both types of HF and is recommended where available, when diagnosis in unclear. The use of BNP in non-acute HF and community outpatient practice remains to be clarified.[3]

Table: Brain natriuretic peptide (BNP mainly secreted by ventricular myocardium**) & prohormone of BNP (NT-proBNP** longer half life, affected by renal fx**) assay cut-off points for the diagnosis of HF** [3]

	Age	HF unlikely	HF possible but consider alternative diagnoses	HF very likely
BNP (pg/mL)	**All**	**<100**	**100-500**	**>500**
NT-proBNP (pg/mL)	**<50**	**<300**	**300-450**	**>450**
	50-75	**<300**	**300-900**	**>900**
	>75	**<300**	**300-1800**	**>1800**

Acknowledgements: Contributors & Reviewers: R. Herman (MD, Pharmacology, Dept Med, Calgary); Dr. J. Akhtar (SHR Cardiology); H. Kertland, (PharmD, Col of Pharmacy, U of T.), B. Semchuk (PharmD, Regina), A. Lindblad (PharmD, Red Deer) & the RxFiles Advisory Committee. Prepared by: *M. Jin, B. Jensen BSP, L. Regier BSP, BA*

References: RxFiles Heart Failure

[1] Arnold JMO, Liu P, Demers C, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis & management. Can J Cardiol 2006;22(1):23-45.

[2] Arnold JMO, Howlett JG, Dorian P, et al. **Canadian Cardiovascular Society-CCS** Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol 2007;23(1):21-45.

Malcom J, Arnold O, Howlett JG, Ducharme A, Ezekowitz JA, Gardner MJ, Giannetti N, Haddad H, Heckman GA, Isaac D, Jong P, Liu P, Mann E, McKelvie RS, Moe GW, Svendsen AM, Tsuyuki RT, O'Halloran K, Ross HJ, Sequeira EJ, White M; Canadian Cardiovascular Society. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure--2008 update: best practices for the transition of care of heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. Can J Cardiol. 2008 Jan;24(1):21-40.

Howlett JG, McKelvie RS, Arnold JM, et al. Canadian Cardiovascular Society. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials. Can J Cardiol. 2009 Feb;25(2):85-105.

HFSA: Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, et al. Evaluation of patients for ventricular dysfunction & heart failure: **HFSA 2010 comprehensive heart failure** practice guideline. J Card Fail **2010** Jun;16(6):e44-56. http://www.heartfailureguideline.org/home/3

McKelvie RS, Moe GW, Cheung A, et al. The 2011 Canadian cardiovascular society heart failure management guidelines update: focus on **sleep apnea, renal dysfunction, mechanical circulatory support, and palliative care**. Can J Cardiol. 2011 May-Jun;27(3):319-38.

Howlett JG, McKelvie RS, Costigan J, et al; Canadian Cardiovascular Society. The 2010 Canadian Cardiovascular Society guidelines for the diagnosis and management of heart failure update: Heart failure in **ethnic minority populations, heart failure and pregnancy, disease management, and quality improvement/assurance programs**. Can J Cardiol. 2010 Apr;26(4):185-202.

McMurray JJV, Adamopoulos S, Anker SD, et al. **ESC guidelines** for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; DOI:10.1093/eurheartj/ehs104.

[3] Guidelines & Protocols Advisory Committee, Heart Failure Care, February 15, 2008; accessed online www.OntarioMD.ca on June 15, 2008.

Gheorghiade Mihai, Braunwald Eugene. A Proposed Model for **Initial Assessment and Management of Acute Heart Failure** Syndromes. JAMA. 2011;305(16):1702-1703.doi:10.1001/jama.2011.515

[4] http://www.saltinstitute.org/teaspoon.html, accessed April 30, 2008

[5] http://www.thecaregroup.com/Education/Education%20CD/PDF%20Files/Average%20Sodium%20Content%20of%20Foods.pdf, accessed April 30, 2008

[6] http://www.geocities.com/Heartland/4269/nutrition.html, accessed April 30, 2008

[7] http://www.mcdonalds.ca/en/food/calculator.aspx, accessed April 30, 2008

Strazzullo Pasquale, D'Elia Lanfranco, et al. **Salt** intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567, doi: 10.1136/bmj.b4567 (24 November 2009).

[8] Garg R. Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials.[see comment][erratum appears in JAMA 1995 Aug 9;274(6):462]. [Journal Article. Meta-Analysis] JAMA. 273(18):1450-6, 1995 May 10.

[9] Clelan JGF, Tendera M, Adamus J et al. The perindopril in elderly people with chronic heart failure (PeP-CHF) study. Eur Heart J 2006;27:2338-45.

[10] Borrello F, Beahan M, Klein L, et al. Reappraisal of beta-blocker therapy in the acute and chronic post-myocardial infarction period. Rev Cardiovasc Med. 2003;4 Suppl 3:S13-24.

[11] Chen ZM, Pan HC, Chen YP, et al.; **COMMIT** (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5;366(9497):1622-32. Second Chinese Cardiac Study COMMIT/CCS-2. Mean age 61, Fibrinolytic therapy 54%, Metoprolol 5mg IV over 2-3mins x 3 if HR & BP ok, then 15mins later 50mg po q6h Day 0-1, then 200mg controlled release od vs placebo x ~15days. ↓Reinfarction 2 vs 2.5%, ↓Ventricular fibrilation 2.5 vs 3 %, BUT ↑Cardiogenic shock 5 vs 3.9% (risk more with heart failure, systolic BP <120 & in the first 24hrs). INTERPRETATION: The use of early beta-blocker therapy in acute MI reduces the risks of reinfarction & ventricular fibrillation, but increases the risk of cardiogenic shock, esp. during the first day or so after admission. Consequently, it might generally be prudent to consider starting **beta-blocker therapy in hospital only when the haemodynamic condition after MI has stabilised**. (InfoPOEMs: The early use of metoprolol in patients with acute myocardial infarction who are also receiving thrombolytics and aspirin provides no short-term benefit compared with placebo. Since the early use, however, increases the risk of cardiogenic shock, it may be wise to delay starting metoprolol until the patient is hemodynamically stable. (LOE = 1b)).

[12] Packer M. Coats AJ. Fowler MB. Katus HA. Krum H. Mohacsi P. Rouleau JL. Tendera M. Castaigne A. Roecker EB. Schultz MK. DeMets DL. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure.[see comment]. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] New England Journal of Medicine. 344(22):1651-8, 2001 May 31.

[13] Anonymous. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial.[see comment]. [Clinical Trial. Comparative Study. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Lancet. 353(9146):9-13, 1999 Jan 2.

[14] Poole-Wilson PA. Swedberg K. Cleland JG. Di Lenarda A. Hanrath P. Komajda M. Lubsen J. Lutiger B. Metra M. Remme WJ. Torp-Pedersen C. Scherhag A. Skene A. Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (**COMET**): randomised controlled trial.[see comment]. [Clinical Trial. Comparative Study. Journal Article. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Lancet. 362(9377):7-13, 2003 Jul 5

[15] **MERIT-HF** Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-07

[16] Cohn JN. Tognoni G. Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure.[see comment][summary for patients in J Card Fail. 2002 Apr;8(2):56-8.Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't.New England Journal of Medicine. 345(23):1667-75, 2001 Dec 6.

Anand IS, Bishu K, Rector TS, et al. Proteinuria, Chronic Kidney Disease, and the Effect of an Angiotensin Receptor Blocker in Addition to an Angiotensin-Converting Enzyme Inhibitor in Patients With Moderate to Severe Heart Failure. Circulation. 2009 Oct 5.

[17] Granger CB. McMurray JJ. Yusuf S. Held P. Michelson EL. Olofsson B. Ostergren J. Pfeffer MA. Swedberg K. **CHARM** Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial.[see comment]. [Clinical Trial. Comparative Study. Journal Article. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Lancet. 362(9386):772-6, 2003 Sep 6

Eklind-Cervenka M, Benson L, Dahlström U, et al. Association of **candesartan vs losartan** with all-cause mortality in patients with heart failure. JAMA 2011; 305:175-182.

[18] McMurray JJ. Ostergren J. Swedberg K. Granger CB. Held P. Michelson EL. Olofsson B. Yusuf S. Pfeffer MA. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial.[see comment]. [Clinical Trial. Comparative Study. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Lancet. 362(9386):767-71, 2003 Sep 6.

[19] Pitt B. Poole-Wilson PA. Segal R. Martinez FA. Dickstein K. Camm AJ. Konstam MA. Riegger G. Klinger GH. Neaton J. Sharma D. Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study **ELITE II**.[see comment]. [Clinical Trial. Comparative Study. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] Lancet. 355(9215):1582-7, 2000 May 6.

[20] Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; the **I-PRESERVE** Investigators. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N Engl J Med. 2008 Nov 11. [Epub ahead of print]

Zile MR, Gaasch WH, Anand IS, et al. Mode of Death in Patients With Heart Failure and a Preserved Ejection Fraction. Results From the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) Trial. Circulation. 2010 Mar 15.

[21] Granger CB, McMurray JJ, Yusuf S, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the **CHARM-Alternative** trial. Lancet. 2003 Sep 6;362(9386):772-6. (Granger BB, et al.; for the CHARM investigators. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet. 2005 Dec 10;366(9502):2005-2011.)

[22] Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [**RALES**]). Am J Cardiol. 1996 Oct 15;78(8):902-7. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999 Sep 2;341(10):709-17. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004 Aug 5;351(6):543-51.

TOP

[23] Taylor AL. Ziesche S. Yancy C. Carson P. D'Agostino R Jr. Ferdinand K. Taylor M. Adams K. Sabolinski M. Worcel M. Cohn JN. African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure.[see comment][erratum appears in N Engl J Med. 2005 Mar 24;352(12):1276]. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't] New England Journal of Medicine. 351(20):2049-57, 2004 Nov 11.

[24] Anonymous. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group.[see comment]. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] New England Journal of Medicine. 336(8):525-33, 1997 Feb 20.

[25] Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. **DIG study**. JAMA. 2003 Feb 19;289(7):871-8.

[26] Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, Gheorghiade M. Relationship of serum digoxin concentration to mortality and morbidity in **women** in the digitalis investigation group trial: a retrospective analysis. **DIG study.** J Am Coll Cardiol. 2005 Aug 2;46(3):497-504.

Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med. 2002 Oct 31;347(18):1403-11.

Gheorghiade M, Braunwald E. Reconsidering the Role for Digoxin in the Management of Acute Heart Failure Syndromes. JAMA. 2009 Nov 18;302(19):2146-2147.

Chan, Kevin E., Lazarus, J. Michael, Hakim, Raymond M. Digoxin Associates with Mortality in **ESRD**. J Am Soc Nephrol 2010 21: 1550-1559.

Georgiopoulou VV, Kalogeropoulos AP, Giamouzis G, et al. Digoxin therapy does not improve outcomes in patients with advanced heart failure on contemporary medical therapy. Circ Heart Fail. 2009;2:90 –97.

Additional references:

Abdel-Qadir HM, Tu JV, Yun L, Austin PC, Newton GE, Lee DS. Diuretic dose and long-term outcomes in elderly patients with **heart failure** after hospitalization. Am Heart J. 2010 Aug;160(2):264-271.e1.

Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; **OPTIMIZE-HF** Investigators and Coordinators. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol. 2008 Jul 29;52(5):347-56.

Abraham WT, Adamson PB, Bourge RC, et al, for the **CHAMPION** Trial Study Group. **Wireless pulmonary artery haemodynamic monitoring** (CardioMEMS) in chronic heart failure: a randomised controlled trial. Lancet 2011; published online Feb 10. DOI:10.1016/S0140-6736(11)60101-3.

AHA Writing Group Members, Roger VL, Go AS, Lloyd-Jones DM, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Roger VL, Turner MB; On behalf of the American Heart Association Heart Disease and Stroke Statistics Writing Group. Executive Summary: **Heart Disease and Stroke Statistics**—2011 Update: A Report From the American Heart Association. Circulation. 2011 Feb 1;123(4):459-463.

Ahmad T, Patel CB, Milano CA, Rogers JG. When the heart runs out of heartbeats: treatment **options for refractory end-stage heart failure**. Circulation. 2012 Jun 12;125(23):2948-55.

AlJaroudi W, Alraies MC, Halley C, et al. Impact of progression of **diastolic dysfunction on mortality** in patients with normal ejection fraction. Circulation. 2012;125:782–788.

Akinkuolie AO, Aleardi M, Ashaye AO, et al. **Height** and Risk of Heart Failure in the Physicians' Health Study. Am J Cardiol. 2012 Jan 3.

Alexandre J, Foucault A, Coutance G et al. **Digitalis intoxication** induced by an acute accidental poisoning by **lily of the valley**. Circulation. 2012 Feb 28;125(8):1053-5.

Al-Mohammad A, Mant J, Laramee P, et al.; Chronic Heart Failure Guideline Development Group. **Diagnosis and management** of adults with chronic heart failure: summary of updated **NICE guidance**. BMJ. 2010 Aug 25;341:c4130. doi: 10.1136/bmj.c4130.

Al Suwaidi J, Al-Qahtani A, Asaad N et al. Comparison of **women versus men** hospitalized with heart failure (from a 20-year registry in a middle-eastern country 1991-2010). Am J Cardiol. 2012 Feb 1;109(3):395-400.

Albert Nancy M.; Yancy Clyde W.; Liang Li; et al.Use of Aldosterone Antagonists (**spironolactone**) in Heart Failure. JAMA. 2009;302(15):1658-1665.

Alehagen Urban, Dahlström Ulf, Rehfeld Jens F., et al. Association of **Copeptin and N-Terminal proBNP** Concentrations With Risk of Cardiovascular Death in Older Patients With Symptoms of Heart Failure. JAMA. 2011;305(20):2088-2095.doi:10.1001/jama.2011.666

Allen LA, Turer AT, Dewald T, et al. **Continuous versus bolus dosing of Furosemide** for patients hospitalized for heart failure. Am J Cardiol. 2010 Jun 15;105(12):1794-7.

Allen LA, Stevenson LW, Grady KL, et al. **Decision making (shared)** in advanced heart failure. Circulation 2012; DOI: 10.1161/cir.0b013e31824f2173.

Almeida O P, Garrido G J, Beer C, et al. **Cognitive and brain changes** associated with ischemic heart disease and heart failure. Eur Heart J 2012

Altay H, Zorlu A, Binici S, et al. Relation of **Serum Parathyroid Hormone** Level to Severity of Heart Failure. Am J Cardiol. 2011 Oct 12.

Andriole, Gerald L., Bostwick, David G., Brawley, Otis W., et al. the REDUCE Study Group, Effect of **Dutasteride** on the Risk of Prostate Cancer. N Engl J Med 2010 362: 1192-1202.

Anjan VY, et al. Prevalence, Clinical Phenotype, and Outcomes Associated With **Normal B-Type Natriuretic Peptide** Levels in Heart Failure With **Preserved** Ejection Fraction. Am J Cardiol. 2012 Jun 6.

Anker SD, Comin Colet J, Filippatos G, et al. the **FAIR-HF** Trial Investigators. **Ferric Carboxymaltose** in Patients with Heart Failure and Iron Deficiency. N Engl J Med. 2009 Nov 17. [Epub ahead of print]

Anker SD, Koehler F, Abraham WT. **Telemedicine** and remote management of patients with heart failure. Lancet. 2011 Aug 20;378(9792):731-9.

Antoniou T, Gomes T, Mamdani MM, et al. **Trimethoprim-sulfamethoxazole induced hyperkalaemia** in elderly patients receiving **spironolactone**: nested case-control study. BMJ. 2011 Sep 12;343:d5228.

Arif Sally A, Mergenhagen KA, et al. Treatment of Systolic Heart Failure in the **Elderly**: An Evidence-Based Review. Ahead of Print 1Oct 2010, DOI 10.1345/aph.1P128. Ann Pharmacother ;44:1604-1614.

Arroll B, Doughty R, Andersen V. **Investigation and management of congestive heart failure**. BMJ. 2010 Jul 14;341:c3657. doi: 10.1136/bmj.c3657.

Aurigemma GP, Gaasch WH. Clinical practice. **Diastolic heart failure**. N Engl J Med. 2004 Sep 9;351(11):1097-105.

Badheka AO, Rathod A, Kizilbash MA, et al. Comparison of Mortality and Morbidity in Patients With **Atrial Fibrillation and Heart Failure With Preserved Versus Decreased Left Ventricular Ejection** Fraction. Am J Cardiol. 2011 Aug 18.

Baker WL, White WB. Safety of mineralocorticoid receptor antagonists (**spironolactone**) in patients receiving **hemodialysis**. Ann Pharmacother. 2012 Jun;46(6):889-94.

Beavers Craig James, Dunn Steven P, Macaulay Tracy E. The Role of Angiotensin Receptor Blockers in Patients with Angiotensin-Converting Enzyme Inhibitor–**Induced Angioedema**. Articles Ahead of Print published on 1 April 2011, DOI 10.1345/aph.1P630. Ann Pharmacother ;45:520-524.

Belin RJ, Greenland P, Martin L, et al. **Fish intake** and the risk of incident heart failure: The Women's Health Initiative. Circ Heart Fail 2011; DOI:10.1161/CIRCHEARTFAILURE.110.960450.

Biggar RJ, Wohlfahrt J, Oudin A, et al. **Digoxin use and the risk of breast cancer** in women. J Clin Oncol. 2011 Jun 1;29(16):2165-70.

Birks EJ, George RS, Hedger M, et al. Reversal of severe heart failure with a **continuous-flow left ventricular assist device** (LVAD) and pharmacological therapy: a prospective study. Circulation. 2011 Feb 1;123(4):381-90.

Blum A. Treating heart failure with **sildenafil**. Congest Heart Fail. 2009 Jul-Aug;15(4):181-5.

Böhm M, Swedberg K, Komajda M.; et al. **SHIFT** Investigators. **Heart rate** as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010 Sep 11;376(9744):886-94.

Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction (**STICH**). N Engl J Med 2011. DOI: 10.1056/NEJMoa1100358. (CABG vs medical therapy)

Bonow RO et al. **ACCF/AHA/AMA**-PCPI 2011 **Performance Measures for Adults With Heart Failure**: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. J Am Coll Cardiol. 2012 May 5;59(20):1812-32.

Bursi F, McNallan SM, Redfield MM, et al. **Pulmonary pressures** and death in heart failure a community study. J Am Coll Cardiol2012; 59:222-231.

Butt AA.; Chang C-C; Kuller L; et al. Risk of Heart Failure With **Human Immunodeficiency Virus** in the Absence of Prior Diagnosis of Coronary Heart Disease. Arch Intern Med. 2011;171(8):737-743.

Canadian Hypertension Education Program. 2011 CHEP recommendations for the management of hypertension. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf

Chae CU, Albert CM, Moorthy MV, et al. **Vitamin E** supplementation and the risk of heart failure in women (Women's Health Study –**WHS**). Circulation 2012.

Chan AL, Wang MT, et al. Risk of digoxin intoxication caused by **clarithromycin**-digoxin interactions in heart failure patients: a population-based study. Eur J Clin Pharmacol. 2009 Aug 5.

Chaudhry SI et al. **Telemonitoring** in patients with heart failure (**Tele-HF**) . N Engl J Med 2010 Nov 16; [e-pub ahead of print]. (NS primary outcome)

Chen J, Normand SLT, Wang Y, Krumholz HM. **National and regional trends in heart failure hospitalization and mortality rates** for Medicare beneficiaries, 1998-2008. JAMA 2011; 306:1669-1678.

Cherubini Antonio; Oristrell Joaquim; Pla Xavier; et al. The Persistent **Exclusion of Older Patients From Ongoing Clinical Trials** Regarding Heart Failure Arch Intern Med. 2011;171(6):550-556.

Cice G, Di Benedetto A, D'Isa S, et al. Effects of **telmisartan** added to angiotensin-converting enzyme inhibitors on mortality and morbidity in **hemodialysis patients with chronic heart failure**: a double-blind, placebo-controlled trial. J Am Coll Cardiol. 2010;56:1701-8.

Clark AL, Johnson MJ, Squire I. Does home **oxygen** benefit people with chronic heart failure? BMJ. 2011 Feb 4;342:d234. doi: 10.1136/bmj.d234.

Clark AL, Chyu J, Horwich TB. The **Obesity Paradox** in Men Versus Women With Systolic Heart Failure. Am J Cardiol. 2012 Apr 10.

Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. (**CARE-HF**) N Engl J Med 2005; 352:1539-1549.

Colucci VJ, Berry BD. Heart failure worsening and exacerbation after **venlafaxine** and **duloxetine** therapy. Ann Pharmacother. 2008 Jun;42(6):882-7. Epub 2008 Apr 29.

Cowie MR, Lobos AA. **Telemonitoring** for patients with heart failure. CMAJ. 2012 Mar 20;184(5):509-10.

Cresci S, Kelly RJ, Cappola TP, et al. Clinical and **genetic** modifiers of long-term survival in heart failure. J Am Coll Cardiol 2009; 54:432-444). DOI:10.1016/j.jacc.2009.05.009.

Cubbon RM, Witte KK. **Cardiac resynchronisation therapy** for chronic heart failure and conduction delay. BMJ. 2009 Apr 28;338:b1265. doi: 10.1136/bmj.b1265.

Cvelich RG, Roberts SC, Brown JN. **Phosphodiesterase type 5 inhibitors** as adjunctive therapy in the management of systolic heart failure. Ann Pharmacother. 2011 Dec;45(12):1551-8.

Dai W, Kloner RA. Is inhibition of phosphodiesterase type 5 by **sildenafil** a promising therapy for volume-overload heart failure? Circulation. 2012 Mar 20;125(11):1341-3.

Dickson G. **Gynescomastia**. Am Fam Physician. 2012 Apr 1;85(7):716-722.

TOP

Davis BR, Kostis JB, Simpson LM, et al. for the ALLHAT Collaborative Research Group. **Heart Failure** With Preserved and Reduced Left Ventricular Ejection Fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation. 2008 Nov 10. [Epub ahead of print] In **ALLHAT**, with adjudicated outcomes, **chlorthalidone** significantly reduced the occurrence of new-onset hospitalized HFPEF and HFREF compared with amlodipine and doxazosin. Chlorthalidone also reduced the incidence of new-onset HFPEF compared with lisinopril. Among high-risk hypertensive men and women, HFPEF has a better prognosis than HFREF.

deFilippi Christopher R.; de Lemos James A.; Christenson Robert H.; et al. Association of Serial Measures of **Cardiac Troponin T** Using a Sensitive Assay With Incident Heart Failure and Cardiovascular Mortality in Older Adults. JAMA. 2010;0(2010):jama.2010.1708.

Dicpinigaitis PV. **Angiotensin-converting enzyme inhibitor**-induced **cough**: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(suppl):169-73S.

Djoussé L, Driver JA, Gaziano JM. Relation between modifiable **lifestyle factors** and lifetime risk of heart failure. JAMA. 2009 Jul 22;302(4):394-400.

Dunlay SM, Swetz KM, Mueller PS, Roger VL. **Advance Directives** in Community Patients With Heart Failure. Circ Cardiovasc Qual Outcomes. 2012 May 11.

Edelmann F, Gelbrich G, Düngen H-D, et al. **Exercise training** improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780 –91.

Egstrup M, Schou M, Tuxen CD, et al. Prediction of Outcome by **Highly Sensitive Troponin T** in Outpatients With Chronic Systolic Left Ventricular Heart Failure. Am J Cardiol. 2012 May 9.

Ellenbogen Kenneth A., Gold Michael R., Meyer Timothy E., et al. Primary Results From the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (**SMART-AV**) Trial: A Randomized Trial Comparing Empirical, Echocardiography-Guided, and Algorithmic Atrioventricular Delay Programming in Cardiac Resynchronization Therapy. Circulation published November 15, 2010, doi:10.1161/CIRCULATIONAHA.110.992552

Eklind-Cervenka M, Benson L, Dahlstro¨m U, et al. Association of **candesartan vs losartan** with all-cause mortality in patients with **heart failure**. JAMA. 2011;305(2):175-182.

Ekman I, Chassany O, Komajda M et al. Heart rate reduction with **ivabradine** and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J 2011

Epstein AM, Jha AK, Orav JE. The relationship between **hospital readmission rates and rehospitalizations**. N Engl J Med 2011; 365:2287-2295.

ESC Task Force for Diagnosis and Treatment of **Acute and Chronic Heart Failure 2008** of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008 Oct;29(19):2388-442. Epub 2008 Sep 17. http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf

ESC McMurray JJV, Adamopoulos S, Anker SD, et al. **ESC guidelines** for the diagnosis and treatment of acute and **chronic heart failure 2012**: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012.

Ewer MS, Ewer SM. **Troponin I** provides insight into cardiotoxicity and the anthracycline-**trastuzumab** interaction. J Clin Oncol 2010; 28: 3901-3904.

Felker GM et al for the NHLBI Heart Failure Clinical Research Network. **Diuretic strategies** in patients with acute decompensated heart failure. (DOSE trial) N Engl J Med 2011 Mar 3; 364:797.

Flynn KE, Piña IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: **HF-ACTION** randomized controlled trial. JAMA. 2009 Apr 8;301(14):1451-9.

Fonarow GC, Abraham WT, Albert NM, et al. OPTIMIZE-HF Investigators and Coordinators. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. J Am Coll Cardiol. 2008 Jul 15;52(3):190-9. The continuation of beta-blocker therapy in patients hospitalized with decompensated HF is associated with lower post-discharge mortality risk and improved treatment rates. In contrast, withdrawal of beta-blocker therapy is associated with worse risk and propensity-adjusted mortality.

Fonarow GC, Albert NM, Curtis AB, et al. Associations Between Outpatient Heart Failure **Process-of-Care Measures** and Mortality. Circulation. 2011 Apr 19;123(15):1601-10.Current and emerging outpatient HF process measures are positively associated with patient survival. These HF measures may be useful for assessing and improving HF care.

Fonarow GC, Yancy CW, Hernandez AF, et al. Potential impact of **optimal implementation of evidence-based heart failure therapies** on **mortality**. Am Heart J. 2011 Jun;161(6):1024-1030.e3

Fonarow GC, Albert NM, Curtis AB, et al. Incremental **reduction in risk of death** associated with use of **guideline-recommended** therapies in patients with heart failure: a nested case-control analysis of **IMPROVE HF**. J Am Heart Assoc Cardiovasc Cerebrovasc Dis 2012.

Francis GS, Greenberg BH, Hsu DT, et al. ACCF/AHA/ACP/HFSA/ISHLT 2010 clinical competence statement on management of patients with **advanced heart failure and cardiac transplant**: a report of the ACCF/AHA/ACP Task Force on Clinical Competence and Training. Circulation. 2010 Aug 10;122(6):644-72.

Georgiopoulou VV, Kalogeropoulos AP, Giamouzis G, et al. **Digoxin therapy does not** improve outcomes in patients with advanced heart failure on contemporary medical therapy. Circ Heart Fail. 2009;2:90 –97.

Gerdes AM, Iervasi G. **Thyroid replacement** therapy and heart failure. Circulation. 2010 Jul 27;122(4):385-93.

Ghanbari Hamid; Dalloul Ghassan; Hasan Reema; et al. Effectiveness of **Implantable Cardioverter-Defibrillators** for the Primary Prevention of Sudden Cardiac Death in Women With Advanced Heart Failure: A Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2009;169(16):1500-1506.

Gheorghiade Mihai, Braunwald Eugene. A Proposed Model for **Initial Assessment and Management of Acute Heart Failure** Syndromes. JAMA. 2011;305(16):1702-1703.doi:10.1001/jama.2011.515

Gheorghiade M, Eugene Braunwald E. **Hospitalizations** for heart failure in the United States—a sign of hope. JAMA 2011; 306:1705-1706.

Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs (**NSAIDs**) in chronic heart failure. Arch Intern Med. 2009 Jan 26;169(2):141-9.

Gissi-Hf Investigators. Effect of **n-3 polyunsaturated fatty acids** in patients with chronic heart failure (the **GISSI-HF** trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Aug 29. A simple and safe treatment with n-3 PUFA can provide a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure in a context of usual care.

Gissi-Hf Investigators. Effect of **rosuvastatin** in patients with chronic heart failure (the **GISSI-HF** trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Aug 29. [Epub ahead of print] Rosuvastatin 10 mg daily did not affect clinical outcomes in patients with chronic heart failure of any cause, in whom the drug was safe

Givertz MM. **Ventricular assist devices**: important information for patients and families. Circulation. 2011 Sep 20;124(12):e305-11.

Goldenberg I, Hall WJ, Beck CA, et al. Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: **MADIT-CRT** (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011; 58:729-737.

Goldberger ZD, Goldberger AL. Therapeutic Ranges of Serum **Digoxin** Concentrations in Patients With Heart Failure. Am J Cardiol. 2012 Apr 11.

Guazzi M, Vicenzi M, Arena R, Guazzi MD. **Pulmonary hypertension** in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition (**sildenafil**) in a 1-year study. Circulation. 2011 Jul 12;124(2):164-74.

Guerrera M. et al. Therapeutic Uses of **Magnesium**. Am Fam Physician. 2009; 80(1):157-162.

Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. **Mortality rate in patients with diastolic dysfunction** and normal systolic function. Arch Intern Med. 2011;171(12): 1082-1087.

Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, et al. **Spironolactone** use at discharge was associated with improved survival in hospitalized patients with systolic heart failure. Am Heart J. 2010 Dec;160(6):1156-62.

Hamm CW, Bassand JP, Agewall S, et al. **ESC** Guidelines for the management of **acute coronary syndromes** in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Sep 21.

Hawkins NM, Petrie MC, MacDonald MR, et al. Heart failure and **chronic obstructive pulmonary disease**. The quandary of **beta-blockers** and beta-agonists. J Am Coll Cardiol 2011; 57:2127-2138.

Heran BS, Musini VM, Bassett K, et al. **Angiotensin receptor blockers for heart failure**. Cochrane Database Syst Rev. 2012 Apr 18;4:CD003040. In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity. ARBs are better tolerated than ACEIs but do not appear to be as safe and well tolerated as placebo in terms of withdrawals due to adverse effects. Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.

Hernandez Adrian F.; Greiner Melissa A.; Fonarow Gregg C.; et al. Relationship Between **Early Physician Follow-up** and 30-Day Readmission Among Medicare Beneficiaries Hospitalized for Heart Failure. JAMA. 2010;303(17):1716-1722.

HFSA: Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, et al. Evaluation of patients for ventricular dysfunction and heart failure: **HFSA 2010 comprehensive heart failure** practice guideline. J Card Fail **2010** Jun;16(6):e44-56. http://www.heartfailureguideline.org/home/3

Holland DJ, Kumbhani DJ, Ahmed SH, Marwick TH. Effects of Treatment on Exercise Tolerance, Cardiac Function, and Mortality in Heart Failure With **Preserved Ejection Fraction** A Meta-Analysis. J Am Coll Cardiol. 2011 Apr 19;57(16):1676-1686.

Holzmeister J, Leclercq C. **Implantable cardioverter defibrillators** and **cardiac resynchronisation therapy**. Lancet. 2011 Aug 20;378(9792):722-30.

Homma S, Thompson JLP, Pullicino PM, et al. **Warfarin and aspirin** in patients with **heart failure** and sinus rhythm. (**WARCEF**) N Engl J Med 2012. DOI: 10.1056/NEJMoa1202299.

Howlett JG, McKelvie RS, Arnold JM, et al. **Canadian** Cardiovascular Society. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: diagnosis and management of **right-sided heart failure, myocarditis, device therapy and recent important clinical trials**. Can J Cardiol. 2009 Feb;25(2):85-105.

Howlett JG, McKelvie RS, Costigan J, et al; **Canadian** Cardiovascular Society (**CCS**). The 2010 Canadian Cardiovascular Society guidelines for the diagnosis and management of heart failure update: Heart failure in **ethnic minority populations, heart failure and pregnancy, disease management, and quality improvement/assurance programs**. Can J Cardiol. 2010 Apr;26(4):185-202.

Hsu JC, Solomon SD, Bourgoun M, et al. Predictors of super-response to **cardiac resynchronization therapy** and associated improvement in clinical outcome: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study. J Am Coll Cardiol 2012 59:2366-2373.

Hummel SL, DeFranco AC, Skorcz S, et al. Recommendation of **low-salt diet** and short-term outcomes in heart failure with preserved systolic function. Am J Med. 2009 Nov;122(11):1029-36.

Hunt SA, Abraham WT, Chin MH, et al. **2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure** in Adults. A Report of

TOP

the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009 Mar 26. [Epub ahead of print] http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192065v1

Ibrahim A, Baibars M, Alraies MC, Oliveira GH. Q: Should target **natriuretic peptide levels** be used for outpatient management of chronic heart failure? Cleve Clin J Med. 2012 Jan;79(1):22-5.

In the Clinic: Heart Failure Lee R. Goldberg Ann Intern Med June 1, 2010 152:ITC6-1

Inglis SC, Clark RA, McAlister FA, et al. **Structured telephone support or telemonitoring programmes** for patients with chronic heart failure. Cochrane Database Syst Rev. 2010 Aug 4;8:CD007228. Structured telephone support and telemonitoring are effective in reducing the risk of all-cause mortality and CHF-related hospitalisations in patients with CHF; they improve quality of life, reduce costs, and evidence-based prescribing.

Ip Dorothy, Syed Hafiz, Cohen Maurice. Digoxin specific antibody fragments (**Digibind**) in digoxin toxicity. BMJ 2009;339:b2884, doi: 10.1136/bmj.b2884 (Published 3 September 2009)

Jabbour A, Macdonald PS, Keogh AM, et al. Differences between **beta-blockers** in patients with chronic **heart failure and chronic obstructive pulmonary disease**: a randomized crossover trial. J Am Coll Cardiol. 2010 Apr 27;55(17):1780-7.

Jackson CE, Solomon SD, Gerstein HC, et al. **Albuminuria** in chronic heart failure: prevalence and prognostic importance (**Charm**). Lancet 2009; 374:543-550.

Jacobson AF, Senior R, Cerqueira MD, et al. **Myocardial iodine-123 meta-iodobenzylguanidine imaging** and cardiac events in heart failure results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 2010; DOI:10.1016/j.jacc.2010.01.014.

Januzzi JL Jr, Rehman SU, Mohammed AA, et al. Use of **amino-terminal pro-B-type natriuretic peptide** to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction (**PROTECT**). J Am Coll Cardiol 2011; 58:1881-1889.

Jessup M, Abraham WT, Casey DE, et al. **Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. **2009** Mar 26. [Epub ahead of print] http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192064v1

Jilek C, Tzeis S, Vrazic H, et al. Safety of screening procedures with **handheld metal detectors** among patients with implanted **cardiac rhythm devices**. Ann Intern Med 2011; 155:587-592.

Jondeau Guillaume, Neuder Yannick, Eicher Jean-Christophe, et al. , and for the **B-CONVINCED** Investigators. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. European Heart Journal Advance Access published on August 30, 2009, DOI 10.1093/eurheartj/ehp323.

Jones RH, Velazquez EJ, Michler RE, et al.; the **STICH** Hypothesis 2 Investigators. Coronary Bypass Surgery with or without Surgical Ventricular Reconstruction. N Engl J Med. 2009 Mar 29.

Jones CD, Loehr L, Franceschini N, et al. **Orthostatic hypotension** as a risk factor for incidence heart failure. The ARIC study. Hypertension 2012

Jorgenson, D. **Digoxin Dosing in Systolic Heart Failure**. RapidRx Q&A Jan 2007. Accessed online at: http://www.medicine.usask.ca/family/newsletters/rapid-rx/january-4-2007-pdf/Digoxin%20dosing%20in%20systolic%20heart%20failure.pdf

Jourdain P, Jondeau G, et al. Plasma brain **natriuretic peptideguided** therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol. 2007;49(16):1733-1739.

Joynt Karen E, Orav E John, Jha AK. The Association Between **Hospital Volume and Processes**, Outcomes, and Costs of Care for Congestive Heart Failure. Ann Intern Med Jan 18, 11 154:94-102.

Kalahasty G, Ellenbogen KA. Management of the Patient With **Implantable Cardioverter-Defibrillator (ICD) Lead Failure**. Circulation 123: 1352-1354, doi:10.1161/CIRCULATIONAHA.110.986828

Kantharia B, Patel S, Kulkarni G, et al. **Reuse of explanted permanent pacemakers** donated by funeral homes. Am J Cardiol 2011

Kansagara Devan, Englander Honora, Salanitro Amanda, et al. **Risk Prediction Models for Hospital Readmission**: A Systematic Review. JAMA. 2011;306(15):1688-1698.doi:10.1001/jama.2011.1515

Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular **diastolic dysfunction** and risk of heart failure. JAMA. 2011 Aug 24;306(8):856-63.

Kapoor JR, Heidenreich PA. **Obesity** and survival in patients with heart failure and preserved systolic function: A U-shaped relationship. Am Heart J 2010; 159:75-80.

Kaul P, McAlister FA, Ezekowitz JA, et al. Resource use in the **last 6 months of life** among patients with heart failure in **Canada**. Arch Intern Med 2010: DOI: 10.1001/archinternmed.2010.365.

Kelder JC, Cramer MJ, van Wijngaarden J, et al. The Diagnostic Value of Physical Examination and Additional Testing (eg. **NT-proBNP**) in Primary Care Patients With Suspected Heart Failure. Circulation. 2011 Nov 21.

Khanna A, White WB. The management of **hyperkalemia** in patients with cardiovascular disease. Am J Med. 2009 Mar;122(3):215-21.

Khawaja O, Kotler G, Gaziano JM, Djoussé L. Usefulness of **Desirable Lifestyle Factors** to Attenuate the Risk of Heart Failure Among Offspring Whose Parents Had Myocardial Infarction Before Age 55 Years. Am J Cardiol. 2012 Apr 18.

Kiefer T, Park L, Tribouilloy C, et al. Association between **valvular surgery** and mortality among patients with **infective endocarditis** complicated by heart failure. JAMA 2011; 306:2239-2247.

Kittleson Michelle M., Kobashigawa Jon A.. Management of **Advanced Heart Failure**: The Role of Heart **Transplantation**. Circulation 123: 1569-1574, doi:10.1161/CIRCULATIONAHA.110.972810

Kober L, Torp-Pedersen C, McMurray JJ,et al; **Dronedarone** Study Group. Increased mortality after dronedarone therapy for severe heart failure.N Engl J Med. 2008 Jun 19;358(25):2678-87.

Koehler F, Winkler S, Schieber M, et al. **Telemedical Interventional Monitoring in Heart Failure** (**TIM-HF**), a randomized, controlled intervention trial investigating the impact of telemedicine on mortality in ambulatory patients with chronic heart failure. Circulation 2010;12:1354-1362.

Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (**TRACE**) Study Group. N Engl J Med. 1995 Dec 21;333(25):1670-6.

Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (**HEAAL** study): a randomised, double-blind trial. Lancet 2009; DOI:10.1016/S0140-6736(09)61913-9.

Krum H, Teerlink JR. **Medical therapy for chronic heart failure. Lancet. 2011** Aug 20;378(9792):713-21.

Ku E, Park J, Vidhun J, Campese V. The **hazards of dual renin-angiotensin blockade** in chronic kidney disease. Arch Intern Med. 2009 Jun 8;169(11):1015-8.

Kuenzli A, Bucher HC, et al. **Meta-analysis** of combined therapy with **angiotensin receptor antagonists versus ACE inhibitors** alone in patients with **heart failure**. PLoS One. 2010 Apr 1;5(4):e9946.

Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, Hamid AK, Nicholls MG, Richards AM. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the **BATTLESCARRED** (**NT-proBNP-Assisted** Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol. 2009 Dec 29;55(1):53-60.

Landolina M, Gasparini M, Lunati M, et al. on behalf of the Cardiovascular Centers Participating in the ClinicalService Project. Long-Term Complications Related to **Biventricular Defibrillator Implantation**: Rate of Surgical Revisions and Impact on Survival: Insights From the Italian ClinicalService Database. Circulation. 2011 Jun 7;123(22):2526-2535.

Lanfear DE, Hrobowski T, Peterson EL, et al. Association of **Beta Blocker Exposure** with Outcomes in Heart Failure Differs Between **African American** and White Patients. Circ Heart Fail. 2012 Jan 19.

Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and **risk factors to heart failure with preserved or reduced ejection fraction**: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. Circulation 2009; 119:3070-3077.

Lee DS, Stukel TA, Austin PC, et al. Improved outcomes with early **collaborative care** of ambulatory heart failure patients discharged from the emergency department. Circulation. 2010 Nov 2;122(18):1806-14.

Lee DS, Stitt A, Austin PC, et al. **Prediction of heart failure mortality in emergent care**: a cohort study. Ann Intern Med. 2012 Jun 5;156(11):767-75.

León H, Shibata MC, Dorgan M, et al. Effect of **fish oil** on arrhythmias and mortality: systematic review. BMJ 2008; DOI: 10.1136/bmj.a2931. Fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. Evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes is insufficient. Fish oils are a heterogeneous product, and the optimal formulations for DHA and EPA remain unclear.

Levitan Emily B.; Wolk Alicja; Mittleman Murray A. Consistency With the **DASH Diet** and Incidence of Heart Failure Arch Intern Med. 2009;169(9):851-857.

Liang Y, Pan W, et al. Meta-Analysis of Randomized Controlled Trials **Comparing Isolated Left Ventricular** and **Biventricular Pacing** in Patients With Chronic Heart Failure. AmJCardiol.2011Aug 1.

Lind M, Bounias I, Olsson M, et al. **Glycaemic control and incidence of heart failure** in 20 985 patients with type 1 diabetes: an observational study. Lancet 2011; published online June 25.

Lipinski MJ, Cauthen CA, Biondi-Zoccai GG, et al. Meta-analysis of randomized controlled trials of **statins** versus placebo in patients with heart failure. Am J Cardiol. 2009 Dec 15;104(12):1708-16.

Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of **dexrazoxane as a cardioprotectant in doxorubicin-treated** children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol. 2010 Oct;11(10):950-61.

Lorenz RA, Elwell RJ. **Pre-dosing metolazone** with loop diuretic combination regimens. Nephrol Nurs J. 2006 Jan-Feb;33(1):78-9.

Lowrie R, Mair FS, Greenlaw N, et al. **Pharmacist** intervention in primary care to improve outcomes in patients with left ventricular systolic dysfunction. (**HOOPS**) Eur Heart J 2011.

MacFadden DR, Crystal E, Krahn AD, et al. **Sex differences** in implantable cardioverter-defibrillator (**ICD**) outcomes: findings from a prospective defibrillator database. Ann Intern Med. 2012;156:195-203.

Macicek SM et al. Acute heart failure syndromes in the **pediatric** emergency department. Pediatrics 2009 Nov; 124:e898.

Mackenzie C, Syed J, Pollak PT, Koren G. Falling between the cracks: a case of **amiodarone toxicity**. CMAJ. 2011 Sep 6;183(12):1393-7.

Maisel WH, Hauser RG, Hammill SC,et al. Recommendations from the Heart Rhythm Society Task Force on **Lead Performance** (ICD) Policies and Guidelines. Heart Rhythm. 2009;6:869–885.

Makani H, Messerli FH, Romero J, et al. Meta-Analysis of Randomized Trials of **Angioedema** as an Adverse Event of Renin-Angiotensin System Inhibitors. Am J Cardiol. 2012 Apr 20.

Mann DL. **Sphingosine 1-phosphate** as a therapeutic target in heart failure: more questions than answers. Circulation. 2012 Jun 5;125(22):2692-4.

Mant J, Abdallah AM, Swain S. Management of chronic heart failure in adults: Synopsis of the National Institute for Health and Clinical Excellence guideline (**NICE**). Ann Intern Med 2011; 155:252-259.

Mant J, Al-Mohammad A, Swain S, Laramée P; Guideline Development Group. Management of chronic **heart failure** in adults: synopsis of the National Institute For Health and clinical excellence guideline. (**NICE**). Ann Intern Med. 2011 Aug 16;155(4):252-9.

Mantziari L, et al. Relation of **dosing of the Renin-Angiotensin system inhibitors** after **cardiac resynchronization therapy** (CRT) to long-term prognosis. Am J Cardiol. 2012 Jun 1;109(11):1619-25.

Mark DB, Anstrom KJ, Sun JL, Clapp-Channing NE, Tsiatis AA, et al. Sudden Cardiac Death in Heart Failure Trial Investigators. (**SCD-HeFT**) Quality of life with **defibrillator** therapy or amiodarone in heart failure. N Engl J Med. 2008 Sep 4;359(10):999-1008. In a large primary-prevention population with moderately symptomatic heart failure, single-lead ICD therapy was not associated with any detectable adverse quality-of-life effects during 30 months of follow-up.

Massie BM, Collins JF, Ammon SE, et al. **WATCH** Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation. 2009 Mar 31;119(12):1616-24. Epub 2009 Mar 16. n=1587. The primary outcome measure and the mortality data do not support the primary hypotheses that warfarin is superior to aspirin and that clopidogrel is superior to aspirin.

Martínez-Selles M, Doughty R N, Poppe K, et al. **Gender** and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. Eur J Heart Fail 2012. (survival better for **females** irrespective of ejection fraction)
Matlock D, Peterson P, Wang Y, et al. Variation in use of **dual-chamber implantable cardioverter-defibrillators**. Arch Intern Med 2012; 172:634-641.
McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: **beta-blocker dose, heart rate reduction**, and death in patients with heart failure. Ann Intern Med. 2009 Jun 2;150(11): 784-94. The magnitude of **heart rate reduction** is statistically significantly associated with the survival benefit of beta-blockers in heart failure, whereas the dose of beta-blocker is not.
McAlister, Finlay A., Zhang, Jianguo, Tonelli, M, et al. The safety of **combining angiotensin-converting-enzyme inhibitors with angiotensin-receptor blockers in elderly** patients: a population-based longitudinal analysis. CMAJ 2011 0: cmaj.101333.
McAlister FA, Ezekowitz JA, et al. **Renal Dysfunction** in Heart Failure Patients with Preserved versus Reduced Ejection Fraction: Impact of the New **CKD-EPI** Formula. Circ Heart Fail. 2012 Mar 22.
McKelvie RS, Moe GW, Cheung A, et al. The 2011 **Canadian Cardiovascular Society (CCS) heart failure management guidelines update: focus on sleep apnea, renal dysfunction, mechanical circulatory support, and palliative care**. Can J Cardiol. 2011 May-Jun;27(3):319-38.
McMurray JJ, Anand IS, et al.; on behalf of the **RED-HF** Committees and Investigators. Design of the Reduction of Events with **Darbepoetin** alfa in **Heart Failure** (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Fail. 2009 Aug;11(8):795-801.
McMurray, John J.V. **Systolic Heart Failure**. N Engl J Med **2010** 362: 228-238.
McMurray JJV, Adamopoulos S, Anker SD, et al. **ESC guidelines** for the diagnosis and treatment of acute and **chronic heart failure 2012**: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; DOI:10.1093/eurheartj/ehs104.
Medical Letter-Treatment Guidelines. **Heart Failure. July 2009**.
Meta-analysis Global Group in Chronic Heart Failur. The **survival of patients with heart failure with preserved or reduced** left ventricular ejection fraction: an individual patient data meta-analysis. (**MAGGIC**) Eur Heart J. 2011 Aug 6.
Metra M, Gheorghiade M, Bonow RO, Dei Cas L. **Postdischarge assessment** after a heart failure hospitalization: the next step forward. Circulation. 2010 Nov 2;122(18):1782-5.
Miller AH, Nazeer S, Pepe P, Estes B, Gorman A, Yancy CW. Acutely decompensated heart failure in a county emergency department: a double-blind randomized controlled comparison of **nesiritide** versus placebo treatment. Ann Emerg Med. 2008 May;51(5):571-8. Epub 2008 Mar 4. Nesiritide (Natrecor), when added to standard therapy for heart failure in the emergency department, does not reduce return visits or hospitalizations over the subsequent 30 days as compared with standard therapy alone. (LOE = 1b)
Miller AL, Wang Y, Curtis J, Masoudi FA, Buxton AE, Wang TY. Optimal medical therapy use among patients receiving **implantable cardioverter/ defibrillators**: insights from the National Cardiovascular Data Registry [online Nov 14, 2011]. Arch Intern Med. doi10.1001/archinternmed.2011.466.
Muzzarelli S et al. Frequency and Predictors of **Hyperkalemia** in Patients ≥60 Years of Age With Heart Failure Undergoing Intense Medical Therapy. Am J Cardiol. 2011 Dec 5.
Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events (**MADIT-CRT**). N Engl J Med 2009; DOI: 10.1056.NEJMa0906431.
Mostofsky E, Levitan EB, Wolk A, et al. **Chocolate Intake** and Incidence of Heart Failure: A Population-Based, Prospective Study of Middle-Aged and Elderly Women. Circ Heart Fail. 2010 Aug 16.
Mozaffarian D, Lemaitre RN, King IB, et al. Circulating long-chain **ω-3 fatty acids** and incidence of congestive heart failure in older adults: the cardiovascular health study: a cohort study. Ann Intern Med. 2011 Aug 2;155(3):160-70.
Mutlak D, Lessick J, Carasso S et al. Utility of **Pulmonary Hypertension** for the Prediction of Heart Failure Following Acute Myocardial Infarction. Am J Cardiol. 2012 Feb 3.
Nawaf S. Al-Majed, Finlay A. McAlister, Jeffrey A. Bakal, et al. Meta-analysis: **Cardiac Resynchronization Therapy** for Patients With Less Symptomatic Heart Failure. Ann Intern Med E-313published ahead of print February 14, 2011.
Nazarian S, Hansford R, Roguin A, et al. A prospective evaluation of a protocol for **magnetic resonance imaging** of patients with **implanted cardiac devices**. Ann Intern Med 2011; 155:415-424.
Neil CJ, Chong CR, et al. Occurrence of Tako-Tsubo Cardiomyopathy in Association with Ingestion of Serotonin/Noradrenaline Reuptake Inhibitors (**venlafaxine**). Heart Lung Circ. 2012 Jan 25.
NICE: National Collaborating Centre for Acute and Chronic Conditions. **Chronic heart failure**. Management of chronic heart failure in adults in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Aug. 45 p. (Clinical guideline; no. 108). http://www.nice.org.uk/nicemedia/live/13099/50526/50526.pdf
Nieuwenhuis MM, Jaarsma T, van Veldhuisen DJ, et al. Long-Term Compliance With **Nonpharmacologic Treatment of Patients With Heart Failure**. Am J Cardiol. 2012 Apr 18.
Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. **Hyperkalaemia**. BMJ. 2009 Oct 23;339:b4114. doi: 10.1136/bmj.b4114.
O`Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: **HF-ACTION** randomized controlled trial. JAMA. 2009 Apr 8;301(14):1439-50.
O'Connor CM, Starling RC, Hernandez AF, et al. Effect of **nesiritide** in patients with acute decompensated heart failure (**Ascend-HF**). N Engl J Med 2011;365:32-43.
Okin PM, Devereux RB, Kjeldsen SE, et al. Incidence of heart failure in relation to **QRS** duration during antihypertensive therapy: the LIFE study. J Hypertens. 2009 Oct 14.
Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J. 2008 Jul;156(1):13-22. **Overweight** and obesity were associated with lower all-cause and cardiovascular mortality rates in patients with CHF and were not associated with increased mortality in any study.
Ohori T, Nozawa T, Ihori H, et al. Effect of Repeated **Sauna Treatment** on Exercise Tolerance and Endothelial Function in Patients With Chronic Heart Failure. Am J Cardiol. 2011 Sep 23.
Parikh K, Weitz H. Can a **bowel preparation exacerbate heart failure**? Cleveland Clinic Journal of Medicine 2011; 78(3):157-160; doi:10.3949/ccjm.77a.10025
Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. **ATLAS** Study Group. Circulation. 1999;100:2312-8.
Perin EC, Willerson JT, Pepine CJ, et al. Effect of transendocardial delivery of **autologous bone marrow mononuclear cells** on functional capacity, left ventricular function and perfusion in chronic heart failure. The **FOCUS-CCTRN** trial. JAMA 2012
Peterson Pamela N., Shetterly Susan M., Clarke Christina L., et al. **Health Literacy** and Outcomes Among Patients With Heart Failure. JAMA. 2011;305(16):1695-1701.doi:10.1001/jama.2011.512.
Pfisterer M, Buser P, Rickli H, et al. **TIME-CHF** Investigators. **BNP**-guided vs symptom-guided heart failure therapy: Trial of Intensified vs Standard Medical Therapy in **Elderly Patients** With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA. 2009 Jan 28;301(4):383-92. Heart failure therapy guided by N-terminal BNP did not improve overall clinical outcomes or quality of life compared with symptom-guided treatment. (BNP guided therapy increases dosages of evidence based medications but not significantly improve overall patient outcomes. Subgroup: The younger <75yr olds may respond better to BNP guided therapy than the >75yr olds.)
Pharmacist's Letter. **Nitrate comparison** chart. Mar, 2010.
Piccini JP, Berger JS, O`Connor CM. **Amiodarone** for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. Eur Heart J. 2009 May;30(10):1245-53. Epub 2009 Mar 31.
Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up (**8.9yr**) of participants with **heart failure** in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT**). Circulation. 2011;124:1811–1818.
Porapakkham Pramote; Porapakkham Pornwalee; Zimmet Hendrik; et al. **B-Type Natriuretic Peptide-Guided** Heart Failure Therapy: A Meta-analysis. Arch Intern Med. 2010;170(6):507-514.
Powell LH, Calvin JE Jr, Richardson D, et al. HART Investigators. **Self-management counseling** in patients with heart failure: the heart failure adherence and retention randomized behavioral trial. JAMA. 2010 Sep 22;304(12):1331-8
Rajagopalan S, Arora A, Shafiq N, et al. Pharmacotherapy of heart failure with **normal ejection fraction (HFNEF)**-a systematic review. Br J Clin Pharmacol. 2011 Sep;72(3):369-80.
Remme WJ, Swedberg K; The Task Force for the Diagnosis and Treatment of Heart Failure. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J. 2001;22(17):1527-1560.
Richards AM, Lainchbury JG, Troughton RW, et al. **NT-proBNP** guided treatment for chronic heart failure: results from the Battlescarred trial. Circulation. 2008; 118:S1035-S1036.
Ritter J M. Therapeutics: **Angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension**. BMJ 2011;342:doi:10.1136/bmj.d1673 (Published 7 April 2011)
Rivero-Ayerza M, Scholte Op Reimer W, et al. New-onset **atrial fibrillation** is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. Eur Heart J. 2008 Jul;29(13):1618-24. Epub 2008 May 31.
Rodondi N, Bauer DC, Cappola AR, et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol. 2008 Sep 30;52(14):1152-9. Compared with euthyroid older adults, those adults with **TSH>or=10.0 mU/l have a moderately increased risk of HF** and alterations in cardiac function but not older adults with TSH<10.0 mU/l. Clinical trials should assess whether the risk of HF might be ameliorated by thyroxine replacement in individuals with TSH>or=10.0 mU/l.
Ross, Joseph S., Normand, Sharon-Lise T., Wang, Yun, et al. Hospital **Volume** and 30-Day **Mortality** for Three Common Medical Conditions. N Engl J Med 2010 362: 1110-1118.
Rossignol P, Ménard J, Fay R, et al. **Eplerenone** survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects: insights from an **EPHESUS** (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) **EPHESUS** substudy. J Am Coll Cardiol 2011; 58:1958-1966.
Rossignol P, Cleland JG, Bhandari S et al. Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the eplerenone post-acute myocardial infarction heart failure efficacy and survival study. Circulation. 2012 Jan 17;125(2):271-9.
Roy B, Pawar PP, Desai RV, et al. A Propensity-Matched Study of the Association of **Diabetes Mellitus With Incident Heart Failure** and Mortality Among Community-Dwelling Older Adults. Am J Cardiol. 2011 Sep 22.
Sagar S, Liu PP, Cooper LT Jr. **Myocarditis**. Lancet. 2011 Dec 16.
Samala RV, Navas V, Saluke E, Ciocon JO. Heart failure in frail, older patients: We can do 'MORE'. Cleve Clin J Med. 2011 Dec;78(12):837-45.
Santangeli P, Di Biase L, Russo AD, et al. Meta-analysis: Age and Effectiveness of Prophylactic **Implantable Cardioverter-Defibrillators** (**ICD**). Ann Intern Med November 2, 2010 153:592-599.
Sawaya H, Sebaq IA, Plana JC, et al. Early detection and prediction of **cardiotoxicity in chemotherapy-treated patients**. Am J Cardiol2011; 107:1375-1380.
Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of **cocaine**. Circulation. 2010 Dec 14;122(24):2558-69.
Sciarretta Sebastiano; Palano Francesca; Tocci G; et al. **Antihypertensive Treatment and Development of Heart Failure** in Hypertension: A Bayesian Network Meta-analysis of Studies in Patients With Hypertension and High Cardiovascular Risk. Arch Intern Med. 2010;0(2010):archinternmed.2010.427.
Serrano C, Cortés J, De Mattos-Arruda L, et al. **Trastuzumab-related cardiotoxicity** in the elderly: a role for cardiovascular risk factors. Ann Oncol. 2011 Aug 9.
Setoguchi S, Schneeweiss S, Avorn J, Katz JN, Weinblatt ME, Levin R, Solomon DH. **Tumor necrosis factor**-alpha antagonist use and heart failure in elderly patients with rheumatoid

TOP

arthritis. Am Heart J. 2008 Aug;156(2):336-41. Epub 2008 Jun 17. TNFAs may increase the risk of both first hospitalization and exacerbation of HF in elderly patients with RA.
Shah MR. STARBRITE: a randomized pilot trial of **BNP-guided** therapy in patients with advanced heart failure. Circulation. 2006;114(II):528.
Sharp RP, Welch EB. Takotsubo cardiomyopathy as a complication of **electroconvulsive therapy**. Ann Pharmacother. 2011 Dec;45(12):1559-65.
Shelton RJ, Clark AL, Goode K, et al. A randomised, controlled study of rate versus rhythm control in patients with chronic **atrial fibrillation** and heart failure: (CAFE-II Study). Heart. 2009 Jun;95(11):924-30. Epub 2009 Mar 11.
Shibata MC, Leon H, Chatterley T, et al. Do **calcium channel blockers** increase the diagnosis of heart failure in patients with hypertension? Am J Cardiol. 2010 Jul 15;106(2):228-35.
Sieswerda E, van Dalen EC, Postma A, et al. Medical interventions for treating **anthracycline-induced symptomatic and asymptomatic cardiotoxicity** during and after treatment for childhood cancer. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD008011. DOI: 10.1002/14651858.CD008011.pub2.
Sipahi I,Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of **QRS duration on clinical event reduction with cardiac resynchronization therapy**: metaanalysis of randomized controlled trials [published online June 13, 2011]. Arch Intern Med. 2011; 171 (16):1454-1462
Slaughter MS, Rogers JG, Milano CA, et al. **HeartMate II** Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009 Dec 3;361(23):2241-51.
Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Mortality and Cost Associated With Cardiovascular **Implantable Electronic Device Infections**. Arch Intern Med. 2011 Sep 12.
Stauffer Brett D.; Fullerton Cliff; Fleming Neil; et al. Effectiveness and Cost of a **Transitional Care Program** for Heart Failure: A Prospective Study With Concurrent Controls. Arch Intern Med. 2011;171(14):1238-1243.
Steinberg BA, Zhao X, et al. **Trends in Patients Hospitalized** with Heart Failure and Preserved Left Ventricular Ejection Fraction - Prevalence, Therapies, and Outcomes. Circulation. 2012 May 21.
Stevenson WG, Hernandez AF, Carson PE, et al. Indications for **cardiac resynchronization therapy** (CRT): 2011 update from the Heart Failure Society of America (**HFSA**) guideline committee. J Card Fail 2012; 18:94-106.
Summaries for patients: management of chronic **heart failure** in adults: guidelines from the National Institute For Health and clinical excellence. Ann Intern Med. 2011 Aug 16;155(4):I-42.
Suzuki S, Sagara K, Otsuka T, et al. A New Scoring System for Evaluating the Risk of **Heart Failure** Events in Japanese Patients With Atrial Fibrillation (**H_2ARDD**). Am J Cardiol. 2012 May 21.
Svanström H, Pasternak B, Hviid A. Association of treatment with **losartan vs candesartan** and mortality among patients with heart failure. JAMA 2012; 307: 1506-1512.
Swedberg K, Komajda M, Böhm M, et al. **Ivabradine** and outcomes in chronic heart failure (**SHIFT**): A randomised placebo-controlled study. Lancet 2010; DOI:10.1016/S01406736(10)61198-1.
Tang AS, Wells GA, Talajic M, et al. **Cardiac-resynchronization therapy** for mild-to-moderate heart failure. (**Raft**) N Engl J Med 2010; 363:2385-2395.
Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of **n-3 polyunsaturated fatty acids** in patients with chronic heart failure (the **GISSI-HF** trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-1230
Terkelsen CJ, Jensen LO, Tilsted HH, et al. Health Care **System Delay** and Heart Failure in Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Follow-up of Population-Based Medical Registry Data. Ann Intern Med. 2011 Sep 20;155(6):361-7.
Thanassoulis George; Brophy James M.; Richard Hugues; et al. Gout, **Allopurinol** Use, and Heart Failure Outcomes. Arch Intern Med. 2010;170(15):1358-1364.
Thibault B, Ducharme A, Harel F, et al. **Left ventricular versus simultaneous biventricular pacing** in patients with heart failure and a QRS complex ≥ 120 milliseconds. (Greater-Earth) Circulation. 2011;124:2874 –2881.
Thomson MR, Nappi JM, Dunn SP, et al. **Continuous versus intermittent** infusion of **furosemide** in acute decompensated heart failure. J Card Fail. 2010 Mar;16(3):188-93.
Toma M, McAlister FA, Coglianese EE, et al. **Testosterone Supplementation** in Heart Failure: A Meta-Analysis. Circ Heart Fail. 2012 Apr 17.
Tomova GS, Nimbal V, Horwich TB. Relation between **hemoglobin A1c and outcomes in heart failure** patients with and without diabetes mellitus. Am J Cardiol 2012.
Torpy JM, Lynm C, Golub RM. JAMA **patient page**. **Heart failure**. JAMA. 2011 Nov 16;306(19):2175.
Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (**N-BNP**) concentrations. Lancet. 2000;355(9210):1126-1130.
Unroe KT, Greiner MA, Hernandez AF, et al. Resource use in the **last 6 months of life among Medicare** beneficiaries with heart failure, 2000-2007. Arch Intern Med 2010.
Udelson JE. Heart failure with **preserved ejection fraction**. Circulation. 2011 Nov 22;124(21):e540-3.
van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease **undergoing noncardiac surgery**: an analysis of 38 047 patients. Circulation. 2011 Jul 19;124(3):289-96.
van Veldhuisen DJ, Cohen-Solal A, et al.; **SENIORS** Investigators. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol. 2009 Jun 9;53(23):2150-8. The effect of beta-blockade with nebivolol in elderly patients with HF in this study was similar in those with preserved and impaired EF.
Vassallo P, Trohman RG. Prescribing **amiodarone**: an evidence-based review of clinical indications. JAMA. 2007 Sep 19;298(11):1312-22
Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. Circulation 2008; DOI: 10.1161/CIRCULATIONAHA.108.784215.
Velazquez EJ, Lee KL, Deja MA, et al. **Coronary-artery bypass surgery** (CABG) in patients with left ventricular dysfunction (**STITCH**). N Engl J Med 2011. DOI: 10.1056/NEJMoa1100356.
Versteeg H, van den Broek KC, Theuns DA, et al. Effect of **cardiac resynchronization therapy**-defibrillator implantation on health status in patients with mild versus moderate symptoms of heart failure. Am J Cardiol. 2011 Oct 15;108(8):1155-9.
Waller DG, Waller JR. **{beta} blockers** for heart failure with reduced ejection fraction. BMJ. 2011 Sep 26;343:d5603. doi: 10.1136/bmj.d5603.
Wang AYM, Sanderson JE. Current perspectives on diagnosis of heart failure in long-term **dialysis patients**. Am J Kidney Dis. 2011;57:308–19.
Waqar S, Sarkar PK. **Exacerbation of psoriasis** with beta-blocker therapy. CMAJ. 2009 Jul 7;181(1-2):60.
Weeks SG, Glantz SA, De Marco T, Rosen AB, Fleischmann KE. **Secondhand smoke** exposure and quality of life in patients with heart failure. Arch Intern Med. 2011;171(21):1887-1893.
Wei Li, Struthers Allan D, Fahey Tom et al. **Spironolactone** use and renal toxicity: population based longitudinal analysis. BMJ 2010;340:c1768
Weintraub Neal L., Collins Sean P., Pang Peter S., et al., and on behalf of the American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. **Acute Heart Failure Syndromes**: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims: A Scientific Statement From the American Heart Association (**AHA**). Circulation 122: 1975-1996; published online before print as doi:10.1161/CIR.0b013e3181f9a223 http://circ.ahajournals.org/cgi/reprint/122/19/1975
Wells, George, Parkash, Ratika, Healey, Jeffrey S., et al. **Cardiac resynchronization therapy** (**CRT**): a meta-analysis of randomized controlled trials. CMAJ 2011 0: cmaj.101685.
Whitley H, Lindsey W. **Sex-based** differences in drug activity. Am Fam Physician. 2009 Dec 1;80(11):1254-8.
Wilson JR. **Rhetorical techniques** used in the reporting of **cardiac resynchronization trials** [published online June 13, 2011].Arch Intern Med. 2011;171(16): 1500-1502.
Yeh Gloria Y.; McCarthy Ellen P.; Wayne Peter M.; et al. **Tai Chi Exercise** in Patients With Chronic Heart Failure: A Randomized Clinical Trial. Arch Intern Med. 2011;171(8):750-757.
Yip GW, Wang M, Wang T et al. The Hong Kong diastolic heart failure study: a randomized controlled trial of **diuretics**, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a **normal ejection fraction**. Heart. 2008 94:573-580.
Yu, Cheuk-Man, Chan, Joseph Yat-Sun, Zhang, Qing, et al. **Biventricular Pacing** in Patients with Bradycardia and Normal Ejection Fraction. N Engl J Med 2009 0: NEJMoa0907555.
Zannad F, McMurray JJV, Krum H, et al. **Eplerenone** in patients with systolic heart failure and mild symptoms. (**Emphasis-HF**) N Engl J Med 2011; 364:11-21.
Zhang Y, Fonarow GC, Sanders PW, et al. A Propensity-Matched Study of the Comparative Effectiveness of **Angiotensin Receptor Blockers Versus Angiotensin-Converting Enzyme Inhibitors** in Heart Failure Patients Age ≥65 Years. Am J Cardiol. 2011 Sep 3.
Zhang L, Lu Y, Jiang H, et al. Additional use of **trimetazidine** in patients with chronic heart failure: a meta-analysis. J Am Coll Cardiol. 2012 Mar 6;59(10):913-22.
Zile MR et al. for the **I-PRESERVE**. Prevalence and Significance of Alterations in **Cardiac Structure** and Function in Patients With Heart Failure and a Preserved Ejection Fraction. Circulation. 2011 Dec 6;124(23):2491-2501.

TOP

Additional articles

Green Lee A. Cholesterol-Lowering Therapy for Primary Prevention: Still Much We Don't Know. Arch Intern Med. 2010;170(12):1007-1008.

Ray Kausik K.; Seshasai Sreenivasa Rao Kondapally; Erqou Sebhat; et al. Statins and All-Cause Mortality in High-Risk Primary Prevention: A Meta-analysis of 11 Randomized Controlled Trials Involving 65 229 Participants. Arch Intern Med. 2010;170(12):1024-1031.

REFERENCES: *The RxFiles*- Lipid Lowering Agents ALL-CAUSE MORTALITY OUTCOMES from MAJOR LIPID TRIALS

[1] Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (**4S**). Lancet 1994;344:1383-9.

[2] Strandberg TE, Pyorala K, Cook TJ, et al; **4S** Group. Mortality and incidence of cancer during **10-year** follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet. 2004 Aug 28;364(9436):771-7. (Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. Am J Kidney Dis. 2007 Mar;49(3):373-82.)

[3] Long-Term Intervention with Pravastatin in Ischeamic Heart Disease (**LIPID**) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339:1349-1357.

4 **LIPID** Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease). Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet. 2002 Apr 20;359(9315):1379-87.

[5]Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels (**CARE**). N Engl J Med 1996;335:1001-9. Tonelli M, et al. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial (**CARE**). BMJ. 2006 May 19; [Epub ahead of print] The presence or absence of proteinuria on dipstick urinalysis may be used to refine estimates of risk based on kidney function alone.

[6] Heart Protection Study (**HPS**)- Preliminary data from: www.hpsinfo.org

[7] MRC/BHF Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience (**HPS**). Eur Heart J 1999;20:725-41.

[8] Heart Protection Study Group.MRC/BHF **HPS** study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-22. (**11,609** of 32,145 pts in 4-6 wk run in treatment with simvastatin 40mg/d **were excluded**)

[9] Heart Protection Study Group.MRC/BHF **HPS** study of cholesterol lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003 Jun 14;361(9374):2005-16..

[10] Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004 Mar 6;363(9411): 757-67.
(Heart Protection Study Group. **Lifetime cost effectiveness** of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20 536 people. (**HPS**) BMJ. 2006 Nov 10; [Epub ahead of print])
Heart Protection Study (HPS) Collaborative Group. **C-reactive protein** concentration and the vascular benefits of statin therapy: an analysis of 20 536 patients in the Heart Protection Study. *Lancet* 2011; DOI:10.1016/S0140-6736(10)62174-5.
Hopewell JC, Parish S, Clarke R, et al. No impact of KIF6 genotype on vascular risk and statin response among 18 348 randomized patients in the Heart Protection Study. J Am Coll Cardiol 2011; DOI:10.1016/j.jacc.2011.02.015.
Heart Protection Study Collaborative Group. Effects on **11-year mortality and morbidity** of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet 2011; online Nov 23.

11 BIP Study Group. Secondary prevention (n=3090) by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The bezafibrate infarction prevention (BIP) study. Circulation 2000;102:21-27. (Tenenbaum A, Motro M, Fisman EZ, et al. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. Arch Intern Med. 2005 May 23;165(10):1154-60 & McCormack J, Loewen P. The other side of the bezafibrate infarction prevention trial data. Arch Intern Med. 2005 Nov 14;165(20):2431-2; author reply 2432.) (Tenenbaum A, et al. Attenuation of progression of insulin resistance in patients with coronary artery disease by bezafibrate. Arch Intern Med. 2006 Apr 10;166(7):737-41.)
Goldenberg I, et al. Secondary prevention with bezafibrate therapy for the treatment of dyslipidemia: an extended follow-up of the BIP trial. J Am Coll Cardiol. 2008 Jan 29;51(4):459-65. The data demonstrate that bezafibrate therapy in the BIP trial was associated with significant long-term cardiovascular protection that was attenuated by an unbalanced usage of nonstudy LLDs during the course of the trial.
Goldenberg I, Boyko V, Tennebaum A, et al. Long-term benefit of high-density lipoprotein cholesterol-raising therapy with bezafibrate. (16yr follow up)Arch Intern Med 2009; 169: 508-514.

[12] Bloomfield Rubins A, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol (**VA-HIT**). N Engl J Med 1998; 339:1349-57.

[13] Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atovastatin Diabetes Study (CARDS). Lancet 2004;364:685-96. Colhoun HM, et al.; on behalf of the CARDS Investigators. Rapid emergence of effect of atorvastatin on cardiovascular outcomes in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia. 2005 Nov 12;:1-4 [Epub ahead of print] RESULTS: A reduction in the primary endpoint of major CVD events was apparent and statistically significant as soon as 18 months after treatment initiation. The effect of atorvastatin on CHD events was apparent by 6 months, and at 1 year was similar to the 37% relative risk reduction observed at trial closure.) (Neil HA, et al. CARDS Study Investigators. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84.)
Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS Investigators. Effects of Atorvastatin on Kidney Outcomes and Cardiovascular Disease in Patients With Diabetes: An Analysis From the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009 Jun 18. [Epub ahead of print] A modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria, was observed. Atorvastatin did not influence albuminuria incidence. Atorvastatin was effective at decreasing CVD in those with and without a moderately decreased eGFR and achieved a high absolute benefit.

[14] Peter S Sever, Björn Dahlöf et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the **Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm** (**ASCOT-LLA**): a multicentre randomised controlled trial Lancet 2003; **361:** 1149-58. Online April 2, 2003.
Sever PS, et al. The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure. Eur Heart J. 2008 Feb;29(4):499-508. Epub 2008 Jan 5. Carry-over benefits from those originally assigned atorvastatin but no longer taking the drug may account for unchanged relative risk reductions in most cardiovascular endpoints observed 2 years after ASCOT-LLA closed.
Sever PS, Poulter NR, Dahlof B, Wedel H; on behalf of the ASCOT investigators. Antihypertensive therapy and the benefits of atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial: lipid-lowering arm extension. J Hypertens. 2009 Mar 21. [Epub ahead of print]
Sever PS, Chang CL, Gupta AK, et al. Anglo-Scandinavian Cardiac Outcomes Trial (Ascot): **11-year mortality follow-up** of the lipid-lowering arm in the UK. Eur Heart J 2011. (Less mortality mainly from less non-cardiovascular deaths)

[15] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia (**WOSCOPS**). N Engl J Med 1995;333:1383-9. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM; West of Scotland Coronary Prevention Study Group. Long-term follow-up of the West of Scotland Coronary Prevention Study. (Woscops) N Engl J Med. 2007 Oct 11;357(15):1477-86. In the period approximately 10 years after completion of the trial, the risk of death from coronary heart disease or nonfatal myocardial infarction was 10.3% in the placebo group and 8.6% in the pravastatin group (P=0.02); over the entire follow-up period, the rate was 15.5% in the placebo group and 11.8% in the pravastatin group (P<0.001). In this analysis, 5 years of treatment
with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolemia who did not have a history of myocardial infarction.
Logue J, Murray HM, Welsh P, et al. Obesity is associated with fatal coronary heart disease independently of traditional risk factors and deprivation (WOSCOPS). Heart 2011; DOI:10.1136/hrt.2010.211201.

[16] Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of (**AFCAPS/TexCAPS**). JAMA 1998;279:1615-22.
Clearfield M, Downs JR, Lee M, et al. Implications from the Air Force/Texas Coronary Atherosclerosis Prevention Study for the Adult Treatment Panel III Guidelines. Am J Cardiol. 2005 Dec 15;96(12):1674- 80. Epub 2005 Nov 2.
Cui Y, Watson DJ, Girman CJ, et al. Effects of increasing high-density lipoprotein cholesterol and decreasing low-density lipoprotein cholesterol on the incidence of first acute coronary events (from the Air Force/Texas Coronary Atherosclerosis Prevention Study). Am J Cardiol. 2009 Sep 15;104(6):829-34.

[17] Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study (**HHS**): Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45. (Tenkanen L, et al. Gemfibrozil in the Treatment of Dyslipidemia: An **18-Year** Mortality Follow-up of the Helsinki Heart Study. (HHS) Arch Intern Med. 2006 Apr 10;166(7):743-8.)

TOP

[18] Committee of Principal Investigators (**WHO-Clof**). A co-operative trial in the primary prevention of ischeamic heart disease using clofibrate. British Heart Journal 1978;40:1069-1118.

[19] Implications of Recent Clinical Trials for the NCEP ATP Panel III Guidelines July **2004** {HPS: serum lipids at basline were determined on nonfasting samples and calculated by the direct LDL method. Most other trials determined on fasting samples and LDL-C calculated by the Friedewald equation. If HPS was calculated by the Friedewald eqation, the baseline LDL would be **~15% higher**. http://www.acc.org/clinical/adoptions/ncep_report.pdf

[20] Walsh, J.M., Pignone M. Drug Treatment of Hyperlipidemia in Women. JAMA. 2004 May 12;291(18):2243-2252.

[21] Bandolier: Cholesterol and Statins; Extra April 2004 http://www.jr2.ox.ac.uk/bandolier/Extraforbando/statin.pdf

[22] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004 Apr 8;350(15):1495-504. Epub 2004 Mar 08.

[23] Marco Studer, MD; Matthias Briel, MD; Bernd Leimenstoll, MD; et al. Effect of Different Antilipidemic Agents and Diets on Mortality A Systematic Review. Arch Intern Med. 2005;165:725-730. (InfoPOEMs: Only statin lipid-lowering drugs have been shown to decrease overall mortality in patients with high cholesterol but without evidence of heart disease. However, most patients treated with one of these drugs will not benefit: 228 have to be treated for 3.3 years to prevent 1 additional death during this period. In pts with known heart dx, statins & fish oil both have been shown to decrease mortality. Niacin, resins, & diet have not been shown to decrease mortality. Fibrates (gemfibrozil & others) actually increase overall mortality & at the same time decrease cardiac mortality. (LOE =1a))

24. LaRosa JC. et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease (**TNT**) . N Engl J Med. 2005 Mar 8;352 online. (InfoPOEMs: The benefit of intensive lipid therapy in patients with known heart disease is very modest: a number needed to treat (NNT) of 45 for 5 years to prevent any cardiovascular outcome. There was no difference in all-cause mortality between intensive and less intensive treatment groups (5.6% vs 5.7%), and the study was large enough and long enough to be able to detect such a benefit if one existed. Since the benefit of lipid lowering is greatest in patients with known disease, any benefit is certainly much less lower for patients without known disease who are at much lower risk. (LOE = 1b)) (**5461** of 15,464 pts in 8 wk open-label treatment with atorvastatin 10mg/d **were excluded**). McGowan MP; Treating to New Target (TNT) Study Group. There is no evidence for an increase in acute coronary syndromes after short-term abrupt discontinuation of statins in stable cardiac patients. Circulation. 2004 Oct 19;110(16):2333-5. Epub 2004 Oct 11. Shepherd J, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care. 2006 Jun;29(6):1220-6. Deedwania P, et al. Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet. 2006 Sep 9;368(9539):919-28. Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK; Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Ann Intern Med. 2007 Jul 3;147(1):1-9. The analysis suggests that additional clinical benefit can be achieved by treating older patients with CHD more aggressively to reduce low-density lipoprotein cholesterol levels to less than 2.6 mmol/L (<100 mg/dL). The findings support the use of intensive low-density lipoprotein cholesterol-lowering therapy in high-risk older persons with established cardiovascular disease. Larosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H; Treating to New Targets (TNT) Steering Committee and Investigators. Safety and Efficacy of Atorvastatin-Induced Very Low-Density Lipoprotein Cholesterol Levels in Patients With Coronary Heart Disease (a Post Hoc Analysis of the Treating to New Targets [TNT] Study). Am J Cardiol. 2007 Sep 1;100(5):747-52. Epub 2007 Jun 14. In conclusion, the present analysis adds support to the concept that for patients with established atherosclerotic cardiovascular disease, a further risk reduction without sacrifice of safety can be achieved by reducing LDL cholesterol to very low levels. (Barter P, Gotto AM, LaRosa JC, Maroni J, et al; Treating to New Targets Investigators (TNT). HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007 Sep 27;357(13):1301-10. In this post hoc analysis, HDL was predictive of major cardiovascular events in patients treated with statins. This relationship was also observed among patients with LDL cholesterol levels below 70 mg per deciliter.) Wenger NK, Lewis SJ, Welty FK, Herrington DM, Bittner V. Beneficial effects of aggressive LDL cholesterol lowering in women with stable coronary heart disease in the Treating to New Targets (TNT) study. Heart. 2007 Dec 10; [Epub ahead of print] Conclusion Intensive lipid-lowering treatment with atorvastatin 80 mg produced significant reductions in relative risk for major cardiovascular events compared with atorvastatin 10 mg in both women and men with stable CHD.
Shepherd J, Kastelein JJ, et al.; TNT (Treating to New Targets) Investigators. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. J Am Coll Cardiol. 2008 Apr 15;51(15):1448-54. [PubMed - in process] Aggressive lipid lowering with atorvastatin 80 mg was both safe and effective in reducing the excess of cardiovascular events in a high-risk population with CKD and CHD.
Shepherd J, Kastelein JP, Bittner VA, Carmena R, Deedwania PC, Breazna A, Dobson S, Wilson DJ, Zuckerman AL, Wenger NK; Treating to New Targets Steering Committee and Investigators. Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. Mayo Clin Proc. 2008 Aug;83(8):870-9. The absolute risk reduction in patients with diabetes and CKD was substantial, yielding a number needed to treat of 14 to prevent 1 major cardiovascular event over 4.8 years.
Patients with diabetes, stable coronary artery disease, and mild to moderate CKD experience marked reduction in cardiovascular events with intensive lipid lowering, in contrast to previous observations in patients with diabetes and end-stage renal disease.
Bangalore S, Messerli FH, Wun CC, et al. Treating to New Targets Steering Committee and Investigators. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) trial. Eur Heart J. 2010 Sep 16.
Mora S, Wenger NK, DeMicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation. 2012;125:1979 –1987.

25. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R; Heart Protection Study Collaborative Group.**HPS**: **Cost-effectiveness** of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20,536 individuals. Lancet. 2005 May;365(9473):1779-85 & ACP Journal Club .

25. Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. 2005 Jul 20;294(3):326-33. (Nissen SE, Tuzcu EM, Schoenhagen P, et al.; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005 Jan 6;352(1):29-38.) (Nicholls SJ, et al. Effects of obesity on lipid-lowering, anti-inflammatory, and antiatherosclerotic benefits of atorvastatin or pravastatin in patients with coronary artery disease (from the REVERSAL Study). Am J Cardiol. 2006 Jun 1;97(11):1553-7. Epub 2006 Apr 6.)

26. Cowell SJ, Newby DE, Prescott RJ, et al.; Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (**SALTIRE**) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med. 2005 Jun 9;352(23):2389-97. CONCLUSIONS: Intensive lipid-lowering therapy does not halt the progression of calcific aortic stenosis or induce its regression. This study cannot exclude a small reduction in the rate of disease progression or a significant reduction in major clinical end points. Long-term, large-scale, randomized, controlled trials are needed to establish the role of statin therapy in patients with calcific aortic stenosis.

27. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (**CTT**) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-78. Epub 2005 Sep 27. (InfoPOEMs: Statins reduce 5-year overall mortality, and specifically decrease cardiovascular mortality and morbidity. The patients at highest baseline risk derive the greatest benefit. (LOE = 1a))

28. Packard CJ, Ford I, Robertson M, et al. Plasma Lipoproteins and Apolipoproteins as Predictors of Cardiovascular Risk and Treatment Benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Circulation. 2005 Nov 7; [Epub ahead of print] Ford I, Bezlyak V, Stott DJ, Sattar N, Packard CJ, Perry I, Buckley BM, Jukema JW, de Craen AJ, Westendorp RG, Shepherd J. Reduced glomerular filtration rate and its association with clinical outcome in older patients at risk of vascular events: secondary analysis. (Prosper) PLoS Med. 2009 Jan 20;6(1):e16.

29. Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized **trials stopped early** for benefit: a systematic review. JAMA. 2005 Nov 2;294(17):2203-9.

30. Pedersen TR, Faergeman O, et al. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The **IDEAL** Study: A Randomized Controlled Trial. JAMA.2005Nov16;294(19):2437-2445. (InfoPOEMs: The intensive reduction of low-density lipoprotein (LDL) levels to well below 100 mg/dL (2.5 mmol/L) did not result in a significant reduction in the recurrence of major coronary events or all-cause mortality among patients with stable coronary artery disease. Intensive lowering is associated with an increased risk of discontinuing medication because of adverse events and significant drug costs. Aiming for an LDL of approximately 100 mg/dL (2.5 mmol/L) seems optimal for the majority of patients with stable disease. (LOE = 1b-))
Tikkanen MJ, Holme I, Cater NB, et al.; Incremental DEcrease through Aggressive Lipid Lowering Investigators. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 versus >or=65 years with coronary heart disease (from the Incremental DEcrease through Aggressive Lipid Lowering [IDEAL] study). Am J Cardiol. 2009 Mar 1;103(5):577-82. Epub 2009 Jan 17. Rates of any reported serious adverse event were higher in older patients, but did not differ between the 2 statin groups. In conclusion, except for any CV events in the older group, significant reductions in primary and secondary end points were observed only in patients <65 years of age. The safety of atorvastatin (80 mg) and simvastatin (20 to 40 mg) was similar in patients aged <65 and >65 years with stable coronary disease.
Tikkanen MJ, Szarek M, Fayyad R, et al. IDEAL Investigators. Total cardiovascular disease burden: comparing intensive with moderate statin therapy insights from the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial. J Am Coll Cardiol. 2009 Dec 15;54(25):2353-7.
Pedersen TR, Cater NB, Faergeman O, et al. Comparison of atorvastatin 80 mg/day versus simvastatin 20 to 40 mg/day on frequency of cardiovascular events late (five years) after acute myocardial infarction (from the Incremental Decrease in End Points through Aggressive Lipid Lowering [IDEAL] trial). Am J Cardiol. 2010 Aug 1;106(3):354-9.

31. Keech A, Simes RJ, Barter P, et al. **FIELD** study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005 Nov 26;366(9500):1849-61. INTERPRETATION: Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations. The higher rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit. (But some **non-significant** concerns with fenofibrate vs placebo such as: an ↑ in cardiac mortality 2.2 vs 1.9%, an ↑ in total CVD events for those with previous CVD 25.5 vs 25.1%, an excess in non-cardiovascular disease deaths 4.4 vs 4% & an ↑ in total mortality 7.3 vs 6.6%). But may benefit albuminuria & retinopthy. (InfoPOEMs: In this study, patients with type 2 diabetes treated with fenofibrate (Antara, Lofibra, Tricor) had no significant reduction in coronary events compared with patients treated with placebo. There was a small reduction, however, in nonfatal myocardial infarctions, total cardiovascular disease, and revascularization. (LOE = 1b)) Keech AC, Mitchell P, Summanen PA, et al, for the FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007;370(9600):1687-1697. In patients with type 2 diabetes mellitus fenofibrate (Antara, Lofibra, Tricor) modestly reduces the number of laser treatments for retinopathy. (LOE = 1b)
Rajamani K et al. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): A prespecified analysis of a randomised controlled trial. Lancet 2009 May 23; 373:1780.
Davis TM, Ting R, Best JD, et al. Fenofibrate Intervention and Event Lowering in Diabetes Study investigators. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lo

TOP

(FIELD) Study. Diabetologia. 2011 Feb;54(2):280-90.
32. Houslay E, et al. **Progressive coronary calcification despite** intensive lipid-lowering therapy: a randomised controlled trial. Heart. 2006 Jan 31; [Epub ahead of print]
33. Nissen SE, et al. Effect of Very High-Intensity Statin (rosuvastatin 40mg/d, 2yr, n=507) Therapy on Regression of Coronary Atherosclerosis: The **ASTEROID** Trial.JAMA. 2006 Mar 13; [Epub ahead of print]
34. Hooper L, et al. Risks and benefits of **omega 3 fats** for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006 Mar 24; [Epub ahead of print]
35. Costa J, Borges M, David C, Carneiro AV. Efficacy of lipid lowering drug treatment for **diabetic and non-diabetic** patients: meta-analysis of randomised controlled trials. BMJ. 2006 Apr 3; [Epub ahead of print]
36. Manuel DG, et al. Effectiveness and efficiency of **different guidelines** on statin treatment for preventing deaths from coronary heart disease: **modelling study**. BMJ. 2006 Jun 17;332(7555):1419. Epub 2006 May 31.
37. Knopp RH, et al. Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (**ASPEN**). Diabetes Care. 2006 Jul;29(7):1478-85.
38. Amarenco P, et al.; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (**SPARCL**) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006 Aug 10;355(6):549-59. (Kent DM. Stroke--an equal opportunity for the initiation of statin therapy. N Engl J Med. 2006 Aug 10;355(6):613-5.) Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, Hennerici M, Simunovic L, Zivin JA, Welch KM; SPARCL Investigators. Effects of Intense Low-Density Lipoprotein Cholesterol Reduction in Patients With Stroke or Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2007 Oct 25; [Epub ahead of print] As compared with having no change or an increase in LDL-C, achieving a >/=50% lowering was associated with a greater reduction in the risk of stroke and major coronary events with no increase in brain hemorrhages. Goldstein LB, Amarenco P, Szarek M, Callahan A 3rd, Hennerici M, Sillesen H, Zivin JA, Welch KM; On behalf of the SPARCL Investigators. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology. 2007 Dec 12; [Epub ahead of print] Hemorrhagic stroke was more frequent in those treated with atorvastatin, in those with a hemorrhagic stroke as an entry event, in men, and increased with age. Those with Stage 2 hypertension at the last visit prior to the hemorrhagic stroke were also at increased risk. Treatment did not disproportionately affect the hemorrhagic stroke risk associated with these other factors. There were no relationships between hemorrhage risk and baseline low-density lipoprotein (LDL) cholesterol level or recent LDL cholesterol level in treated patients.
Sillesen H, Amarenco P, Hennerici MG, et al. on Behalf of the SPARCL Investigators. Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis. A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2008 Oct 9. [Epub ahead of print] Consistent with the overall results of the SPARCL intention to treat population, intense lipid lowering with atorvastatin reduced the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis. The carotid stenosis group may have greater benefit.
Amarenco P, Benavente O, Goldstein LB, et al.; on behalf of the SPARCL Investigators. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes. Stroke. 2009 Feb 19. [Epub ahead of print] Atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other cardiovascular events, irrespective of baseline ischemic stroke subtype.
Goldstein LB, Amarenco P, Zivin J, Messig M, Altafullah I, Callahan A, Hennerici M, Macleod MJ, Sillesen H, Zweifler R, Welch KM; on behalf of the SPARCL Investigators. Statin Treatment and Stroke Outcome in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2009 Sep 10.
Callahan Alfred; Amarenco Pierre; Goldstein Larry B.; et al. the SPARCL Investigators. Risk of Stroke and Cardiovascular Events After Ischemic Stroke or Transient Ischemic Attack in Patients With Type 2 Diabetes or Metabolic Syndrome: Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial Arch Neurol. 2011;0(2011):archneurol.2011.146.
39. Hayward RA, Hofer TP, Vijan S. Narrative review: **lack of evidence** for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med. 2006 Oct 3;145(7):520-30.
40. Cannon CP, Braunwald E, McCabe CH, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004 Apr 8;350(15):1495-504. Epub 2004 Mar 8. Erratum in: N Engl J Med. 2006 Feb 16;354(7):778. (Ahmed S, Cannon CP, Murphy SA, et al.Acute coronary syndromes and **diabetes**: Is intensive lipid lowering beneficial? Results of the **PROVE IT-TIMI 22** trial. Eur Heart J. 2006 Oct;27(19):2323-9. Epub 2006 Sep 5.)
Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute Coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. J Am Coll Cardiol. 2009 Dec 15;54(25):2358-62.
41. Nakamura H, et al. **Primary prevention** of cardiovascular disease with pravastatin in Japan (**MEGA** Study): a prospective randomised controlled trial. Lancet. 2006 Sep 30;368(9542):1155-63. Treatment with a low dose of pravastatin reduces the risk of coronary heart disease in Japan by much the same amount as higher doses have shown in Europe and the USA.
Mizuno K, Nakaya N, Ohashi Y, et al; for the MEGA Study Group. Usefulness of Pravastatin in Primary Prevention of Cardiovascular Events in Women. Analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA Study). Circulation. 2008 Jan 2; [Epub ahead of print] Treatment with pravastatin in women with elevated cholesterol but no history of cardiovascular disease provides a benefit similar to that seen in men, and this benefit is more marked in older women.
42. Taylor AJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol **(ARBITER) 2**: a double-blind, placebo-controlled study of extended-release **niacin** on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004 Dec 7;110(23):3512-7. Epub 2004 Nov 10. Erratum in: Circulation. 2004 Dec 7;110(23):3615. Circulation. 2005 Jun 21;111(24):e446.
43. Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. **Primary Prevention** of Cardiovascular Diseases With Statin Therapy: A **Meta-analysis** of Randomized Controlled Trials. Arch Intern Med. 2006 Nov 27;166(21):2307-13. Subjects taking statins for a mean of 4.3 years (n=42 848) had a lower incidence of heart attack, stroke, revascularization, and other events than controls. The authors estimate the following numbers needed to treat for 4.3 years: 60, to prevent one major coronary event; 268 for stroke; 61 for nonfatal myocardial infarction and 93 for revascularization. In patients without CV disease, statin therapy decreases the incidence of major coronary and cerebrovascular events and revascularizations but not coronary heart disease or overall mortality.
44. Wanner C, Krane V, Marz W, et al.; German Diabetes and Dialysis Study Investigators (**4D**). Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005 Jul 21;353(3):238-48.
45. Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'leary DH, Grobbee DE, Bots ML. Effect of Rosuvastatin 40mg od on Progression of Carotid Intima-Media Thickness in Low-Risk Individuals (n=984; Ros=702, placebo=282 over 2 years) With Subclinical Atherosclerosis: The **METEOR** Trial . JAMA. 2007Mar 25; [Epub ahead of print] Rosuvastatin treatment was associated with a 49% reduction in LDL-C level, a 34% reduction in total cholesterol level, an 8% increase in HDL-C level, and a 16% reduction in level of triglycerides. Serious adverse cardiovascular events were infrequent (6 participants [0.86%] had 8 events [1.1%] in the rosuvastatin group vs 0% in the placebo group) In middle-aged adults with an FRS of less than 10% and evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum CIMT over 2 years vs placebo. Rosuvastatin did not induce disease regression.
46. Kjekshus J, Apetrei E, Barrios V, et al. the **CORONA** Group. **Rosuvastatin** in Older Patients (n=5011 over 32.8 months) with **Systolic Heart Failure**. N Engl J Med. 2007 Nov 5; [Epub ahead of print] Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems. The drug did not cause safety problems. Rosuvastatin (Crestor) does not improve clinical outcomes in patients with heart failure and average cholesterol levels (low-density lipoprotein [LDL] = 137 mg/dl). (LOE = 1b)
Cleland JGF, McMurray JJV, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). J Am Coll Cardiol 2009; 54:1850-1859.
47. Murphy SA, Cannon CP, Wiviott SD, de et al Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-thrombolysis in Myocardial Infarction 22 trials). Am J Cardiol. 2007 Oct 1;100(7):1047-51. Epub 2007 Jul 18. All-cause mortality was significantly reduced in the group with intensive statin therapy compared with the group with moderate statin therapy (3.6% vs 4.9%, hazard ratio 0.77, 95% confidence interval 0.63 to 0.95, p = 0.015), without significant interaction by trial (interaction p = 0.63). The reduction in all-cause mortality with intensive statin therapy was consistent across key subgroups.
48. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project (**CDP**) patients: long-term benefit with niacin. J Am Coll Cardiol. 1986 Dec;8(6):1245-55.
49. de Lemos JA, Blazing MA, Wiviott SD, et al.; **A to Z Investigators**. Early intensive vs delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of A to Z trial. JAMA. 2004 Sep 15;292(11):1307-16. Epub 2004 Aug 30.
50. Afilalo J, Duque G, Steele R, et al. **Statins for secondary prevention in elderly patients**. J Am Coll Cardiol. 2008;51:37-45. The posterior median estimate of the number needed to treat to save 1 life was 28 (95% CI 15 to 56). CONCLUSIONS: Statins reduce all-cause mortality in elderly patients and the magnitude of this effect is substantially larger than had been previously estimated. {InfoPOEMs: Treating 28 elderly patients with coronary heart disease (CHD) for 5 years will prevent 1 of them from dying during that period. For every 38 people treated for 5 years, 1 nonfatal myocardial infarction will be prevented; for every 58 patients treated for 5 years, 1 stroke will be prevented. (LOE = 1a) }
51. Cholesterol Treatment Trialists' (**CTT**) Collaboration. Efficacy of cholesterol-lowering therapy in 18 686 people with **diabetes** in 14 randomised trials of statins: A meta-analysis. Lancet 2008; 371:117-125.
52. Strippoli GF, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with **chronic kidney disease**: meta-analysis and meta-regression of randomised controlled trials. BMJ. 2008 Feb 25; [Epub ahead of print] Statins significantly reduce lipid concentrations and cardiovascular end points in patients with chronic kidney disease, irrespective of stage of disease, but no benefit on all cause mortality or the role of statins in primary prevention has been established. Reno-protective effects of statins are uncertain because of relatively sparse data and possible outcomes reporting bias.
53. Liakopoulos OJ, , et al. Impact of preoperative statin therapy on adverse **postoperative outcomes** in patients undergoing cardiac surgery: a meta-analysis of over 30 000 patients. Eur Heart Journal 2008; DOI:10.1093/eurheartj/ehn198.
54. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive

TOP

randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT-LLT**). JAMA. 2002 Dec 18;288(23):2998-3007.
Rahman M, Baimbridge C, Davis BR, et al. **ALLHAT** Collaborative Research Group. Progression of Kidney Disease in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin Versus Usual Care: A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Am J Kidney Dis. 2008 Aug 1. [Epub ahead of print] In hypertensive patients with moderate dyslipidemia and decreased eGFR, pravastatin was not superior to usual care in preventing clinical renal outcomes.

55. Gissi-Hf Investigators. Effect of rosuvastatin in patients with chronic heart failure (the **GISSI-HF** trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Aug 29. [Epub ahead of print] Rosuvastatin 10 mg daily did not affect clinical outcomes in patients with chronic heart failure of any cause, in whom the drug was safe
56. Ridker PM, Danielson E, Fonseca FA, Genest J, et al. the **JUPITER** Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med. 2008 Nov 9. [Epub ahead of print] In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (Hlatky MA. Expanding the Orbit of Primary Prevention -- Moving beyond JUPITER. N Engl J Med. 2008 Nov 9. [Epub ahead of print])
Ridker PM, Danielson E, Fonseca FA, et al. JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009 Apr 4;373(9670):1175-82. Epub 2009 Mar 28.
Everett BM, Glynn RJ, MacFadyen JG, Ridker PM. Rosuvastatin in the prevention of **stroke** among men and women with elevated levels of C-reactive protein: justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Circulation. 2010 Jan 5;121(1):143-50.
Mora S, Glynn RJ, Hsia J, Macfadyen JG, Genest J, Ridker PM. Statins for the Primary Prevention of Cardiovascular Events in Women With Elevated High-Sensitivity C-Reactive Protein or Dyslipidemia. Results From the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and Meta-Analysis of **Women** From Primary Prevention Trials. Circulation. 2010 Feb 22.
Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in **older persons** with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010 Apr 20;152(8):488-96, W174.
de Lorgeril Michel; Salen Patricia; Abramson John; et al. Cholesterol Lowering, Cardiovascular Diseases, and the Rosuvastatin-**JUPITER Controversy**: A Critical Reappraisal. Arch Intern Med. 2010;170(12):1032-1036.
Ridker PM, Genest J, Boekholdt SM, et al. JUPITER Trial Study Group. **HDL** cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. Lancet. 2010 Jul 31;376(9738):333-9.
Ridker PM, MacFayden JG, Nordestgaard BG, et al. Rosuvastatin for primary prevention among individuals with elevated high-sensitivity C-reactive protein and 5% to 10% and 10% to 20% 10-year risk. Circ Cardiovasc Qual Outcomes 2010; DOI: 10.1161/circoutcomes.110938118.
Koenig W, Ridker PM. Rosuvastatin for primary prevention in patients with European systematic coronary risk evaluation **risk >5% or Framingham risk >20%:** Post hoc analyses of the JUPITER trial requested by the European health authorities. Eur Heart J 2010; DOI: 10.1093/eurheartj/ehq370.
Hsia J, MacFayden JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dL with rosuvastatin. (JUPITER) J Am Coll Cardiol 2011; 57: 1666-1675.
Vidt Donald G., Ridker Paul M., Monyak JT, et al. Longitudinal Assessment of Estimated **Glomerular Filtration Rate** in Apparently Healthy Adults: A Post hoc Analysis from the JUPITER Study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). Clinical Therapeutics, Volume 33, Issue 6, June 2011, Pages 717-725, ISSN 0149-2918, DOI: 10.1016/j.clinthera.2011.05.004.
Novack V, Macfadyen J, Malhotra A, et al. The effect of rosuvastatin on **incident pneumonia**: results from the JUPITER trial. CMAJ. 2012 Mar 19.

57. Fellström BC, Jardine AG, Schmieder RE, et al. the **AURORA** Study Group. Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis. N Engl J Med. 2009 Mar 30. [Epub ahead of print] In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
58. Mills EJ, Rachlis B, et al. **Primary prevention** of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008 Nov 25;52(22):1769-81.
59. Brugts J, Yetgin T, Hoeks S, Gotto A, et al. The benefits of statins in people **without** established **cardiovascular disease** but with cardiovascular risk factors: meta-analysis of RCTs. BMJ 2009;338:2376. http://www.bmj.com/cgi/content/abstract/338/jun30_1/b2376
InfoPoems: Lowering cholesterol in 173 patients at risk for developing cardiovascular disease for slightly more than 4 years prevented 1 of them from dying prematurely. One major coronary event was prevented for every 81 patients, and one cerebrovascular event was prevented for every 245 patients treated. (LOE = 1a)
60. Connor A, Tomson C. Should statins be prescribed for **primary prevention** of cardiovascular disease in patients with **chronic kidney disease**? BMJ. 2009 Aug 20;339:b2949. doi: 10.1136/bmj.b2949.
61. Schouten O, Boersma E, Hoeks SE, et al. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. Fluvastatin and perioperative events in patients undergoing vascular surgery. (**Decrease III**) N Engl J Med. 2009 Sep 3;361(10):980-9. In patients undergoing vascular surgery, perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome.
62. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. (**HATS**) N Engl J Med. 2001 Nov 29;345(22):1583-92.
63. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, Genest J, et al. Effect of **fibrates** on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009 Oct;122(10):962.e1-8. Epub 2009 Aug 19.
64. Sharma M, Ansari MT, Abou-Setta AM, et al. Systematic review: comparative effectiveness and harms of combination therapy and **monotherapy** for dyslipidemia. Ann Intern Med. 2009 Nov 3;151(9):622-30.
65. Navaneethan SD, Pansini F, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for people with **chronic kidney disease not requiring dialysis**. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD007784.
66. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-Release Niacin or Ezetimibe and Carotid Intima-Media Thickness. (**ARBITER 6-HALTS**) N Engl J Med. 2009 Nov 15. [Epub ahead of print].
67. Chan KL, Teo K, Dumesnil JG, et al. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis. (**Astronomer**) Circulation 2010; 121: 306-314.
68. Navaneethan SD, Nigwekar SU, Perkovic V, Johnson DW, Craig JC, Strippoli GF. HMG CoA reductase inhibitors **(statins) for dialysis** patients. Cochrane Database Syst Rev. 2009;(2):CD004289.
69. Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors **(statins) for kidney transplant** recipients. Cochrane Database Syst Rev. 2009;(2):CD005019.
70. **ACCORD** Study Group, Effects of Combination **Lipid** Therapy (**simvastatin** with fenofibrate) in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001282.
71. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL et al. **Triglyceride**-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010 May 8;375(9726):1634-9.
72. Jun M, Foote C, Lv J et al. Effects of **fibrates** on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010 May 10.
73. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, et al. **Statins for children with familial hypercholesterolemia**. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD006401.
Statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. It seems to be safe in the short term but long-term safety is unknown. Children treated with statins should be carefully followed up by their pediatricians. Large long-term randomized controlled trials are needed to establish the long-term safety of statins.
74. Buchwald H, Rudser KD, Williams SE, et al. Overall mortality, incremental life expectancy, and cause of death at 25 years in the program on the **surgical control of the hyperlipidemias**. Ann Surg. 2010 Jun;251(6):1034-40.
75. McGuinness B, O`Hare J, Craig D, et al. Statins for the treatment of **dementia**. Cochrane Database Syst Rev. 2010 Aug 4;8:CD007514. There is insufficient evidence to recommend statins for the treatment of dementia. Analysis from the studies available, including one large RCT, indicate statins have no benefit on the outcome measures ADAS-Cog or MMSE. We need to await full results from CLASP 2008 before we can be certain.
76. Marrs JC, Saseen JJ. Effects of lipid-lowering therapy on reduction of cardiovascular events in patients with **end-stage renal disease requiring hemodialysis**. Pharmacotherapy. 2010 Aug;30(8):823-9.
77. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (**SEARCH**) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. The Lancet, Early Online Publication, 9 November 2010 doi:10.1016/S0140-6736(10)60310-8.
78. Cholesterol Treatment Trialists' (**CTT**) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet, Early Online Publication, 9 November 2010. doi:10.1016/S0140-6736(10)61350-5. In this analysis of patient data pooled from multiple studies, intensive statin therapy was more effective than less intensive statin therapy in reducing the rate of major cardiovascular events. Additionally, statins are more effective than controls in preventing major cardiovascular events. In spite of the authors' attempts to link these data to low-density lipoprotein (LDL) concentrations, none of the trials randomly assigned patients to specific LDL targets. (LOE = 1a) These authors pooled the patient-level data from 26 studies each involving at least 1000 patients and having at least 2 years of follow-up. Five of the trials compared intensive statin therapy with less intensive statin therapy and 21 compared statins with controls. Of the 5 trials comparing statin intensity, 2 evaluated 8659 patients with acute coronary syndromes (2.1 years of follow-up) and 3 evaluated 30,953 patients with stable coronary artery disease (5.8 years of follow-up). After 1 year of treatment, the LDL cholesterol levels decreased by an average 0.51 mmol/L (20 mg/dL). The annual rate of major vascular events cardiovascular death, nonfatal myocardial infarction, revascularization, or stroke) was 4.5% in the intensive therapy group and 5.3% in the less intense therapy group (number needed to treat [NNT] = 200 per year). Of the 14 trials comparing statin therapy with control (128,596 patients with 4.8 years of follow-up), 6 appear to be primary prevention studies and the remainder were for secondary prevention. In these 14 studies, after 1 year of treatment the LDL cholesterol levels decreased by 1.07 mmol/L (41 mg/dL). The annual rate of major vascular events was 2.8% in the patients taking statins compared with 3.6% in patients taking a control agent (NNT = 125 per year). Although they don't report the annual rate of death from any cause for each treatment group, the authors report the total death rate for the intensively treated patients plus the statin-treated patients (2.1%) compared with the rate of the less intensively treated patients plus control patients (2.3%). This works out to a number needed to treat of 500 per year. The authors also try to correlate the outcomes data with the LDL levels achieved by the various interventions. However, since none of the trials actually randomized patients to specific lipid targets, this information should be interpreted cautiously and is best used to generate hypotheses. If you subscribe to the lipid theory of atherogenesis, you will love this part of the study. If you subscribe to alternat

TOP

inflammation, plaque stability, and so forth) or are a methodologic purist, you will be annoyed by the authors' extrapolations.
79. **SHARP** Collaborative Group. Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9438 patients with chronic kidney disease. Am Heart J 2010; DOI:10.1016/j.ahj.2010.08.012. (Ezetimibe 10mg / simvastatin 20mg vs placebo)
Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection-**SHARP**): a randomized placebo-controlled trial. Lancet 2011.
80. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and **abnormal liver tests** in the Greek Atorvastatin and Coronary Heart Disease Evaluation (**GREACE**) Study: A post hoc analysis. Lancet 2010; DOI:10.1016/S0140-6736(10)61272-X.
81. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in **80+-year olds**. Age Ageing. 2010 Nov;39(6):674-80.
82. Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. **Statins for the primary prevention** of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub4. Although reductions in all-cause mortality, composite endpoints and revascularisations were found with no excess of adverse events, there was evidence of selective reporting of outcomes, failure to report adverse events and inclusion of people with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.
83. CDC: Centers for Disease Control & Prevention. **Prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol—United States**, 1999-2002 & 2005-2008. MMWR Morb Mortal Wkly Rep 2011; 60:7-12.
84. Farzadfar F, Finucane MM, et al. **National, regional, and global trends in serum total cholesterol since 1980**: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 2011.
85. Rahimi Kazem, Emberson Jonathan, McGale Paul, et al., PWM is acting on behalf of the PROSPER Executive. Effect of **statins on atrial fibrillation**: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. BMJ 342:doi:10.1136/bmj.d1250 (Published 16 Mar 2011)
86. Jackevicius Cynthia A, Tu Jack V, Ross Joseph S, et al. Use of **Fibrates in the United States and Canada**. JAMA. 2011;305(12):1217-1224.doi:10.1001/jama.2011.353
87. Mills EJ, Wu P, Chong G, et al. Efficacy and safety of statin treatment for cardiovascular disease: a **network meta-analysis** of 170,255 patients from 76 randomized trials. QJM. 2011 Feb;104(2):109-24.
88. Waters, David D., Ho, Jennifer E., DeMicco, David A., et al. Predictors of **New-Onset Diabetes in Patients Treated With Atorvastatin**: Results From 3 Large Randomized Clinical Trials (Ideal, TNT,Sparcl). J Am Coll Cardiol 2011 57: 1535-1545.
89. West AM, Anderson JD, Meyer CH, et al. The effect of **ezetimibe on peripheral arterial atherosclerosis** depends upon statin use at baseline. Atherosclerosis 2011; DOI:10.1016/j.atherosclerosis.2011.04.005.
90. National Institutes of Health. NIH stops clinical trial (**AIM-HIGH**) on combination cholesterol treatment [press release]. May 26, 2011. Available here. A trial of extended-release **niacin** (Niaspan, Abbott) given in addition to statin therapy in patients with a history of cardiovascular disease, high triglycerides, and low levels of HDL cholesterol has been halted prematurely, 18 months ahead of schedule, because niacin offered no additional benefits in this patient population. There was also a small, unexplained increase in ischemic stroke (1.6 vs 0.7%)in the high-dose, extended-release niacin group, in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study, according to a statement from the **National Heart Lung and Blood Institute** (NHLBI), which sponsored it. N=3414, 32months. AIM-HIGH enrolled 3,414 participants in the US and Canada with a history of cardiovascular disease, low HDL cholesterol, and high triglycerides, who were all prescribed simvastatin and who were also randomized to either high-dose, extended-release niacin in gradually increasing doses up to 2000 mg per day (n=1718) or placebo (n=1696). Of the participants, 515 were given a second LDL-cholesterol-lowering drug, ezetimibe (Zetia, Merck/Schering-Plough), in order to maintain LDL-cholesterol levels at the target range between 40 and 80 mg/dL.
AIM-HIGH investigators. **Niacin** in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med2011; DOI:10.1056/oa1107579.
91. Holdaas H, et al. Assessment of LEscol in Renal Transplantation (**ALERT**) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: multicentre randomised placebo-controlled trial. Lancet. 2003 Jun 14;361(9374):2024-31.
92. Rossebø AB, Pedersen TR, Boman K, et al. **SEAS** Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008 Sep 25;359(13):1343-56.
93. Preiss D, Seshasai SR, Welsh P, et al. Risk of **incident diabetes with intensive-dose compared with moderate-dose statin** therapy. JAMA 2011; 305:2556-2564.
94 n-3 fatty acid trials:
Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of **marine omega-3 fatty acids**. Lancet. 2010 Aug 14;376(9740):540-50. Epub 2010 Jul 15.
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the **GISSIPrevenzione** trial. Lancet 1999;354:447- 55.
Pottala JV, Garg S, Cohen BE, Whooley MA, Harris WS. Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul study. Circ Cardiovasc Qual Outcomes 2010;3: 406-12.
Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (**DART**). Lancet 1989;2:757-61.
Yokoyama M, Origasa H, Matsuzaki M,et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (**JELIS**): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090-8.
Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the **GISSI-HF** trial): a randomised, doubleblind, placebo-controlled trial. Lancet 2008; 372:1223-30.
Kromhout D, Giltay EJ, Geleijnse JM. n–3 Fatty acids and cardiovascular events after myocardial infarction (**Alpha Omega**). N Engl J Med 2010;363:2015-26.
De Caterina Raffaele. **n–3 Fatty Acids** in Cardiovascular Disease. N Engl J Med 2011; 364:2439-2450.
95. Kawut SM, Bagiella E, Lederer DJ, et al; on behalf of the **ASA-STAT Study** Group. Randomized Clinical Trial of **Aspirin and Simvastatin for Pulmonary Arterial Hypertension**: ASA-STAT. Circulation. 2011 Jun 28;123(25):2985-2993.
96. Liu ZL, Liu JP, Zhang AL, et al. **Chinese herbal medicines** for hypercholesterolemia. Cochrane Database Syst Rev. 2011 Jul 6;7:CD008305. Some herbal medicines may have cholesterol-lowering effects. Our findings have to be interpreted with caution due to high or unclear risk of bias of the included trials.
97. Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of **simvastatin to treat Alzheimer disease**. Neurology. 2011 Aug 9;77(6):556-63. (no benefit)
98. Lee KH, Jeong MH, Kim HM, et al. Benefit of early statin therapy in patients with acute myocardial infarction who have **extremely low low-density lipoprotein cholesterol**. J Am Coll Cardiol 2011; 58:1664-1671.
99. Tonelli Marcello, Lloyd Anita, Clement F, et al. Efficacy of **statins for primary prevention** in people at low cardiovascular risk: a meta-analysis. CMAJ October 11, 2011 cmaj.101280; published ahead of print October 11, 2011, doi:10.1503/cmaj.101280
100. Schanberg L, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, et al. Use of atorvastatin in **systemic lupus erythematosus** in children and adolescents (**APPLE**). Arthritis Rheum 2011
101. Vale N, Nordmann AJ, Schwartz GG, et al. Statins for **acute coronary syndrome**. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD006870. DOI: 10.1002/14651858.CD006870.pub2. Based on available evidence, initiation of statin therapy within 14 days following ACS does not reduce death, myocardial infarction, or stroke up to four months, but reduces the occurrence of unstable angina at four months following ACS.
102. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin (**atrovastatin 80mg vs rosuvastatin 40mg**) regimens on progression of coronary disease. (**Saturn**) N Engl J Med 2011; DOI: 10.1056/NEJMoa1110874. SATURN trial, high doses of rosuvastatin and atorvastatin resulted in similar degrees of atherosclerosis regression, despite greater reductions in LDL levels with rosuvastatin.
103. Hayward RA, Krumholz HM. Three reasons to **abandon low-density lipoprotein targets**: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. Circ Cardiovasc Qual Outcomes 2012.
104. Vandermeer ML et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed **influenza virus infections**: a multistate study. J Infect Dis. 2012 Jan;205(1):13-9.
105. Kostis WJ, Cheng JQ, Dobrzynski JM, et al. Meta-analysis of **statin effects in women** versus men. J Am Coll Cardiol 2012; 59:572-582.
106. Newson RS, Felix JF, Heeringa J, et al. Association between **serum cholesterol and noncardiovascular mortality in older age**. J Am Geriatr Soc. 2011 Oct;59(10):1779-85.
107. Waubant E, Pelletier D, et al. behalf of the **ITN STAyCIS** Study Group; ITN020AI Study Management Team. Randomized controlled trial of **atorvastatin** in clinically isolated syndrome: The STAyCIS study. Neurology. 2012 Apr 10;78(15):1171-1178.

TOP

LIPID LOWERING THERAPY: DYSLIPIDEMIA Comparison Chart

[1] Fodor JG, Frohlich JJ, Jacques JG et al. **Canadian** Recommendations for the management and treatment of dyslipidemia. CMAJ **2000**;162:1441-7.

[2]NCEP Expert Panel. Executive summary-3rd national cholesterol education program on detection, evaluation and treatment of high blood cholesterol in adults (**A**dult **T**reatment **P**anel **III**). JAMA **2001**;285:2486-97. Implications of Recent Clinical Trials for the NCEP ATP Panel III Guidelines July **2004** http://www.acc.org/clinical/adoptions/ncep_report.pdf

Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. **Hypertriglyceridemia** and its pharmacologic treatment among US adults. Arch Intern Med. 2009 Mar 23;169(6):572-8.

[3] Knopp RH. Drug treatment of lipid disorders. N Eng J Med 1999;341:498-511.(Gibson K, Rindone JP. Experience with statin use in patients with chronic **hepatitis C infection**. Am J Cardiol. 2005 Nov 1;96(9):1278-9. Epub 2005 Sep 8)

[4] Davidson MH. Safety profiles for the HMG-CoA Reductase Inhibitors. Drugs 2001;61:197-206

[5] Link N, Tanner M. Hyperlipidemia: Part 1. Evaluation and dietary management. WJM 2001;175:246-250.

[6] Link N, Tanner M. Hyperlipidemia: Part 2. Pharmacologic management. WJM 2001;175:396-401.

[7] Anonymous. Choice of lipid-regulating drugs. Med Lett 2001;43:43-48.

Onofrei MD, et al. Safety of statin therapy in patients with preexisting liver disease. Pharmacotherapy. 2008 Apr;28(4):522-9.

Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and **abnormal liver tests** in the Greek Atorvastatin and Coronary Heart Disease Evaluation (**GREACE**) Study: A post hoc analysis. Lancet 2010; DOI:10.1016/S0140-6736(10)61272-X.

Gillett RC Jr, Norrell A. Considerations for safe use of statins: **liver enzyme abnormalities and muscle toxicitiy**. Am Fam Physician. 2011 Mar 15;83(6):711-6.

[8] **Treatment Guidelines**: **Drugs for Lipid Disorders**. **The Medical Letter**: August, **2003**; (12) pp. 77-82 & March, **2005**; (3;31) pp. 15-22. Feb **2008** pages 9-16. **Mar 2011**.

Micromedex 2005; Drugs in Pregnancy and Lactation, 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Baltimore, MD: 2011.; Hansten & Horn-Drug Interactions 2005.

[9] Rizvi K, Hampson JP, Harvey JN. Do lipid-lowering drugs cause erectile dysfunction? A systematic review. Fam Pract 2002;19(1):95-8.

[10] Thompson PD, Clarkson P, Karas RH. Statin-associated **myopathy**. JAMA. 2003 Apr 2;289(13):1681-90. (Hansen KE, Hildebrand JP, Ferguson EE, Stein JH. Outcomes in 45 patients with statin-associated myopathy. Arch Intern Med. 2005 Dec 26;165(22):2671-6.) The SEARCH Collaborative Group. SLCO1B1 Variants and Statin-Induced Myopathy -- A Genomewide Study. N Engl J Med. 2008 Jul 23. [Epub ahead of print] We have identified common variants in **SLCO1B1** that are strongly associated with an increased risk of statin-induced **myopathy**. Genotyping these variants may help to achieve the benefits of statin therapy more safely and effectively.

Sathasivam S, Lecky B. Statin induced myopathy. BMJ. 2008 Nov 6;337:a2286. doi: 10.1136/bmj.a2286.

Joy T. R., Hegele R. A. Narrative Review: Statin-Related Myopathy. Ann Intern Med 2009; 858-868.

Mohaupt MG, Karas RH, Babiychuk EB, et al. Association between statin-associated myopathy and skeletal muscle damage. CMAJ. 2009 Jul 7;181(1-2):E11-8.

Voora D, Shah SH, Spasojevic I, Ali S, Reed CR, Salisbury BA, Ginsburg GS. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol. 2009 Oct 20;54(17):1609-16.

Bre wer HB Jr. Benefit -risk assessment of rosuvastatin 10 to 40 milli gram s. Am J Cardiol 2003; 92(suppl):23K–29K.

Fernandez G, Spatz ES, Jablecki C et al. **Statin myopathy**: A common dilemma not reflected in clinical trials Cleveland Clinic Journal of Medicine 2011; 78(6):393-403; doi:10.3949/ccjm.78a.10073

Mammen AL, Chung T, Christopher-Stine L, et al. **Autoantibodies** against 3-hydroxy-3-methylglutaryl-coenzyme a reductase (**HMGCR**) in patients with statin-associated autoimmune myopathy. Arthritis Rheum. 2010 Nov 19.

[11] Herman, RJ. Drug interactions and the statins. CMAJ 1999;161:1281-6.

[12] Carswell CI, Plosker GL, Jarvis B. Rosuvastatin. Drugs. 2002;62(14):2075-85; discussion 2086-7.

[13] Rosuvastatin--a new lipid-lowering drug. Med Lett Drugs Ther. 2003 Oct 13;45(1167):81-3. Approved in Canada in 2003.

Ridker PM, Danielson E, Fonseca FA, Genest J, et al. the **JUPITER** Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med. 2008 Nov 9. [Epub ahead of print] In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Glynn RJ, Danielson E, Fonseca FA, Genest J, et al. A Randomized Trial of Rosuvastatin in the Prevention of Venous **Thromboembolism**. (Jupiter) N Engl J Med. 2009 Mar 29. [Epub ahead of print]

Koenig W, Ridker PM. Rosuvastatin for primary prevention in patients with European systematic coronary risk evaluation **risk >5% or Framingham risk >20%:** Post hoc analyses of the JUPITER trial requested by the European health authorities. Eur Heart J 2010; DOI: 10.1093/eurheartj/ehq370.

[14] Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The Safety of Rosuvastatin as Used in Common Clinical Practice. A Postmarketing Analysis. Circulation. 2005 May 23; [Epub ahead of print] (InfoPOEMs: The United States Federal Drug Administration (FDA), Health Canada, and European regulators have recently issued advisories to physicians regarding higher doses of rosuvastatin. These data -- though inherently limited by their voluntary nature and the possibility of reporting bias -- lend credence to concerns that rosuvastatin is less safe than other statins. It is also the only statin for which we do not have patient-oriented outcome data. (LOE = 2c))

[15] Jones P, et al. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia (The **CURVES** study). Am J Cardiol 1998;81:582-7.

[16] Three new drugs for hyperlipidemia. Med Lett Drugs Ther. 2003 Mar 3;45(1151):17-9.

Bays HE, Moore PB, Drehobl MA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin Ther* 2001; 23:1209-30. (**low dose reduces LDL**)

[17] Grundy SM, Vega GL, McGovern ME, et al. Diabetes Multicenter Research Group. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med. 2002 Jul 22;162(14):1568-76.

[18] Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the **ADMIT** study: A randomized trial. Arterial Disease Multiple Intervention Trial. JAMA. 2000 Sep 13;284(10):1263-70. (& What You Should Know About **Niacin**. Pharmacist's Letter. Dec, 2005).

[19] Jacobson TA. Combination Lipid-Altering Therapy. Current Atherosclerosis Reports 2001;3:373-382.

[20] Mantel-Teeuwisse AK, Kloosterman ME, Maitland-van der Zee AH, et al. Drug-induced lipid changes. Drug Safety 2001;24:443-56.

[21] Unintended serum lipid level changes induced by some commonly used drugs. Drugs & Therapy Perspectives 2001; 17(23).

[22] Din JN, Newby DE, Flapan AD. Omega 3 fatty acids and cardiovascular disease--fishing for a natural treatment. BMJ. 2004 Jan 3;328(7430):30-5. & Omacor (Omega-3- acid Ethyl Esters), Pharmacist's Letter, Oct 2005 & Omega-3 Polyunsaturated Fatty Acids (**Omacor**) for Hypertriglyceridemia. The Medical Letter. Nov 7,2005. p 91-92. (O'Keefe JH Jr, et al. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. Am J Cardiol. 2006 Apr 15;97(8):1127-30. Epub 2006 Mar 3.) (Fish Oil Supplements Medical Letter July 17,2006) (Pharmacists Letter. Omega-3 Fatty Acids: An Update. Aug 2007.)

Brunzell JD. Clinical practice. **Hypertriglyceridemia**. N Engl J Med. 2007 Sep 6;357(10):1009-17.

Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of **marine omega-3 fatty acids**. Lancet. 2010 Aug 14;376(9740):540-50. Epub 2010 Jul 15.

Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the **GISSIPrevenzione** trial. Lancet 1999;354:447- 55.

Pottala JV, Garg S, Cohen BE, Whooley MA, Harris WS. Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul study. Circ Cardiovasc Qual Outcomes 2010;3: 406-12.

Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (**DART**). Lancet 1989;2:757-61.

Yokoyama M, Origasa H, Matsuzaki M,et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (**JELIS**): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090-8.

Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the **GISSI-HF** trial): a randomised, doubleblind, placebo-controlled trial. Lancet 2008; 372:12

TOP

Kromhout D, Giltay EJ, Geleijnse JM. n–3 Fatty acids and cardiovascular events after myocardial infarction (**Alpha Omega**). N Engl J Med 2010;363:2015-26.
De Caterina Raffaele. **n–3 Fatty Acids** in Cardiovascular Disease. N Engl J Med 2011; 364:2439-2450.

[23] Genest J, McPherson R, Frohlich J, et al. **2009 Canadian** Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol. 2009 Oct;25(10):567-79.
McPherson R, Frohlich J, Fodor G, Genest J. **Canadian 2006** Cardiovascular Society position statement -- Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol. 2006 Sep;22(11):913-27. (Genest J, Frohlich J, Fodor G, McPherson R; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the **Canadian 2003 update**. CMAJ. 2003 Oct 28;169(9):921-4. http://www.cmaj.ca/cgi/data/169/9/921/DC1/1 Full Report.)

[24] Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med. 2006 Oct 3;145(7):520-30.

[25] New Zealand Guideline Group. http://www.nzgg.org.nz/library/gl_complete/bloodpressure/table1.cfm (access verified Jan 30/03).

[26] Jackson R. Updated New Zealand cardiovascular disease risk-benefit prediction guide. BMJ 2000;320:709-10.

[27] Campbell NRC, Drouin D, Feldman RD, for the Canadian Hypertension Recommendations Working Group. The **2001 Canadian** hypertension recommendations take-home messages. CMAJ 2002:167(6):661-8.

[28] Canadian Hypertension Society-**2011 Canadian** Hypertension **Recommendations** Working Group-downloadable Summary & Slides; www.hypertension.ca

[29] **Canadian 2008 Diabetes Guidelines (Sept 2008):** http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
Canadian 2003 Diabetes Guidelines http://www.diabetes.ca/cpg2003/download.aspx (Meltzer S, Leiter L, Daneman D, et al 1998. Clinical practice guidelines for the management of diabetes in Canada. CMAJ 1998;159 (8 Suppl).)

[30] Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/**American Geriatrics Society** Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc. **2003** May;51(5 Suppl Guidelines):S265-80.

30. Nissen S, Tuzcu E, et al. Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis A Randomized Controlled Trial (**REVERSAL**). JAMA. 2004;291:1071-1080.
31. Heart Protection Study (**HPS**) Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004 Mar 6;363(9411): 757-67. Heart Protection Study Group.MRC/BHF **HPS** study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-22. (**11,609** of 32,145 pts in 4-6 wk run in treatment with simvastatin 40mg/d **were excluded**)
Heart Protection Study Collaborative Group. Effects on **11-year mortality and morbidity** of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet 2011; online Nov 23.
32. Cannon CP, Braunwald E, McCabe CH, ET AL. Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. (**PROVE IT-TIMI 22**) N Engl J Med. 2004 Mar 8 (Ahmed S, Cannon CP, Murphy SA, Braunwald E. Acute coronary syndromes and **diabetes**: Is intensive lipid lowering beneficial? Results of the **PROVE IT-TIMI 22** trial. Eur Heart J. 2006 Oct;27(19):2323-9. Epub 2006 Sep 5.)
33. Colhoun HM, Betteridge DJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (**CARDS**): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21;364(9435):685-96.
Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS Investigators. Effects of Atorvastatin on Kidney Outcomes and Cardiovascular Disease in Patients With Diabetes: An Analysis From the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009 Jun 18. [Epub ahead of print] A modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria, was observed. Atorvastatin did not influence albuminuria incidence. Atorvastatin was effective at decreasing CVD in those with and without a moderately decreased eGFR and achieved a high absolute benefit.
34. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (**ASCOT-LLA**): a multicentre randomised controlled trial. Lancet. 2003 Apr 5;361(9364):1149-58.
Sever PS, et al. The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended **observations 2 years** after trial closure. Eur Heart J. 2008 Feb;29(4):499-508. Epub 2008 Jan 5. Carry-over benefits from those originally assigned atorvastatin but no longer taking the drug may account for unchanged relative risk reductions in most cardiovascular endpoints observed 2 years after ASCOT-LLA closed.
Sever PS, Poulter NR, Dahlof B, et al.; the ASCOT investigators. Antihypertensive therapy and the benefits of atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial: lipid-lowering arm extension. J Hypertens. 2009 Mar 21. [Epub ahead of print]
35. De Lemos et al. Early Intensive vs a Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes Phase Z of the **A to Z Trial** JAMA. 2004 Sept 15;292 (11):1307-16.
36. LaRosa JC. et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease (**TNT**) . N Engl J Med. 2005 Mar 8;352 online. (InfoPOEMs: The benefit of intensive lipid therapy in patients with known heart disease is very modest: a number needed to treat (NNT) of 45 for 5 years to prevent any cardiovascular outcome. There was no difference in all-cause mortality between intensive and less intensive treatment groups (5.6% vs 5.7%), and the study was large enough and long enough to be able to detect such a benefit if one existed. Since the benefit of lipid lowering is greatest in patients with known disease, any benefit is certainly much less lower for patients without known disease who are at much lower risk. (LOE = 1b)) (**5461** of 15,464 pts in 8 wk open-label treatment with atorvastatin 10mg/d **were excluded**)
McGowan MP; Treating to New Target (TNT) Study Group. There is no evidence for an increase in acute coronary syndromes after short-term abrupt discontinuation of statins in stable cardiac patients. Circulation. 2004 Oct 19;110(16):2333-5. Epub 2004 Oct 11. Shepherd J, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and **diabetes**: the Treating to New Targets (TNT) study. Diabetes Care. 2006 Jun;29(6):1220-6. (Deedwania P, et al. Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and **metabolic syndrome**: analysis of the Treating to New Targets study. Lancet. 2006 Sep 9;368(9539):919-28.) Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK; Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low-dose atorvastatin in patients **65 years of age or older** with stable coronary heart disease. Ann Intern Med. 2007 Jul 3;147(1):1-9. The analysis suggests that additional clinical benefit can be achieved by treating older patients with CHD more aggressively to reduce low-density lipoprotein cholesterol levels to less than 2.6 mmol/L (<100 mg/dL). The findings support the use of intensive low-density lipoprotein cholesterol-lowering therapy in high-risk older persons with established cardiovascular disease. Larosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H; Treating to New Targets (TNT) Steering Committee and Investigators. Safety and Efficacy of Atorvastatin-Induced Very Low-Density Lipoprotein Cholesterol Levels in Patients With Coronary Heart Disease (a Post Hoc Analysis of the Treating to New Targets [TNT] Study). Am J Cardiol. 2007 Sep 1;100(5):747-52. Epub 2007 Jun 14. In conclusion, the present analysis adds support to the concept that for patients with established atherosclerotic cardiovascular disease, a further risk reduction without sacrifice of safety can be achieved by reducing LDL cholesterol to very low levels. (Barter P, Gotto AM, LaRosa JC, et al; Treating to New Targets Investigators (TNT). **HDL cholesterol, very low levels of LDL cholesterol**, and cardiovascular events. N Engl J Med. 2007 Sep 27;357(13):1301-10. In this post hoc analysis, HDL was predictive of major cardiovascular events in patients treated with statins. This relationship was also observed among patients with LDL cholesterol levels below 70 mg per deciliter.)
Wenger NK, Lewis SJ, Welty FK, Herrington DM, Bittner V. Beneficial effects of aggressive LDL cholesterol lowering in **women** with stable coronary heart disease in the Treating to New Targets (TNT) study. Heart. 2007 Dec 10; [Epub ahead of print] Conclusion Intensive lipid-lowering treatment with atorvastatin 80 mg produced significant reductions in relative risk for major cardiovascular events compared with atorvastatin 10 mg in both women and men with stable CHD. Shepherd J, Kastelein JJ, et al.; TNT (Treating to New Targets) Investigators. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and **chronic kidney disease**: the TNT (Treating to New Targets) study. J Am Coll Cardiol. 2008 Apr 15;51(15):1448-54. [PubMed - in process] Aggressive lipid lowering with atorvastatin 80 mg was both safe and effective in reducing the excess of cardiovascular events in a high-risk population with CKD and CHD.
37. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. JAMA. 2004 Apr 21;291(15):1864-70.
38. Wei L, Ebrahim S, Bartlett C, ET AL. Statin use in the secondary prevention of coronary heart disease in primary care: cohort study and comparison of inclusion and outcome with patients in randomised trials. BMJ. 2005 Apr 9;330(7495):821. Epub 2005 Mar 24.
39. Douglas G. Manuel, Peter Tanuseputro, Cameron Aet al. The 2003 Canadian recommendations for dyslipidemia management: Revisions are needed. CMAJ 2005 172: 1027-1031; doi:10.1503/cmaj.1040202
40. Graham DJ, Staffa JA, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004 Dec 1;292(21):2585-90.(Per year of therapy, the number needed to treat to observe 1 case of rhabdomyolysis was 22,727 for statin monotherapy, 484 for older patients with diabetes mellitus who were treated with both a statin and fibrate, and ranged from 9.7 to 12.7 for patients who were treated with cerivastatin plus fibrate.)
41. Gardner CD, Coulston A, Chatterjee L, Rigby A, Spiller G, Farquhar JW. The effect of a **plant-based diet** on plasma lipids in hypercholesterolemic adults: a randomized trial. Ann Intern Med. 2005 May 3;142(9):725-33.
42. Sever PS, Poulter NR, Dahlof B, et al. Reduction in Cardiovascular Events With Atorvastatin in 2,532 Patients With Type 2 Diabetes: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA). Diabetes Care. 2005 May;28(5):1151-1157.
43. Marco Studer, MD; Matthias Briel, MD; Bernd Leimenstoll, MD; et al. Effect of Different Antilipidemic Agents and Diets on Mortality -A Systematic Review. Arch Intern Med. 2005;165:725-730. (InfoPOEMs: Only statin lipid-lowering drugs have been shown to decrease overall mortality in patients with high cholesterol but without evidence of heart disease. However, most patients treated with one of these drugs will not benefit: 228 have to be treated for 3.3 years to prevent 1 additional death during this period. In patients with known heart disease, statins and fish oil both have been shown to decrease mortality. Niacin, resins, and diet have not been shown to decrease mortality. Fibrates (gemfibrozil and others) actually increase overall mortality and at the same time decrease cardiac mortality. (LOE = 1a))
44. Health Canada Warning July/05 for muscle related side effects possible with all statins http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_77.html
45. Rea TD, Breitner JC, Psaty BM, et al. Statin use and the risk of incident **dementia**: the cardiovascular health study. Arch Neurol. 2005 Jul;62(7):1047-51. CONCLUSIONS: In this cohort study, statin therapy was not associated with a decreased risk of dementia. (InfoPOEMs: In this prospective study, patients older than 65 years old taking statins developed dementia at the same rate as those not using statins. (LOE = 2b))
46. InfoPOEMs July, 2005. More adverse events with rosuvastatin than other statins. Bottom line: The United States Federal Drug Administration (FDA), Health Canada, and European regulators have recently issued advisories to physicians regarding higher doses of rosuvastatin. These data -- though inherently limited by their voluntary nature and the possibility of reporting bias- lend credence to concerns that rosuvastatin is less safe than other statins. It is also the only statin for which we do not have patient-oriented outcome data. (LOE = 2c). *Circulation* 20

TOP

47. Wanner C, Krane V, Marz W, et al.; German Diabetes and Dialysis Study Investigators (4D). Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005 Jul 21;353(3):238-48.

Other articles:

Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009 Oct;122(10):962.e1-8. Epub 2009 Aug 19.

ACCORD Study Group, Effects of Combination Lipid Therapy (simvastatin ≤ 40mg od +/- fenofibrate ≤ 160mg od) in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001282. n=5518, 4.7yr.

Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients. J Am Coll Cardiol. 2008;51:37-45. The posterior median estimate of the number needed to treat to save 1 life was 28 (95% CI 15 to 56).
CONCLUSIONS: Statins reduce all-cause mortality in elderly patients and the magnitude of this effect is substantially larger than had been previously estimated. (InfoPOEMs: Treating 28 elderly patients with coronary heart disease (CHD) for 5 years will prevent 1 of them from dying during that period. For every 38 people treated for 5 years, 1 nonfatal myocardial infarction will be prevented; for every 58 patients treated for 5 years, 1 stroke will be prevented. (LOE = 1a))

Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart 2007;93(8):914-921.
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1727734 9&dopt=Abstract> Intensive statin therapy will decrease overall mortality rates compared with lower doses in patients with a recent history of acute coronary syndrome (ACS) but not in patients with stable coronary heart disease. However, 80 patients must be treated to prevent 1 additional death over 2 years. Intensive treatment decreases overall hospital admissions for heart failure in both groups and decreases major cardiac events in pts with stable coronary heart disease, but, again, the results are not striking. (LOE = 1a)

Amend KL, Landon J, Thyagarajan V, Niemcryk S, McAfee A. Incidence of Hospitalized Rhabdomyolysis with Statin and Fibrate Use in an Insured US Population (October). Ann Pharmacother. 2011 Sep 13. The number needed to harm was lower for combination statin-gemfibrozil therapy (2753) compared with that for statin therapy alone (454,545).

AIM-HIGH: National Institutes of Health. NIH stops clinical trial on combination cholesterol treatment [press release]. May 26, 2011. Available here. A trial of extended-release niacin (Niaspan, Abbott) given in addition to statin therapy in patients with a history of cardiovascular disease, high triglycerides, and low levels of HDL cholesterol has been halted prematurely, 18 months ahead of schedule, because niacin offered no additional benefits in this patient population. There was also a small, unexplained increase in ischemic stroke (1.6 vs 0.7%)in the high-dose, extended-release niacin group, in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study, according to a statement from the National Heart Lung and Blood Institute (NHLBI), which sponsored it. N=3414, 32months. AIM-HIGH enrolled 3,414 participants in the US and Canada with a history of cardiovascular disease, low HDL cholesterol, and high triglycerides, who were all prescribed simvastatin and who were also randomized to either high-dose, extended-release niacin in gradually increasing doses up to 2000 mg per day (n=1718) or placebo (n=1696). Of the participants, 515 were given a second LDL-cholesterol-lowering drug, ezetimibe (Zetia, Merck/Schering-Plough), in order to maintain LDL-cholesterol levels at the target range between 40 and 80 mg/dL.

AIM-HIGH investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med2011; DOI:10.1056/oa1107579.

Akduman B, Tandberg DJ, O'Donnell CI, et al. Effect of Statins on Serum Prostate-specific Antigen (PSA) Levels. Urology. 2010 Jun 3.

Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer. J Am Coll Cardiol 2007; 50:409-418. DOI: 10.1016/j.jacc.2007.02.073.
Available at: http://content.onlinejacc.org. Risk of statin-associated elevated liver enzymes or rhabdomyolysis is not related to the magnitude of LDL-C lowering. However, the risk of cancer is significantly associated with lower achieved LDL-C levels.

Alsheikh-Ali AA, Trikalinos TA, Kent DM, Karas RH. Statins, low-density lipoprotein cholesterol, and risk of cancer. J Am Coll Cardiol. 2008 Sep 30;52(14):1141-7. There is an inverse association between on-treatment LDL-C and incident cancer. However, statins, despite producing marked reductions in LDL-C, are not associated with an increased risk of cancer.

Ali-Alsheikh AA, Karas RH. Ezetimibe, and the combination of ezetimibe/simvastatin, and risk of cancer: a post-marketing analysis. *J Clin Lipidol* 2009; DOI:10.1016.2009.02.005.

Amarenco P, et al.; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006 Aug 10;355(6):549-59. (Kent DM. Stroke--an equal opportunity for the initiation of statin therapy. N Engl J Med. 2006 Aug 10;355(6):613-5.) (InfoPOEMs: High-dose atorvastatin reduces the risk of recurrent stroke, but does not improve mortality rates. A reduction in the risk of transient ischemic attack (TIA) or unclassified stroke was partially offset by an increase in the risk of hemorrhagic stroke. (LOE = 1b)) Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, Hennerici M, Simunovic L, Zivin JA, Welch KM; SPARCL Investigators. Effects of Intense Low-Density Lipoprotein Cholesterol Reduction in Patients With Stroke or Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2007 Oct 25; [Epub ahead of print] As compared with having no change or an increase in LDL-C, achieving a >/=50% lowering was associated with a greater reduction in the risk of stroke and major coronary events with no increase in brain hemorrhages. Goldstein LB, Amarenco P, Szarek M, Callahan A 3rd, Hennerici M, Sillesen H, Zivin JA, Welch KM; On behalf of the SPARCL Investigators. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology. 2007 Dec 12; [Epub ahead of print] Hemorrhagic stroke was more frequent in those treated with atorvastatin, in those with a hemorrhagic stroke as an entry event, in men, and increased with age. Those with Stage 2 hypertension at the last visit prior to the hemorrhagic stroke were also at increased risk. Treatment did not disproportionately affect the hemorrhagic stroke risk associated with these other factors. There were no relationships between hemorrhage risk and baseline low-density lipoprotein (LDL) cholesterol level or recent LDL cholesterol level in treated patients.

Amarenco P, Labreuche J. Lipid management in the prevention of stroke: Review and updated meta-analysis of statins for stroke prevention. Lancet Neurol 2009; 8:453-463.

American Dietetic Association. Disorders of lipid metabolism. Evidence-based nutrition practice guideline. Chicago (IL): American Dietetic Association; 2011 Mar. https://www.adaevidencelibrary.com/tmp/prn9960934415842E340048AE5C7D4C4F2D.pdf

American College of Cardiology Foundation, , American Heart Association Task Force on Practice Guidelines, , Society for Cardiovascular Angiography and Interventions, , Levine, Glenn N., Bates, Eric R., Blankenship, Et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: Executive Summary. J Am Coll Cardiol 2011 0: j.jacc.2011.08.006. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.08.006v1.pdf

American College of Cardiology Foundation, , American Heart Association Task Force on Practice Guidelines, , American Association for Thoracic Surgery, , Society of Cardiovascular Anesthesiologists, , Society of Thoracic Surgeons, Hillis, L. David, Smith, Peter K., Anderson, Jeffrey L., et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: Executive Summary. J Am Coll Cardiol 2011 0: j.jacc.2011.08.008. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.08.008v1.pdf

Ando H, Tsuruoka S, Yanagihara H, et al. Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. Br J Clin Pharmacol. 2005 Nov;60(5):494-7.

Arca M. Atorvastatin Efficacy in the Prevention of Cardiovascular Events in Patients with Diabetes Mellitus and/or Metabolic Syndrome. Drugs. 2007;67 Suppl 1:43-54. (Cards, Ascot-LLA, Greace, TNT, Prove-It, Aspen) In summary, several patient populations, from definitive, large-scale studies, are now available to corroborate the integral place of atorvastatin - in line with various regional and internationally accepted disease management guidelines - in the primary and secondary prevention of cardiovascular events in patients with diabetes and/or metabolic syndrome.

Athyros VG, Tziomalos K, Gossios TD, et al.; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010;376(9756):1916-1922.

Backes JM, Moriarty PM, Ruisinger JF, Gibson CA. Effects of once weekly rosuvastatin among patients with a prior statin intolerance. Am J Cardiol. 2007 Aug 1;100(3):554-5.

Bader T, Fazili J, Madhoun M, et al. Fluvastatin Inhibits Hepatitis C Replication in Humans. Am J Gastroenterol. 2008 Apr 9. [Epub ahead of print] FLV used as monotherapy in vivo showed suppressive effects of HCV clinically that are modest, variable, and often short-lived. These findings support "proof-of-concept" for pilot trials combining fluvastatin with standard therapy. Statins and fluvastatin, in particular, appear to be safe for use in hepatitis C.

Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy & safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-78. Epub 2005 Sep 27. (InfoPOEMs: Statins reduce 5-year overall mortality, and specifically decrease cardiovascular mortality and morbidity. The patients at highest baseline risk derive the greatest benefit. (LOE = 1a))

Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection-SHARP): a randomized placebo-controlled trial. Lancet 2011.

Banaszewska B, et al. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective randomized cross-over trial. J Clin Endocrinol Metab. 2006 Nov 14; [Epub ahead of print] n=48

Baruch L, Agarwal S, Gupta B, et al. Effect on serum lipid levels of switching dose of ezetimibe from 10 to 5 mg. Am J Cardiol. 2009 Jun 1;103(11):1568-71. Epub 2009 Apr 22.

Becker D. J., Gordon R. Y., et al. Red Yeast Rice for Dyslipidemia in Statin-Intolerant Patients: A Randomized Trial. Ann Intern Med 2009; 830-839.

Bell KJL et al. Monitoring adherence to drug treatment by using change in cholesterol concentration: Secondary analysis of trial data. BMJ 2011 Jan 21; 342:d12.

Bertagnolli MM, Hsu M, Hawk ET, et al. Statin use and colorectal adenoma risk: Results from the Adenoma Prevention with Celecoxib trial. Cancer Prev Res 2010. DOI:10.1158/1940-6207.CAPR-09-0271.

Berthold HK, et al. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. JAMA. 2006 May 17;295(19):2262-9. In patients with hypercholesterolemia or combined hyperlipidemia, the sugar cane-derived policosanol in usual and high doses does not demons High-dose atorvastatin reduces the risk of recurrent stroke, but does not improve mortality rates. A reduction in the risk of transient ischemic attack (TIA) or unclassified stroke was partially offset by an increase in the risk of hemorrhagic stroke. (LOE = 1b) trate a reduction in lipid levels beyond placebo.

Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. BMJ. 2008 Aug 21;337:a993. doi: 10.1136/bmj.a993.

Bhatt DL, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006 Jan 11;295(2):180-9.

TOP

Biffi A, Devan WJ, Anderson CD, et al. Statin use and outcome after intracerebral hemorrhage: Case-control study and meta-analysis. Neurology. 2011 May 3;76(18):1581-8.
BIP Study Group. Secondary prevention ()n=3090) by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The bezafibrate infarction prevention (BIP) study. Circulation 2000;102:21-27. (Tenenbaum A, et al. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. Arch Intern Med. 2005 May 23;165(10):1154-60 & McCormack J, Loewen P. The other side of the bezafibrate infarction prevention trial data. Arch Intern Med. 2005 Nov 14;165(20):2431-2; author reply 2432. Tenenbaum A, et al. Attenuation of progression of insulin resistance in patients with coronary artery disease by bezafibrate. Arch Intern Med. 2006 Apr 10;166(7):737-41.) Goldenberg I, et al. Secondary prevention with bezafibrate therapy for the treatment of dyslipidemia: an extended follow-up of the BIP trial. J Am Coll Cardiol. 2008 Jan 29;51(4):459-65. The data demonstrate that bezafibrate therapy in the BIP trial was associated with significant long-term cardiovascular protection that was attenuated by an unbalanced usage of nonstudy LLDs during the course of the trial.
Birnbaum G, Cree B, Altafullah I, Zinser M, Reder AT. Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. Neurology. 2008 Jun 4. [Epub ahead of print]
Blaha MJ, Nasir K, Blumenthal RS. Statin therapy for healthy men identified as "increased risk." JAMA 2012; 307: 1489-1490.
Blanco M,Nombela F, CastellanosM, et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology. 2007;69: 904-10
Bodmer Michael; Brauchli Yolanda B.; Krahenbuhl Stephan; et al. Statin Use and Risk of Gallstone Disease Followed by Cholecystectomy. *JAMA*. 2009;302(18):2001-2007.
Boekholdt, SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, Non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins. JAMA 2012; 307:1302-1309.
Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Statins and Cancer Risk: A Literature-Based Meta-Analysis and Meta-Regression Analysis of 35 Randomized Controlled Trials. J Clin Oncol. 2006 Sep 25; [Epub ahead of print] Our findings do not support a protective effect of statins against cancer. However, this conclusion is limited by the relatively short follow-up periods (4.5 years on average) of the studies analyzed.
Bookstaver DA, Burkhalter NA, et al. Effect of Coenzyme Q10 Supplementation (60mg po bid) on Statin-Induced Myalgias. Am J Cardiol. 2012 May 17. n=76 no more effective than placebo
Briel M, Studer M, Glass TR, Bucher HC. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med. 2004 Oct 15;117(8):596-606.
Briel M, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA. 2006 May 3;295(17):2046-56. Based on available evidence, initiation of statin therapy within 14 days following onset of ACS does not reduce death, MI, or stroke up to 4 months. (see also InfoPOEMs July 2006)
Brindle P, et al. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart. 2006 Dec;92(12):1752-9. Epub 2006 Apr 18.
Brugts JJ, et al. Benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ. 2009 Jun 30;338:b2376. doi: 10.1136/bmj.b2376.
Buchwald H, Rudser KD, Williams SE, et al. Overall mortality, incremental life expectancy, and cause of death at 25 years in the program on the surgical control of the hyperlipidemias. Ann Surg. 2010 Jun;251(6):1034-40.
Callahan Alfred; Amarenco Pierre; Goldstein Larry B.; et al. for the SPARCL Investigators. Risk of Stroke and Cardiovascular Events After Ischemic Stroke or Transient Ischemic Attack in Patients With Type 2 Diabetes or Metabolic Syndrome: Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial Arch Neurol. 2011;0(2011):archneurol.2011.146.
Canadian Adverse Reaction Newsletter Oct 2005: Statins and memory loss. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n4_e.pdf
Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). Am J Cardiol. 2005 Jan 15;95(2):254-7.
Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006; 48:438-445.
Cannon Christopher P., Shah Sukrut, Dansky Hayes M, for the DEFINE Investigators. Safety of Anacetrapib in Patients with or at High Risk for Coronary Heart Disease. November 17, 2010 (10.1056/NEJMoa1009744)
Carroll MD, Lacher DA, Sorlie PD, Cleeman JI, Gordon DJ, Wolz M, Grundy SM, Johnson CL. Trends in serum lipids and lipoproteins of adults, 1960-2002. JAMA. 2005 Oct 12;294(14):1773-81.
Cauley JA, et al. Women's Health Initiative Research Group. Statin use and breast cancer: prospective results from the Women's Health Initiative. J Natl Cancer Inst. 2006 May 17;98(10):700-7.
CDC: Centers for Disease Control & Prevention. Prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol—United States, 1999-2002 & 2005-2008. MMWR Morb Mortal Wkly Rep 2011; 60:7-12.
Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology. 2004 May;126(5):1287-92.
Chan KL, Teo K, Dumesnil JG, et al. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis. (Astronomer)*Circulation* 2010; 121: 306-314.
Chapman MJ, Ginsberg HN, Amarenco P, et al. Triglyceride-risk lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management (EAS). Eur Heart J 2011; 32:1345-1361.
Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: A meta-analysis. Lancet 2008; 371:117-125. Statin therapy should be considered for all diabetic individuals who are at sufficiently high risk of vascular events.
Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet, Early Online Publication, 9 November 2010. doi:10.1016/S0140-6736(10)61350-5. Further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1·0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2—3 mmol/L would reduce risk by about 40—50%.
Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; online May 17.
Chopra V, Wesorick DH, Sussman JB, et al. Effect of Perioperative Statins on Death, Myocardial Infarction, Atrial Fibrillation, and Length of Stay: A Systematic Review and Meta-analysis. Arch Surg. 2012 Feb;147(2):181-9.
Clockaerts S, Van Osch GJ, Bastiaansen-Jenniskens YM, et al. Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study. Ann Rheum Dis 2012;71:642–47.

Cognition, Cognitive effects:
Galatti L, Polimeni G, Salvo F, Romani M, Sessa A, Spina E. Short-term memory loss associated with rosuvastatin. Pharmacotherapy. 2006 Aug;26(8):1190-2.
King DS, Wilburn AJ, Wofford MR, Harrell TK, Lindley BJ, Jones DW. Cognitive impairment associated with atorvastatin and simvastatin. Pharmacotherapy. 2003 Dec;23(12):1663-7.
Padala KP, Padala PR, Potter JF. Simvastatin-induced decline in cognition. Ann Pharmacother. 2006 Oct;40(10):1880-3.
Peters JT, Garwood CL, Lepczyk M. Behavioral changes with paranoia in an elderly woman taking atorvastatin. Am J Geriatr Pharmacother. 2008 Mar;6(1):28-32.
Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. Drug Saf. 2007;30(3):195-201.
Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy. 2003 Jul;23(7):871-80.

Cohen JC, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006 Mar 23;354(12):1264-72.. These data indicate that moderate lifelong reduction in the plasma level of LDL cholesterol is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non-lipid-related cardiovascular risk factors.
Cohen DE, Anania FA, Chalasani N; National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists. Am J Cardiol. 2006 Apr 17;97(8A):77C-81C. Epub 2006 Feb 3.
Colivicchi F, Bassi A, Santini M, Caltagirone C. Discontinuation of statin therapy and clinical outcome after ischemic stroke. Stroke. 2007 Oct;38(10):2652-7. Epub 2007 Aug 30. A large number of patients discontinue their use of statins early after acute stroke. Moreover, patients discontinuing statins have a significantly increased mortality during the first year after the acute cerebrovascular event.
Conly J, Clement F, Tonelli M, et al. Cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk. CMAJ 2011;183:E1180-8.
Connor A, Tomson C. Should statins be prescribed for primary prevention of cardiovascular disease in patients with chronic kidney disease? BMJ. 2009 Aug 20;339:b2949. doi: 10.1136/bmj.b2949.
Cooper A, O'Flynn N; on behalf of the Guideline Development Group. Risk assessment and lipid modification for primary and secondary prevention of cardiovascular disease: summary of NICE guidance. BMJ. 2008 May 31;336(7655):1246-1248. NICE May 2008 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11982
Costa J, Borges M, David C, Carneiro AV. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ. 2006 Apr 3; [Epub ahead of print] In Primary prevention trials the major coronary event rates vs placebo were in diabetics 10 → 8% (not significant) & non-diabetics 8→ 6%. In Secondary prevention trials the major coronary event rates vs placebo: in diabetics 34 → 27% & non-diabetics 22 → 17%.
Cowell SJ, Newby DE, Prescott RJ, et al.; Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med. 2005 Jun 9;352(23):2389-97. CONCLUSIONS: Intensive lipid-lowering therapy does not halt the progression of calcific aortic stenosis or induce its regression. This study cannot exclude a small reduction in the rate of disease progression or a significant reduction in major clinical end points. Long-term, large-scale, randomized, controlled trials are needed to establish the role of statin therapy in patients with calcific aortic stenosis.

TOP

Crouse JR 3rd, Raichlen JS, Riley WA, et al. Effect of Rosuvastatin 40mg od on Progression of Carotid Intima-Media Thickness in Low-Risk Individuals (n=984; Ros=702, placebo=282 over 2 years) With Subclinical Atherosclerosis: The METEOR Trial . JAMA. 2007 Mar 25; [Epub ahead of print] Rosuvastatin treatment was associated with a 49% reduction in LDL-C level, a 34% reduction in total cholesterol level, an 8% increase in HDL-C level, and a 16% reduction in level of triglycerides. Serious adverse cardiovascular events were infrequent (6 participants [0.86%] had 8 events [1.1%] in the rosuvastatin group vs 0% in the placebo group) In middle-aged adults with an FRS of less than 10% and evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum CIMT over 2 years vs placebo. Rosuvastatin did not induce disease regression.

Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative (WHI). Arch Intern Med 2012.

Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA. 2006 Jan 4;295(1):74-80.

Daniels SR, Greer FR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008 Jul;122(1):198-208.

Dansky HM, Bloomfield D, Gibbons P, et al. Efficacy and safety after cessation of treatment with the cholesteryl ester transfer protein inhibitor anacetrapib (MK-0859) in patients with primary hypercholesterolemia or mixed hyperlipidemia. Am Heart J. 2011 Oct;162(4):708-16.

Dagenais GR, Lu J, Faxon DP, et al. Effects of Optimal Medical Treatment With or Without Coronary Revascularization on Angina and Subsequent Revascularizations in Patients With Type 2 Diabetes Mellitus and Stable Ischemic Heart Disease. Circulation. 2011 Mar 28. (BARI 2D)

David WS, Chad DA, Kambadakone A, et al. Case records of the Massachusetts General Hospital. Case 7-2012. A 79-year-old man with pain and weakness in the legs. N Engl J Med. 2012 Mar 8;366(10):944-54.

De Caterina Raffaele. n–3 Fatty Acids in Cardiovascular Disease. N Engl J Med 2011; 364:2439-2450.

Deedwania P, et al. Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets (TNT study). Lancet. 2006 Sep 9;368(9539):919-28.

de Jong HJ, Klungel OH, van Dijk L, et al. Use of statins is associated with an increased risk of rheumatoid arthritis. Ann Rheum Dis. 2011 Oct 6.

de Lorgeril Michel; Salen Patricia; Abramson John; et al. Cholesterol Lowering, Cardiovascular Diseases, and the Rosuvastatin-JUPITER Controversy: A Critical Reappraisal. Arch Intern Med. 2010;170(12):1032-1036.

De Vera MA, Choi H, Abrahamowicz M, Kopec J, Goycochea-Robles MV, Lacaille D. Statin discontinuation and risk of acute myocardial infarction in patients with rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis. 2011 Mar 6.

Di Angelantonio E et al. for the Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009 Nov 11; 302:1993. One approach supported by this study is to use nonfasting cholesterol profiles.

Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. Ann Intern Med. 2006 Jul 18;145(2):117-24.

Dowse GK, et al. Changes in population cholesterol concentrations and other cardiovascular risk factor levels after fi ve years of the non-communicable disease intervention programme in Mauritius. BMJ 1995; 311: 1255–59. (switch from palm to soya oil)

Drozda J. Jr., Messer JV, Spertus J, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. J Am Coll Cardiol 2011;58:xxx–xxx. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.05.002v1.pdf

Egan Amy, Colman Eric. Weighing the Benefits of High-Dose Simvastatin against the Risk of Myopathy. June 15, 2011 (10.1056/NEJMp1106689)

Egeland GM, Cao Z, Young TK. Hypertriglyceridemic-waist phenotype and glucose intolerance among Canadian Inuit: the International Polar Year Inuit Health Survey for Adults 2007-2008. CMAJ. 2011 Jun 14;183(9):E553-8.

Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Serum lipids, lipid-lowering drugs, and the risk of breast cancer. Arch Intern Med. 2005 Oct 24;165(19):2264-71.

Emerging Risk Factors Collaboration. Major Lipids, Apolipoproteins, and Risk of Vascular Disease. *JAMA*. 2009;302(18):1993-2000.Lipid assessment in vascular disease can be simplified by measurement of either total and HDL cholesterol levels or apolipoproteins without the need to fast and without regard to triglyceride.

Emerging Risk Factors Collaboration. Lipid-related markers and cardiovascular disease prediction. JAMA 2012; 307:2499-2506.

Engelter ST, Soinne L, Ringleb P, et al. IV thrombolysis and statins. Neurology. 2011 Aug 17.

Ericsson CG, Hamsten A, Nilsson J, et al. Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. (BECAIT)Lancet. 1996 Mar 30;347(9005):849-53.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011 Nov 14. http://www.nhlbi.nih.gov/guidelines/cvd_ped/

Ezetimibe: Using half doses of Zetia or Vytorin. Pharmacist's Letter Nov 2006.

Farzadfar F, Finucane MM, Danaei G, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 2011.

Fayad ZA, Mani V, Woodward M, et al, for the dal-PLAQUE Investigators. Safety and effi cacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet 2011; online Sept 12.

FDA Mar/10 notified healthcare professionals and patients that, based on review of data from a large clinical trial and other sources, there is an increased risk of muscle injury in patients taking the highest approved dose of the cholesterol-lowering medication, Zocor (simvastatin) 80 mg, compared to patients taking lower doses of simvastatin and possibly other drugs in the "statin" class. Reviewing preliminary data from one clinical trial, the agency found that muscle injury, including rhabdomyolysis, was more common among patients on the 80-mg dose of simvastatin versus a 20-mg dose (0.9% vs. 0.02%). In addition, 11 (0.02%) of the patients in the simvastatin-80-mg group developed rhabdomyolysis compared with no patients in the simvastatin-20-mg group.

FDA June/11: Food and Drug Administration drug safety communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. June 8, 2011. Limit using the 80-mg dose unless the patient has already been taking the drug for 12 months and there is no evidence of myopathy.

FDA Nov/11 notified healthcare professionals the cholesterol-lowering medicine Trilipix (fenofibric acid) may not lower a patient's risk of having a heart attack or stroke.

FDA Feb/12 has approved important safety label changes for the class of cholesterol-lowering drugs known as statins. The changes include removal of routine monitoring of liver enzymes from drug labels. Information about the potential for generally non-serious and reversible cognitive side effects and reports of increased blood sugar and glycosylated hemoglobin (HbA1c) levels has been added to the statin labels. The lovastatin label has been extensively updated with new contraindications and dose limitations when it is taken with certain medicines that can increase the risk for muscle injury.

FDA Mar/12 notified healthcare professionals of updates to the prescribing information concerning interactions between protease inhibitors (HIV & HCV) and certain statin drugs. Protease inhibitors and statins taken together may raise the blood levels of statins and increase the risk for muscle injury (myopathy/ rhabdomyolysis).

Feldman HH, Doody RS, Kivipelto M, et al. On behalf of the LEADe Investigators. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease. LEADe. Neurology. 2010 Mar 3.

Fellström BC, Jardine AG, Schmieder RE, et al. the AURORA Study Group. Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis. N Engl J Med. 2009 Mar 30. [Epub ahead of print] In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Ferrer-Garcia JC, et al. Alternate-day dosing of atorvastatin: effects in treating type 2 diabetic patients with dyslipidaemia. Acta Diabetol. 2006 Nov;43(3):75-8. LDL-C decreased 39% after the every-day period & 23% after the alternate-day atorvastatin dosing period (p<0.05). The target LDL-C concentration of <100 mg/dl was maintained in 19 patients (57.6%) in the alternate-day period. None of the 33 patients showed elevations in liver enzymes or creatine kinase during the alternate-day dosing period. Alternate-day dosing of atorvastatin could be an effective and safe alternative to daily-dosing in some type 2 diabetic patients.

Fleg JL, Mete M, Howard BV, et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol. 2008 Dec 16;52(25):2198-205. Reducing LDL-C to aggressive targets resulted in similar regression of CIMT in patients who attained equivalent LDL-C reductions from a statin alone or statin plus ezetimibe. Common carotid artery IMT increased in those achieving standard targets.

Fletcher B,et al.; AHA: Managing abnormal blood lipids: a collaborative approach. Circulation. 2005 Nov 15;112(20):3184-209.

Fleisher LA, Beckman JA, Brown KA, Calkins H, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation. 2007 Sep 27; [Epub ahead of print]

Flint AC, Kamel H, Navi BB, et al. Inpatient statin use predicts improved ischemic stroke discharge disposition. Neurology. 2012 May 22;78(21):1678-83.

Floyd JS, Keckbert SR, Weiss SR, Carrel DS, Psaty BM. Use of administrative data to estimate the incidence of statin-related rhabdomyolysis. JAMA 2012; 307:1580-1583.

Foody JM, et al. Hydroxymethylglutaryl-CoA reductase inhibitors in older persons with acute myocardial infarction: evidence for an age-statin interaction. J Am Geriatr Soc. 2006 Mar;54(3):421-30. Statin therapy is associated with lower mortality in older patients with AMI younger than 80 but not in those aged 80 and older, as a group.

TOP

Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM; West of Scotland Coronary Prevention Study Group. Long-term follow-up of the West of Scotland Coronary Prevention Study. (Woscops) N Engl J Med. 2007 Oct 11;357(15):1477-86. In this analysis, 5 years of treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolemia who did not have a history of myocardial infarction.

Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med. 2009 Mar 23;169(6):572-8.

Fonarow GC, et al.; National Registry of MI 4 Investigators. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. Am J Cardiol. 2005 Sep 1;96(5):611-6.

Ford ES, Li C, Zhao G, Mokdad AH. Concentrations of low-density lipoprotein cholesterol and total cholesterol among children and adolescents in the United States. Circulation. 2009 Mar 3;119(8):1108-15. Epub 2009 Feb 16.

Freedman DS, Wang YC, Dietz WH, Xu JH, et al. Changes and variability in high levels of low-density lipoprotein cholesterol among children. Pediatrics. 2010 Aug;126(2):266-73. Epub 2010 Jul 19.

Frikke-Schmidt R, Nordestgaard BG, et al.. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. JAMA. 2008 Jun 4;299(21):2524-32. Lower plasma levels of HDL cholesterol due to heterozygosity for loss-of-function mutations in ABCA1 were not associated with an increased risk of IHD.

Gadarla M, Kearns AK, Thompson PD. Efficacy of rosuvastatin (5 mg and 10 mg) twice a week in patients intolerant to daily statins. Am J Cardiol. 2008 Jun 15;101(12):1747-8. Epub 2008 Apr 11.

Gao X, Simon K, Schwarzschild M et al. Prospective Study of Statin Use and Risk of Parkinson Disease Arch Neurol. 2012;69(3):380-384.

Gill PJ, Harnden A, Karpe F. Familial hypercholesterolaemia. BMJ. 2012 May 11;344:e3228.

Gillett RC Jr, Norrell A. Considerations for safe use of statins: liver enzyme abnormalities and muscle toxicitiy. Am Fam Physician. 2011 Mar 15;83(6):711-6.

Gissi-Hf Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Aug 29. [Epub ahead of print] Rosuvastatin 10 mg daily did not affect clinical outcomes in patients with chronic heart failure of any cause, in whom the drug was safe

Glasziou PP, Irwig L, Heritier S, Simes RJ, Tonkin A; LIPID Study Investigators. Monitoring cholesterol levels: measurement error or true change? Ann Intern Med. 2008 May 6;148(9):656-61.

Glynn RJ, Koenig W, Nordestgaard BG, et al. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010 Apr 20;152(8):488-96, W174.

Go AS, et al. Atherosclerotic Disease, Vascular Function & Genetic Epidemiology (ADVANCE) Study. Statin & beta-blockers & the initial presentation of coronary heart disease. Ann Intern Med. 2006 Feb 21;144(4):229-38.

Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. JAMA. 2006 Nov 1;296(17):2105-11.

Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis, and management of pediatric and adult patients. J Clin Lipidol 2011; 5:133-140.

Goldfine AB. Statins: Is It Really Time to Reassess Benefits and Risks? N Engl J Med. 2012 Apr 25.

Golomb BA. Implications of statin adverse effects in the elderly. Expert Opin Drug Saf. 2005 May;4(3):389-97.

Golomb BA, Dimsdale JE, White HL, et al. Reduction in blood pressure with statins. Arch Intern Med 2008; 168: 721-727. Reductions in SBP and DBP occurred with hydrophilic and lipophilic statins and extended to normotensive subjects. These modest effects may contribute to the reduced risk of stroke and cardiovascular events reported on statins.

Gordon RY.; Cooperman T; Obermeyer W; et al. Marked Variability of Monacolin Levels in Commercial Red Yeast Rice Products: Buyer Beware! Arch Intern Med. 2010;170(19):1722-1727.

Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004; 292:2585-90.

Greco A et al. Acute hepatitis caused by a natural lipid-lowering product: when "alternative" medicine is no "alternative" at all. J Hepatology 2009; 50:1273.

Green Lee A. Cholesterol-Lowering Therapy for Primary Prevention: Still Much We Don't Know. Arch Intern Med. 2010;170(12):1007-1008.

Gregoor PJ. Atorvastatin may cause nightmares. BMJ. 2006 Apr 22;332(7547):950.

Greving JP, Visseren FLJ, de Wit GA, et al. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ 2011;342:doi:10.1136/bmj.d1672 (30 March 2011). (seemed not cost-effective in low risk 1º)

Guis S, et al. In vivo and in vitro characterization of skeletal muscle metabolism in patients with statin-induced adverse effects. Arthritis Rheum. 2006 Aug 15;55(4):551-7.

Hackam DG, Austin PC, Huang A, et al. Statins and intracerebral hemorrhage: a retrospective cohort study. Arch Neurol. doi:10.1001/archneurol.2011.228.

Hackam DG, Woodward M, Newby LK, et al. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. Circulation. 2011 Nov 15;124(20):2233-42.

Halbert SC, French B, Gordon RY, et al. Tolerability of red yeast rice (2400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. Am J Cardiol 2010; 105:198-204.

Haney EM, et al. *Screening and Treatment for Lipid Disorders in Children and Adolescents: Systematic Evidence Review for the US Preventive Services Task Force*. Pediatrics. 2007 Jul;120(1):e189-214. Several key issues about screening and treatment of dyslipidemia in children and adolescents could not be addressed because of lack of studies, including effectiveness of screening on adult coronary heart disease or lipid outcomes, optimal ages and intervals for screening children, or effects of treatment of childhood lipid levels on adult coronary heart disease outcomes.

Hannah-Shmouni F, McLeod K, Sirrs S. Recurrent exercise-induced rhabdomyolysis. CMAJ. 2012 Mar 6;184(4):426-30.

Hayward RA., Krumholz HM., Zulman DM., et al. Optimizing Statin Treatment for Primary Prevention of Coronary Artery Disease. Ann Intern Med January 19, 2010 152:69-77.

Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. Circ Cardiovasc Qual Outcomes 2012.

Heart Protection Study Group. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20 536 people. (HPS) BMJ. 2006 Nov 10; [Epub ahead of print]

Heart Protection Study (HPS) Collaborative Group. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20 536 patients in the Heart Protection Study. *Lancet* 2011.

Heart Protection Study Collaborative Group. (HPS) Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet 2011; online Nov 23.

Health Canada Oct/07 Foreign Product Alerts: Red Yeast Rice, Red Yeast Rice/Policosonal Complex and Cholestrix are promoted as dietary supplements for the treatment of high cholesterol. These products may contain lovastatin, a prescription medication for the treatment of high cholesterol that should only be taken under the guidance of a health professional.

Hippisley-Cox J, Coupland C. Effect of statins on the mortality of patients with ischaemic heart disease: population based cohort study with nested case-control analysis. Heart. 2006 Jun;92(6):752-8. Epub 2005 Oct 10.

Hippisley-Cox Julia, Coupland Carol. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010;340.

Holdaas H, et al. Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: multicentre randomised placebo-controlled trial. Lancet. 2003 Jun 14;361(9374):2024-31.

Holtzman CW, Wiggins BS, Spinler SA. Role of P-glycoprotein in statin drug interactions. Pharmacotherapy. 2006 Nov;26(11):1601-7.

Hooper L, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006 Mar 24; [Epub ahead of print] CONCLUSION: Long chain and shorter chain omega 3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer. (InfoPOEMs: Overall, omega 3 fatty acid supplementation does not decrease mortality or cardiovascular disease as compared with placebo. This study combined both primary and secondary prevention; that is, it included people with and without coronary heart disease. (LOE = 1a)) (Brouwer IA, et al. SOFA Study Group. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA. 2006 Jun 14;295(22):2613-9. Our findings do not indicate evidence of a strong protective effect of intake of omega-3 PUFAs from fish oil against ventricular arrhythmia in patients with ICDs.)

Hopewell JC, Parish S, Clarke R, et al. No impact of KIF6 genotype on vascular risk and statin response among 18 348 randomized patients in the Heart Protection Study. J Am Coll Cardiol 2011; DOI:10.1016/j.jacc.2011.02.015.

Houslay E, et al. Progressive coronary calcification despite intensive lipid-lowering therapy: a randomised controlled trial. Heart. 2006 Jan 31; [Epub ahead of print]

Houslay ES, et al. Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression trial Investigators. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. Heart. 2006 Sep;92(9):1207-12. Epub 2006 Jan 31.

Hulten E, et al. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Sep 25;166(17):1814-21. Early, intensive statin therapy reduces death and cardiovascular events after 4 months of treatment.

Huxley RR, Barzi F, Lam TH, et al; for the Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration. Isolated Low Levels of High-Density Lipoprotein Cholesterol Are Associated With an Increased Risk of Coronary Heart Disease: An Individual Participant Data Meta-Analysis of 23 Studies in the Asia-Pacific Region. Circulation. 2011 Nov 8;124(19):2056-2064.

Ikeda M, et al. Different anti-HCV profiles of statins and their potential for combination therapy with interferon. Hepatology. 2006 Jul;44(1):117-25.

Iso H, et al.; JPHC Study Gp. Intake of fish & n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation. 2006 Jan 17;113(2):195-202. Epub 2006 Jan 9.

TOP

Jackevicius Cynthia A, Tu Jack V, Ross Joseph S, et al. Use of Fibrates in the United States and Canada. JAMA. 2011;305(12):1217-1224.doi:10.1001/jama.2011.353

Jafri Haseeb, Alsheikh-Ali Alawi A., Karas Richard H. Meta-analysis: Statin Therapy Does Not Alter the Association Between Low Levels of High-Density Lipoprotein (HDL) Cholesterol and Increased Cardiovascular Risk. *Ann Intern Med December 21, 2010 153:800-808.*

Jenkins DJ, Wong JM, Kendall CW, et al. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. Arch Intern Med. 2009 Jun 8;169(11):1046-54.

Jenkins, David J.A., Chiavaroli, Laura, Wong, Julia M.et al. Adding monounsaturated fatty acids to a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia CMAJ 2010 182: 1961-1967.

Jolliffe CJ, Janssen I. Distribution of lipoproteins by age and gender in adolescents. Circulation. 2006 Sep 5;114(10):1056-62. Epub 2006 Aug 28. For example, in 1-year increments for males starting at age 12 and extending to age 19 years, the high-risk thresholds for total cholesterol were 6.03, 5.83, 5.70, 5.70, 5.77, 5.88, 6.02, and 6.16 mmol/L.

Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol. 2005 Jan 1;95(1):120-2. The findings suggest that the use of fenofibrate in combination with statins results in fewer reports of rhabdomyolysis per million prescriptions dispensed than does the use of gemfibrozil.

Jun M, Foote C, Lv J et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010 May 10.

Kale MS, Bishop TF, Federman AD, Keyhani S. "Top 5" lists top $5 billion. Arch Intern Med 2011; DOI:10.1001/archinternmed.2011.501. (using brand name vs generic statins)

Kapoor AS, et al. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. BMJ. 2006 Nov 6; [Epub ahead of print] The evidence base for routine administration of statins to reduce perioperative cardiovascular risk is inadequate.

Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. (ENHANCE trial) N Engl J Med 2008; 358:1431-1443. In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein.

Keech A, Simes RJ, Barter P, et al. FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005 Nov 26;366(9500):1849-61. INTERPRETATION: Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations. The higher rate of starting statin therapy in patients allocated placebo might have masked a moderately larger treatment benefit. (But some non-significant concerns with fenofibrate vs placebo such as: an ↑ in cardiac mortality 2.2 vs 1.9%, an ↑ in total CVD events for those with previous CVD 25.5 vs 25.1%, an excess in non-cardiovascular disease deaths 4.4 vs 4% & an ↑ in total mortality 7.3 vs 6.6%). But may benefit albuminuria & retinopthy. (InfoPOEMs: In this study, patients with type 2 diabetes treated with fenofibrate (Antara, Lofibra, Tricor) had no significant reduction in coronary events compared with patients treated with placebo. There was a small reduction, however, in nonfatal myocardial infarctions, total cardiovascular disease, and revascularization. (LOE = 1b)) Keech AC, Mitchell P, Summanen PA, et al, for the FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007;370(9600):1687-1697. In patients with type 2 diabetes mellitus fenofibrate (Antara, Lofibra, Tricor) modestly reduces the number of laser treatments for retinopathy. (LOE = 1b) Scott R, O'Brien R, Fulcher G, Pardy C, d'Emden M, Tse D, Taskinen MR, Ehnholm C, Keech A; on behalf of the FIELD Study Investigators. The effects of fenofibrate treatment on cardiovascular disease risk in 9795 people with type 2 diabetes and various components of the metabolic syndrome: the FIELD study. Diabetes Care. 2008 Nov 4. [Epub ahead of print] MS components identify higher CVD risk in people with type 2 diabetes, so the absolute benefits of fenofibrate is likely to be greater when MS features are present. The highest risk and greatest benefits of fenofibrate are seen among those with marked hypertriglyceridemia.

Hiukka A, Westerbacka J, Leinonen ES, et al. Long-term effects of fenofibrate on carotid intima-media thickness and augmentation index in subjects with type 2 diabetes mellitus. (Field) J Am Coll Cardiol. 2008 Dec 16;52(25):2190-7. Fenofibrate treatment was not associated with beneficial changes in IMT, augmentation index, or biomarkers of inflammation and endothelial function.

Rajamani K et al. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): A prespecified analysis of a randomised controlled trial. Lancet 2009 May 23; 373:1780.

Kelly R. Diet and Exercise in the Management of Hyperlipidemia. American Family Physician. May1, 2010.

Khoury J, et al. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. Am J Obstet Gynecol. 2005 Oct;193(4):1292-301. (InfoPOEMs: In this study of low-risk pregnant women, a diet rich in fish and low in other animal fats resulted in a marked decrease in the number of preterm births. These results seem too good to be true and further confirmatory evidence is needed. In the meantime, as long as the fish are free of toxins the potential benefit may be large and there is no apparent risk. (LOE = 1b))

Kjekshus J, Apetrei E, Barrios V, et al. the CORONA Group. Rosuvastatin in Older Patients with Systolic Heart Failure. N Engl J Med. 2007 Nov 5; [Epub ahead of print] Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems. (Cleland JGF, McMurray JJV, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). J Am Coll Cardiol 2009; 54:1850-1859.)

Klein BE, et al. Statin use and incident nuclear cataract. JAMA. 2006 Jun 21;295(23):2752-8. (InfoPOEMs: Statin use is associated with a reduced incidence of nuclear cataracts, the most common type of age-related cataracts. However, this type of study design (prospective cohort study) does not prove a causal relationship between the use of statins and lower risk of developing cataracts. It is possible that other confounding variables (eg, genetics or patient compliance) are causally related. (LOE = 2b)) (Tan JS, Mitchell P, Rochtchina E, Wang JJ. Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. Am J Ophthalmol. 2007 Apr;143(4):687-9. Epub 2006 Dec 20. Statin use was found to reduce by 50% the risk of cataract development, principally nuclear or cortical cataract subtypes.)

Kopin Laurie, Lowenstein Charles, In the Clinic: Dyslipidemia. *Ann Intern Med* August 3, 2010 153:ITC2-1; doi:10.1059/0003-4819-153-3-201008030-01002.

Kostis WJ, Cheng JQ, Dobrzynski JM, et al. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol 2012; 59:572-582.

Knopp RH, et al. Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). Diabetes Care. 2006 Jul;29(7):1478-85.

Kromhout D, Gitay EJ, Geleijnse JM, et al. N-3 fatty acids and cardiovascular events after myocardial infarction. (Alpha Omega Trial)N Engl J Med 2010; DOI:10.1056.NEJM0a.1003603.

Kruger PS, Harward ML, Jones MA, Joyce CJ, Kostner KM, Roberts MS, Venkatesh B. Continuation of statin therapy in patients with presumed infection: a randomized controlled trial. Am J Respir Crit Care Med 2011;183:774–781.

Krum H, et al. Impact of Statin Therapy on Clinical Outcomes in Chronic Heart Failure Patients According to Beta-Blocker Use: Results of CIBIS II. Cardiology. 2006 Sep 8;108(1):28-34 [Epub ahead of print]

Kuklina Elena V.; Yoon Paula W.; Keenan Nora L.. Trends in High Levels of Low-Density Lipoprotein Cholesterol in the United States, 1999-2006. *JAMA*. 2009;302(19):2104-2110

Lachaine J, et al. Persistence and adherence to cholesterol lowering agents: evidence from Regie de l'Assurance Maladie du Quebec data. Am Heart J. 2006 Jul;152(1):164-9.

Ladenson, Paul W., Kristensen, Jens D., Ridgway, E. Chester, et al. Use of the Thyroid Hormone Analogue Eprotirome in Statin-Treated Dyslipidemia. N Engl J Med 2010 362: 906-916.

Last AR, Ference JD, Falleroni J. Pharmacologic treatment of hyperlipidemia. Am Fam Physician. 2011 Sep 1;84(5):551-8.

Laufs U, Custodis F, Bohm M. HMG-CoA reductase inhibitors in chronic heart failure: potential mechanisms of benefit and risk. Drugs. 2006;66(2):145-54.

Lavie CJ, Milani RV, Mehra MR, et al. Omega-3 polyunsaturated fatty acids and cardiovascular disease. J Am Coll Cardiol 2009; 54: 585-594.

Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006 Apr 17;97(8A):52C-60C. Epub 2006 Feb 3.For statins other than cerivastatin, the incidence of rhabdomyolysis in 2 cohort studies was 3.4 (1.6 to 6.5) per 100,000 person-years, an estimate supported by data from 20 randomized controlled trials. Case fatality was 10%. Incidence was about 10 times greater when gemfibrozil was used in combination with statins. Incidence was higher (4.2 per 100,000 person-years) with lovastatin, simvastatin, or atorvastatin (which are oxidized by cytochrome P450 3A4 [CYP3A4], which is inhibited by many drugs) than pravastatin or fluvastatin (which are not oxidized by CYP3A4). In persons taking simvastatin, lovastatin, or atorvastatin, 60% of cases involved drugs known to inhibit CYP3A4 (especially erythromycin and azole antifungals), and 19% involved fibrates, principally gemfibrozil. The incidence of myopathy in patients treated with statins, estimated from cohort studies supported by randomized trials, was 11 per 100,000 person-years. For liver disease, randomized trials reported fewer hepatobiliary disorders in patients allocated statins than in those allocated placebo. The notification rate of liver failure to regulatory authorities was about 1 per million person-years of statin use. Randomized trials show no excess of renal disease or proteinuria in statin-allocated participants, and the decline in glomerular filtration rate was smaller with statins than with placebo. Evidence from 4 cohort studies and case reports suggests that statins cause peripheral neuropathy, but the attributable risk is small (12 per 100,000 person-years). No change in cognitive function was found in randomized trials of statins in elderly patients.

Lazar LD, Pletcher MJ, Coxson PG, et al. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation. 2011 Jul 12;124(2):146-53.

Lebenthal Y, Horvath A, Dziechciarz P, et al. Are treatment targets for hypercholesterolemia evidence based in children ? Systematic review and meta-analysis of randomised controlled trials. Arch Dis Child. 2010 Sep;95(9):673-80.

Lecarpentier E, Morel O, Fournier T, Elefant E, Chavatte-Palmer P, Tsatsaris V. Statins and Pregnancy: Between Supposed Risks and Theoretical Benefits. Drugs. 2012 Apr 5.

Lee KH, Jeong MH, Kim HM, et al. Benefit of early statin therapy in patients with acute myocardial infarction who have extremely low low-density lipoprotein cholesterol. J Am Coll Cardiol 2011; 58:1664-1671.

Lenderink T, et al. Patients using statin treatment within 24 h after admission for ST-elevation acute coronary syndromes had lower mortality than non-users: a report from the first Euro Heart Survey on acute coronary syndromes. Eur Heart J. 2006 Aug;27(15):1799-804. Epub 2006 Jul 4.

Liakopoulos OJ, , et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30 000 patients. Eur Heart Journal 2008; DOI:10.1093/eurheartj/ehn198.

Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, Burns K, Manns B, White C, Madore F, Moist L, Klarenbach S, Barrett B, Foley R, Jindal K, Senior P, Pannu N, Shurraw S, Akbari A, Cohn A, Reslerova M, Deved V, Mendelssohn D, Nesrallah G, Kappel J, Tonelli M; Canadian Society of Nephrology. Guidelines for the management of chronic kidney disease. CMAJ. 2008 Nov 18;179(11):1154-62.

TOP

http://www.cmaj.ca/cgi/data/179/11/1154/DC1/1
Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R; Pravastatin in Chronic Liver Disease Study Investigators. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology. 2007;46(5):1453-1463.
Liakopoulos OJ, Kuhn EW, Slottosch I, et al. Preoperative statin therapy for patients undergoing cardiac surgery. Cochrane Database Syst Rev. 2012 Apr 18;4:CD008493. Preoperative statin therapy reduces the odds of post-operative AF and shortens the stay on the ICU and in the hospital. Statin pretreatment had no influence on perioperative mortality, stroke, myocardial infarction or renal failure. Since analysed studies included mainly patients undergoing myocardial revascularizations the results cannot be extrapolated to patients undergoing other cardiac procedures such as heart valve or aortic surgery.
Li L, Sun T, Zhang P, et al. Statins for primary prevention of venous thromboembolism. Cochrane Database Syst Rev. 2011 Dec 7;12:CD008203. Available evidence showed that rosuvastatin was associated with a reduced incidence of VTE, but the evidence was limited to a single RCT.
Li M, Al-Sarraf A, Sinclair G, Frohlich J. Fish odour syndrome. CMAJ. 2011 Mar 21. (exacerbated by rosuvastatin)
Lim SY, Bae EH, Choi JS, et al. other Korea Acute Myocardial Infarction Registry Investigators. Effect on Short- and Long-Term Major Adverse Cardiac Events of Statin Treatment in Patients With Acute Myocardial Infarction and Renal Dysfunction. Am J Cardiol. 2012 Feb 20.
Lipinski MJ, Cauthen CA, Biondi-Zoccai GG, et al. Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure. Am J Cardiol. 2009 Dec 15;104(12):1708-16.
Liu M, Alafris A, Longo AJ, Cohen H. Irreversible atorvastatin-associated hearing loss. Pharmacotherapy. 2012 Feb;32(2):e27-34. doi: 10.1002/PHAR.1040.
Liu ZL, Liu JP, Zhang AL, et al. Chinese herbal medicines for hypercholesterolemia. Cochrane Database Syst Rev. 2011 Jul 6;7:CD008305. Some herbal medicines may have cholesterol-lowering effects. Our findings have to be interpreted with caution due to high or unclear risk of bias of the included trials. {22 RCTs, n=2130, range of 1-6 months with mean duration 2.3 +/- 1.3 months, high or unclear risk of ibias, no outcome data (too short & too small), no SAEs; Xuezhikang most commonly used; possible TC lowering (-0.90mmol/L vs inositol nicotinate).
Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM; Chinese Coronary Secondary Prevention Study Group. Effect of xuezhikang, an extract from red yeast chinese rice, on coronary events in a chinese population with previous myocardial infarction. Am J Cardiol. 2008 Jun 15;101(12):1689-93. Epub 2008 Apr 11. (n=~5000, 4.5years) In conclusion, long-term therapy with XZK significantly decreased the recurrence of coronary events and the occurrence of new CV events and deaths, improved lipoprotein regulation, and was safe and well tolerated.
MacLean CH, et al. Effects of omega-3 fatty acids on cancer risk: a systematic review. JAMA. 2006 Jan 25;295(4):403-15.
Majumdar SR, et al. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. BMJ. 2006 Oct 23; [Epub ahead of print]
Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-Hydroxy-3-methylglutaryl-coenzyme a reductase (HMGCR) in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2010; DOI: 10.1002/art.30156.
Manuel DG, et al. Effectiveness and efficiency of different guidelines on statin treatment for preventing deaths from coronary heart disease: modelling study. BMJ. 2006 Jun 17;332(7555):1419. Epub 2006 May 31.
Marelli C, Gunnarsson C, Ross S, et al. Statins and risk of cancer. J Am Coll Cardiol 2011; 58:530-537. (no association found)
Marrs JC, Saseen JJ. Effects of lipid-lowering therapy on reduction of cardiovascular events in patients with end-stage renal disease requiring hemodialysis. Pharmacotherapy. 2010 Aug;30(8):823-9.
Martin JE, Cavanaugh TM, Trumbull L, et al. Incidence of adverse events with HMG-CoA reductase inhibitors in liver transplant patients. Clin Transplant. 2008 Jan-Feb;22(1):113-9. Overall, there was a general tolerability with a low incidence of adverse events, no incidence of severe complications, and no alterations in liver function tests in the study population with the use of LLA.
Martin SS, Metkus TS, Horne A, et al. Waiting for the National Cholesterol Education Program Adult Treatment Panel IV Guidelines, and in the Meantime, Some Challenges and Recommendations. Am J Cardiol. 2012 Apr 10.
McGuinness B, O`Hare J, Craig D, et al. Statins for the treatment of dementia. Cochrane Database Syst Rev. 2010 Aug 4;8:CD007514. There is insufficient evidence to recommend statins for the treatment of dementia. Analysis from the studies available, including one large RCT, indicate statins have no benefit on the outcome measures ADAS-Cog or MMSE. We need to await full results from CLASP 2008 before we can be certain.
McKenney JM, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. (N=587 48 wks) J Am Coll Cardiol. 2006 Apr 18;47(8):1584-7. Epub 2006 Mar 30.
McKenney JM, et al. Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels on a background of atorvastatin. J Am Coll Cardiol. 2006 Nov 7;48(9):1782-90.
McKenney JM, Davidson MH, Jacobson TA, Guyton JR; National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006 Apr 17;97(8A):89C-94C. Epub 2006 Feb 28.
Medical Letter. Pitavastatin (Livalo). July 26, 2010.
Mehta JL, et al. Comparison of mortality rates in statin users versus nonstatin users in a United States veteran population. Am J Cardiol. 2006 Oct 1;98(7):923-8. Epub 2006 Aug 7. The benefit observed in this study is unique because almost 1/2 the patients were >/=70 years of age when statin therapy was initiated.
Milionis HJ, Giannopoulos S, Kosmidou M, et al. Statin therapy after first stroke reduces 10-year stroke recurrence and improves survival. Neurology 2009; 72:1816-1822.
Miller M, et al. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors: the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2005 Oct 10;165(18):2063-8. CONCLUSIONS: These data suggest that elevated CRP levels in the general population are in large measure attributable to traditional CHD risk factors. Moreover, CRP level elevation is rare in the absence of borderline or abnormal risk factors. As such, CRP measurements may have limited clinical utility as a screening tool beyond other known CHD risk factors.
Miller Michael, Stone Neil J., Ballantyne Christie, et al. and on behalf of the American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular N. Triglycerides and Cardiovascular Disease: A Scientific Statement From American Heart Association (AHA). April 18, 2011. http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3182160726v1
Mills EJ, Rachlis B, et al. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008 Nov 25;52(22):1769-81.
Mills EJ, Wu P, Chong G, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM. 2011 Feb;104(2):109-24.
Mittleman MA. A 39-year-old woman with hypercholesterolemia. JAMA. 2006 Jul 19;296(3):319-26.
Mohaupt MG, Karas RH, Babiychuk EB, et al. Association between statin-associated myopathy and skeletal muscle damage. CMAJ. 2009 Jul 7;181(1-2):E11-8.
Mora S, Wenger NK, DeMicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation. 2012;125:1979 –1987.
Mumford SL, Schisterman EF, Siega-Riz AM, et al. A Longitudinal Study of Serum Lipoproteins in Relation to Endogenous Reproductive Hormones during the Menstrual Cycle: Findings from the BioCycle Study. J Clin Endocrinol Metab. 2010 Jun 9.
Moreyra AE, Wilson AC, Koraym A. Effect of combining psyllium fiber with simvastatin in lowering cholesterol. Arch Intern Med. 2005 May 23;165(10):1161-6.
Nakamura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006 Sep 30;368(9542):1155-63.
Natsuaki M, et al. CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators. Impact of Statin Therapy on Late Target Lesion Revascularization After Sirolimus-Eluting Stent Implantation (CREDO-Kyoto Registry Cohort-2). Am J Cardiol. 2012 Feb 28.
Navaneethan SD, Pansini F, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD007784.
Navaneethan SD, Nigwekar SU, Perkovic V, Johnson DW, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for dialysis patients. Cochrane Database Syst Rev. 2009;(2):CD004289.
Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev. 2009;(2):CD005019.
Neil HA, et al. CARDS Study Investigators. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84.
New drug: Advicor (Niacin Extended-Release?Lovastatin). Pharmacist's Letter/Prescriber's Letter 2006;22(2):220220
Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. Am J Cardiol. 2006 Jan 1;97(1):61-7. Epub 2005 Nov 15.
Newson RS, Felix JF, Heeringa J, et al. Association between serum cholesterol and noncardiovascular mortality in older age. J Am Geriatr Soc. 2011 Oct;59(10):1779-85.
Nicholls SJ, et al. Effects of obesity on lipid-lowering, anti-inflammatory, and antiatherosclerotic benefits of atorvastatin or pravastatin in patients with coronary artery disease (from the REVERSAL Study). Am J Cardiol. 2006 Jun 1;97(11):1553-7. Epub 2006 Apr 6.
Nichols GA, Vupputuri S, Rosales AG. Change in high-density lipoprotein (HDL) cholesterol and risk of subsequent hospitalization for coronary artery disease or stroke among patients with type 2 diabetes mellitus. Am J Cardiol. 2011 Oct 15;108(8):1124-8.
Nicholls SJ, Brewer HB, Kastelein JJP, et al. Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. JAMA. 2011;306(19):2099-2109.
Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin (atrovastatin 80mg vs rosuvastatin 40mg) regimens on progression of coronary disease. (Saturn) N Engl J Med 2011; DOI: 10.1056/NEJMoa1110874.
Nieuwkerk PT, Nierman MC, Vissers MN, et al. Intervention to Improve Adherence to Lipid-Lowering Medication and Lipid-Levels in Patients With an Increased Cardiovascular Risk. Am J Cardiol. 2012 May 21.

TOP

Nissen SE, et al. Effect of Very High-Intensity Statin (rosuvastatin 40mg/d, 2yr, n=507) Therapy on Regression of Coronary Atherosclerosis: The ASTEROID Trial.JAMA. 2006 Mar 13; [Epub ahead of print]
Onofrei MD, et al. Safety of statin therapy in patients with preexisting liver disease. Pharmacotherapy. 2008 Apr;28(4):522-9.
Oregon Health Sciences University. Drug class review on Statins (Aug 2006) http://www.ohsu.edu/drugeffectiveness/reports/documents/Statins%20Final%20Report%20Update%204%20Unshaded.pdf
Packard CJ, Ford I, et al. Plasma Lipoproteins & Apolipoproteins as Predictors of Cardiovascular Risk and Treatment Benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Circulation. 2005 Nov 7
(Ford I, Bezlyak V, Stott DJ, Sattar N, Packard CJ, Perry I, Buckley BM, Jukema JW, de Craen AJ, Westendorp RG, Shepherd J. Reduced glomerular filtration rate and its association with clinical outcome in older patients at risk of vascular events: secondary analysis. (Prosper) PLoS Med. 2009 Jan 20;6(1):e16.)
Pape GA, Hunt JS, Butler KL, et al. Team-based care approach to cholesterol management in diabetes mellitus: 2-year cluster randomized controlled trial. Arch Intern Med. 2011 Sep 12;171(16):1480-6.
Park Y, Jeong YH, Tantry US, et al. Accelerated platelet inhibition (with clopidogrel) by switching from atorvastatin to a non-CYP3A4-metabolized statin in patients with high platelet reactivity (ACCEL-STATIN) study. Eur Heart J 2012.
Parker BA, Augeri AL, Capizzi JA, et al. Effect of Statins on Creatine Kinase Levels Before and After a Marathon Run. Am J Cardiol. 2011 Oct 27. In conclusion, our results show that statins increase exercise-related muscle injury.
Parra D, Beckey NP, et al.; Veterans Integrated Service Network & Pharmacy Benefits Management Utilization Committee. Effect of splitting simvastatin tablets for control of low-density lipoprotein cholesterol. Am J Cardiol. 2005 Jun 15;95(12):1481-3.
Pasternak RC, et al. American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Circulation. 2002 Aug 20;106(8):1024-8.
Pattanaik S, Malhotra S, et al. Comparison of Alternate-day Atorvastatin Treatment to Daily Treatment in Maintaining LDL-cholesterol Targets in Patients With Variable Coronary Risk Profile. J Cardiovasc Pharmacol. 2012 May;59(5):479-84. (inferior)
Patti G, et al. Randomized Trial of Atorvastatin for Reduction of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. Results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) Study. Circulation. 2006 Sep 25; [Epub ahead of print]
Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. Circulation. 2011 Apr 19;123(15):1622-32.
Pedersen TR, Faergeman O, et al. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The IDEAL Study: A Randomized Controlled Trial. JAMA. 2005 Nov 16;294(19):2437-2445. (InfoPOEMs: The intensive reduction of low-density lipoprotein (LDL) levels to well below 100 mg/dL (2.5 mmol/L) did not result in a significant reduction in the recurrence of major coronary events or all-cause mortality among patients with stable coronary artery disease. Intensive lowering is associated with an increased risk of discontinuing medication because of adverse events and significant drug costs. Aiming for an LDL of approximately 100 mg/dL (2.5 mmol/L) seems optimal for the majority of patients with stable disease. (LOE = 1b-))
Pennisi G, Vacante M, Russo C, Malaguarnera M. Rhabdomyolysis Induced by Rosuvastatin and Sildenafil. South Med J. 2010 Sep 2.
Perk J, De Backer G, Gohlke H, et al. European guidelines (ESC) on cardiovascular disease in clinical practice (version 2012). Eur Heart J2012; DOI:10.1093/eurheartj/ehs092.
Peripheral Arterial Disease: ACC/AHA Guidelines for the Management of Patients With (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic); A Collaborative Report From the AAVS/SVS, SCAI, SIR, SVMB, and the ACC/AHA Task Force on Practice Guidelines http://www.acc.org/clinical/guidelines/pad/summary.pdf
Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. Age Ageing. 2010 Nov;39(6):674-80.
Petri M A, Kiani A N, Post W, et al. Lupus Atherosclerosis Prevention Study (LAPS). Ann Rheum Dis 2011;70:760-765 Published Online First: 21 December 2010 doi:10.1136/ard.2010.136762. (atorvastatin not help over 2yrs)
Pharmacists Letter. Treatment of Hyperlipidemia in Children and Adolescents. January 2012.
Pharmacists Letter. Niacin Abuse in the Attempt to Alter Urine Drugs Tests. June 2007.
Phillips PS, et al.; Scripps Mercy Clinical Research Center. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med. 2002 Oct 1;137(7):581-5.
Pignone M, Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Ann Intern Med. 2006 Mar 7;144(5):326-36. Summary for patients in: Ann Intern Med. 2006 Mar 7;144(5):I29. (InfoPOEMs: From the viewpoint of cost to a third-party payer, the costs of aspirin alone are reasonable in men at low-risk for coronary heart disease (CHD); the addition of a statin to aspirin therapy in these men is above what is considered to be reasonable cost for prevention. However, the combination of aspirin and a statin is cost-effective when men are at high risk (10% or above). (LOE = 2a))
PILL Collaborative Group (2011) An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill ("Polypill") in People with Raised Cardiovascular Risk. PLoS ONE 6(5): e19857. doi:10.1371/journal.pone.0019857.
Pfizer April/08 In a study in patients with mild-to-moderate Alzheimer's disease (AD), the addition of Lipitor (atorvastatin calcium tablets) 80 mg to Aricept® (donepezil HCl) 10 mg showed no significant differences in cognition or global function (key measures of Alzheimer's progression) compared to placebo plus Aricept 10 mg. Furthermore, no statistically significant differences were seen on various cognitive, behavioral and functional secondary endpoints. However, the Lipitor arm was not associated with greater cognitive decline than the placebo arm in this trial. The results were presented today at the annual American Academy of Neurology meeting in Chicago. The 18-month study, called Lipitor's Effect on Alzheimer's Dementia (LEADe), included 640 patients and is the largest statin study in Alzheimer's disease.
Pletcher MJ, Bibbins-Domingo K, Liu K, et al. Nonoptimal Lipids Commonly Present in Young Adults and Coronary Calcium Later in Life: The CARDIA (Coronary Artery Risk Development in Young Adults) Study. Ann Intern Med. 2010 Aug 3;153(3):137-46.
Polinski JM, Schneeweiss S, Maclure M, Marshall B, Ramsden S, Dormuth C. Time series evaluation of an intervention to increase statin tablet splitting by general practitioners. Clin Ther. 2011 Feb;33(2):235-43.
Poynter JN, Gruber SB, Higgins PDR, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352:2184-92. (InfoPOEMs: This observational study found an association between statin use and a reduced risk of colorectal cancer. Large randomized controlled trials are needed to confirm this potential benefit before we begin recommending statins to our patients for this indication, given the relatively small absolute magnitude of benefit, the cost, and the findings of increased risk of cancer in some previous clinical trials. (LOE = 3b))
Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy. JAMA 2011; 305:2556-2564. (New onset diabetes NNH=498, Cardiovascular events NNT=155 per year)
Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation. 2011 Nov 15;124(20):2202-7.
Ray Kausik K.; Seshasai Sreenivasa Rao Kondapally; Erqou Sebhat; et al. Statins and All-Cause Mortality in High-Risk Primary Prevention: A Meta-analysis of 11 Randomized Controlled Trials Involving 65 229 Participants. Arch Intern Med. 2010;170(12):1024-1031.
Reddy KJ, Singh M, Batsell RR, et al. Efficacy of combination drug pulse therapy in maintaining lipid levels in patients intolerant of daily statin use. J Clin Hypertens (Greenwich). 2009 Dec;11(12):766-8.
Reddy P, Ellington D, Zhu Y, et al. Serum concentrations and clinical effects of atorvastatin in patients taking grapefruit juice daily. Br J Clin Pharmacol. 2011 Apr 18. doi: 10.1111/j.1365-2125.2011.03996.x. (no major effect)
Redelmeier DA, Thiruchelvam D, Daneman N. Delirium after elective surgery among elderly patients taking statins. CMAJ. 2008 Sep 23;179(7):645-52.
Riediger ND, Clara I. Prevalence of metabolic syndrome in the Canadian adult population. CMAJ 2011; DOI:10.1503/cmaj.110070.
Roselle H et al. Symptomatic hepatitis associated with the use of herbal red yeast rice. Ann Intern Med 2008; 149:516.
Rossebø AB, Pedersen TR, Boman K, et al. the SEAS Investigators. Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. N Engl J Med. 2008 Sep 2. [Epub ahead of print] (n=1873 52.2months) Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis. Cancer occurred more frequently in the simvastatin-ezetimibe group (105 vs. 70, P=0.01).
Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol. 2006 Jul;17(7):2006-16. Epub 2006 Jun 8.
Schwing W, Hustak L, Taylor HC. Paradoxical Severe Decrease in HDL Cholesterol Due to Rosiglitazone-Fenofibrate Interaction. Endocr Pract. 2010 Jan 9:1-17. [Epub ahead of print]
Scranton RE, Young M, Lawler E, et al. Statin use and fracture risk: study of a US veterans population. Arch Intern Med. 2005 Sep 26;165(17):2007-12.
Sharma M., Ansari M. T., Abou-Setta A. M., Systematic Review: Comparative Effectiveness and Harms of Combinations of Lipid-Modifying Agents and High-Dose Statin Monotherapy. *Ann Intern Med* 2009; 60520-144.
Sharma M, Ansari MT, Abou-Setta AM, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009 Nov 3;151(9):622-30.
Shewmon DA, Craig JM. Creatine supplementation prevents statin-induced muscle toxicity. Ann Intern Med. 2010 Nov 16;153(10):690-2. (n=12
Shiu JR, Pearson GJ, Charrois TL, et al. Frequency of Intensive Statin Therapy in Patients With Acute Coronary Syndrome Admitted to a Tertiary Care Center. Am J Cardiol. 2011 Oct 6.
Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Can J Cardiol. 2006 Feb;22(2):141-4.
Smith SC Jr, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006 May 16;113(19):2363-72. http://circ.ahajournals.org/cgi/reprint/113/19/2363

TOP

Sorensen PS, Lycke J, Erälinna JP, et al; for the SIMCOMBIN study investigators. Simvastatin as add-on therapy to interferon beta-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN): a placebo-controlled randomised phase 4 trial. Lancet Neurol. 2011 Jul 8. (We found no beneficial effect of simvastatin)

Spencer FA, et al.; National Registry of MI. Early withdrawal of statin therapy in patients with non-ST-segment elevation myocardial infarction: national registry of myocardial infarction. Arch Intern Med. 2004 Oct 25;164(19):2162-8.

Steiner MJ, Skinner AC, Perrin EM. Fasting might not be necessary before lipid screening: A nationally representative cross-sectional study. Pediatrics 2011; DOI:10.1542/peds.2011-0844.

Strandberg TE, et al. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study: a randomized, controlled trial. Am Heart J. 2006 Sep;152(3):585-92. (InfoPOEMs: First, the good news: Researchers were able, without unusual effort, to apply evidence-based guidelines to older elderly patients with cardiovascular disease (CVD) and achieve goal blood pressure and cholesterol levels in the majority. Now, the bad news: These interventions did not decrease the likelihood of the patients experiencing a cardiovascular problem over the next 3.4 years. The treated patients did not live any longer over this period, and the treatment did not delay deaths. (LOE = 1b)))

Rahimi Kazem, Emberson Jonathan, McGale Paul, et al., PWM is acting on behalf of the PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. BMJ 342:doi:10.1136/bmj.d1250 (Published 16 Mar 2011)

Rajpathak SN, Kumbhani DJ, Crandall J, et al. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care. 2009 Oct;32(10):1924-9.

Rahimi K, Majoni W, Merhi A et al. Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials. Eur Heart J. 2012 Feb 3.

Ray KK, Cannon CP. Early time to benefit with intensive statin treatment: could it be the pleiotropic effects? Am J Cardiol. 2005 Sep 5;96(5A):54F-60F.

Rayman Margaret P., Stranges Saverio, Griffin Bruce A., et al. Effect of Supplementation With High-Selenium Yeast on Plasma Lipids: A Randomized Trial. Ann Intern Med May 17, 2011 154:656-665.

Redberg RF. Katz MH. Healthy men should not take statins. JAMA 2012; 307:1491-1492.

Reddy P, Ellington D, Zhu Y, et al. Serum concentrations and clinical effects of atorvastatin in patients taking grapefruit juice daily. Br J Clin Pharmacol. 2011 Apr 18. doi: 10.1111/j.1365-2125.2011.03996.x.

Reindl Erin K, Wright Bradley M, Wargo Kurt A. Alternate-Day Statin Therapy for the Treatment of Hyperlipidemia. Ann Pharmacother ;44:1459-1470.

Reiss AB, Wirkowski E. Role of HMG-CoA Reductase Inhibitors in Neurological Disorders : Progress to Date. Drugs. 2007;67(15):2111-20.

Reynolds K, et al. A meta-analysis of the effect of soy protein supplementation on serum lipids. Am J Cardiol. 2006 Sep 1;98(5):633-40. Epub 2006 Jul 12.

Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. 2005 Jul 20;294(3):326-33.

Ridker PM, Danielson E, Fonseca FA, Genest J, et al. the JUPITER Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med. 2008 Nov 9. [Epub ahead of print] In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Ritchie, Susan K., Murphy, Emily C.-S., et al. Universal Versus Targeted Blood Cholesterol Screening Among Youth: The CARDIAC Project. Pediatrics 2010 0: peds.2009-2546.

Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol. 2005 Nov 15;46(10):1855-62. Epub 2005 Oct 24.

Sabate Joan; Oda Keiji; Ros Emilio. Nut Consumption and Blood Lipid Levels: A Pooled Analysis of 25 Intervention Trials. Arch Intern Med. 2010;170(9):821-827.

Sailler L, Pereira C, Bagheri A, et al. Increased exposure to statins in patients developing chronic muscle diseases: a 2-year retrospective study.Ann Rheum Dis. 2008 May;67(5):614-9. Epub 2007 Sep 3. Patients who developed chronic muscle diseases after the age of 50, including DM/PM, had a higher than expected frequency of prior exposure to statins.

Sampathkumar K, et al. Extended release nicotinic acid - a novel oral agent for phosphate control. Int Urol Nephrol. 2006;38(1):171-4.

Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology. 2011 Aug 9;77(6):556-63. (no benefit)

Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; DOI:10.1016/S0140-6736(09)61965-6.

Schanberg L, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, et al. Use of atorvastatin in systemic lupus erythematosus in children and adolescents (APPLE). Arthritis Rheum 2011

Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. Cochrane Database Syst Rev. 2010 Mar 17;3:CD004371.

Schelleman H, Bilker WB, Brensinger CM, et al. Fibrate/statin initiation in warfarin users and gastrointestinal bleeding risk. Am J Med. 2010 Feb;123(2):151-7.

Schouten O, Boersma E, Hoeks SE, et al. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. Fluvastatin and perioperative events in patients undergoing vascular surgery. (Decrease III) N Engl J Med. 2009 Sep 3;361(10):980-9. In patients undergoing vascular surgery, perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome. (Dunkelgrun M et al. Bisoprolol and fluvastatin (fixed dose of 80 mg; NS finding) for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: A randomized controlled trial (DECREASE-IV). Ann Surg 2009 Jun; 249:921.)

Schwartz JS. Primary Prevention of Coronary Heart Disease With Statins: It's Not About the Money. Circulation. 2011 Jul 12;124(2):130-2.

Semb AG, Kvien TK, Demicco D, et al. Effect of intensive lipid lowering on cardiovascular outcome in patients with and without inflammatory joint disease. Arthritis Rheum. 2012 May 10.

Sever P, Dahlof B, Poulter N, et al. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. (ASCOT) Eur Heart J 2006; 27:2982-2988.

Sever PS, Chang CL, Gupta AK, et al. The Anglo-Scandinavian Cardiac Outcomes Trial (Ascot): 11-year mortality follow-up of the lipid-lowering arm in the UK. Eur Heart J 2011

Shalev V, Chodick G, Silber H, et al. Continuation of statin treatment and all-cause mortality. Arch Intern Med 2009; 169:260-268.

Sharma M, Ansari MT, Abou-Setta AM, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009 Nov 3;151(9):622-30.

SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9438 patients with chronic kidney disease. Am Heart J 2010; DOI:10.1016/j.ahj.2010.08.012. (Ezetimibe 10mg / simvastatin 20mg vs placebo)

Siamopoulos KC, et al. Long-term treatment with EPO increases serum levels of high-density lipoprotein in patients with CKD. Am J Kidney Dis. 2006 Aug;48(2):242-9.

Smith S, Benjamin E, Bonow R, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011; DOI:10.1161/CIR.0b013e318235eb4d.

Sniderman AD, Thanassoulis G, Lawler PR, et al. Comparison of Coronary Calcium Screening Versus Broad Statin Therapy for Patients at Intermediate Cardiovascular Risk. Am J Cardiol. 2012 May 9.

Soler A, et al. Effectiveness and tolerance of atorvastatin for antiretroviral therapy-secondary dyslipemia. Med Clin (Barc). 2006 Jul 15;127(7):250-2.

Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med 2012;366:1108-18.

Stein E A, Gipe D, Bergeron J et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: A phase 2 randomised controlled trial. Lancet 2012.

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. The Lancet, Early Online Publication, 9 November 2010 doi:10.1016/S0140-6736(10)60310-8.

Strippoli GF, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ. 2008 Feb 25; [Epub ahead of print] Statins significantly reduce lipid concentrations and cardiovascular end points in patients with chronic kidney disease, irrespective of stage of disease, but no benefit on all cause mortality or the role of statins in primary prevention has been established. Reno-protective effects of statins are uncertain because of relatively sparse data and possible outcomes reporting bias.

Sunman H, Canpolat U, Sahiner L, Aytemir K. Use of Fenofibrate During the First Trimester of Unplanned Pregnancy in a Patient with Hypertriglyceridemia (February). Ann Pharmacother. 2012 Jan 17.

Taylor AJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004 Dec 7;110(23):3512-7. Epub 2004 Nov 10. Erratum in: Circulation. 2004 Dec 7;110(23):3615. Circulation. 2005 Jun 21;111(24):e446.

Taylor AJ, Villines TC, Stanek EJ, et al. Extended-Release Niacin or Ezetimibe and Carotid Intima-Media Thickness. (ARBITER 6-HALTS) N Engl J Med. 2009 Nov 15. [Epub ahead of print].

Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub4. Although reductions in all-cause mortality, composite endpoints and revascularisations were found with no excess of adverse events, there was evidence of selective reporting of outcomes, failure to report adverse events and incl with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.

TOP

Tenkanen L, et al. Gemfibrozil in the Treatment of Dyslipidemia: An 18-Year Mortality Follow-up of the Helsinki Heart Study. (HHS) Arch Intern Med. 2006 Apr 10;166(7):743-8.
Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary Prevention of Cardiovascular Diseases With Statin Therapy: A Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2006 Nov 27;166(21):2307-13. Subjects taking statins for a mean of 4.3 years (n=42 848) had a lower incidence of heart attack, stroke, revascularization, and other events than controls. The authors estimate the following numbers needed to treat for 4.3 years: 60, to prevent one major coronary event; 268 for stroke; 61 for nonfatal myocardial infarction and 93 for revascularization. In patients without CV disease, statin therapy decreases the incidence of major coronary and cerebrovascular events and revascularizations but not coronary heart disease or overall mortality.
Tirosh A, Rudich A, Shochat T, et al. Changes in triglyceride levels and risk for coronary heart disease in young men. Ann Intern Med. 2007 Sep 18;147(6):377-85. Summary for patients in: Ann Intern Med. 2007 Sep 18;147(6):I45. Two triglyceride measurements obtained 5 years apart may assist in assessing CHD risk in young men. A decrease in initially elevated triglyceride levels is associated with a decrease in CHD risk compared with stable high triglyceride levels. However, this risk remains higher than in those with persistently low triglyceride levels.
Tleyjeh IM, Kashour T, Hakim FA, et al. Statins for the prevention and treatment of infections: a systematic review and meta-analysis. Arch Intern Med. 2009 Oct 12;169(18):1658-67.
Tobe SW, Stone JA, Brouwers M, et al. Harmonization of guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE Initiative. CMAJ. 2011 Sep 12.
Toleikyte I, Retterstøl K, Leren PT, Iversen PO. Pregnancy outcomes in familial hypercholesterolemia: a registry-based study. Circulation. 2011; 124:1606 –1614.
Tonelli Marcello, Lloyd Anita, Clement F, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. CMAJ October 11, 2011 cmaj.101280; published ahead of print October 11, 2011, doi:10.1503/cmaj.101280
Tonkin AM, et al J; LIPID Study Group. Cost-effectiveness of cholesterol-lowering therapy with pravastatin in patients with previous acute coronary syndromes aged 65 to 74 years compared with younger patients: results from the LIPID study. Am Heart J. 2006 Jun;151(6):1305-12. (InfoPOEMs: From the viewpoint of a health system, it is cost-effective to treat high-risk patients older than 65 years with pravastatin (Pravachol) no matter what their level of initial cholesterol level. The increased cost of treatment is partially offset by savings in other areas. This analysis did not take into account any effect on the quality of the life extension by pravastatin. (LOE = 2c))
Tsivgoulis G, et al. Presymptomatic neuromuscular disorders disclosed following statin treatment. Arch Intern Med. 2006 Jul 24;166(14):1519-24.
Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010 May 8;375(9726):1634-9.
Vale N, Nordmann AJ, Schwartz GG, et al. Statins for acute coronary syndrome. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD006870. DOI: 10.1002/14651858.CD006870.pub2. Based on available evidence, initiation of statin therapy within 14 days following ACS does not reduce death, myocardial infarction, or stroke up to four months, but reduces the occurrence of unstable angina at four months following ACS.
Van den Hoek HL, Bos WJW, De Boer A, van de Garde EMW. Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials. BMJ 2011;343:d7281.
Vandermeer ML et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis. 2012 Jan;205(1):13-9.
Varbo A, Nordestgaard BG, Tybjaerg-Hansen A, et al. Nonfasting triglycerides, cholesterol, and ischemic stroke in the general population. Ann Neurol. 2011 Feb 18. doi: 10.1002/ana.22384.
Venkitachalam L, Wang K, Porath A, et al on behalf of the REACH Registry Investigators. Global variation in the prevalence of elevated cholesterol in outpatients with established vascular disease or 3 cardiovascular risk factors according to national indices of economic development and health system performance. Circulation 2012.
Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort (8.5yr) study. BMJ. 2008 Nov 11;337:a2423. doi: 10.1136/bmj.a2423. In January 1990, 413 (21%) of the patients had started statin treatment, and during follow-up another 1294 patients (66%) started after a mean delay of 4.3 years. Most patients received simvastatin (n=1167, 33 mg daily) or atorvastatin (n=211, 49 mg daily). Lower statin doses than those currently advised reduced the risk of coronary heart disease to a greater extent than anticipated in patients with familial hypercholesterolaemia. With statin treatment, such patients no longer have a risk of myocardial infarction significantly different from that of the general population.
Vesper HW, Kuiper HC, Mirel LB, Johnson CL, Pirkle JL. Levels of plasma trans-fatty acids in non-Hispanic white adults in the United States in 2000 and 2009. JAMA. 2012 Feb 8;307(6):562-3.
Viljoen A, Wierzbicki AS. Investigating mixed hyperlipidaemia. BMJ. 2011 Aug 25;343:d5146.
Villines TC, Stanek EJ, Devine PJ, et al. The ARBITER-6 HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6—HDL and LDL Treatment Strategies in Atherosclerosis). J Am Coll Cardiol 2010; DOI: 10.1016/j.jacc.2010.03.017.
Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet 2012; published online May 17. (not lower MI risk)
Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, et al. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD006401. Statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. It seems to be safe in the short term but long-term safety is unknown. Children treated with statins should be carefully followed up by their pediatricians. Large long-term randomized controlled trials are needed to establish the long-term safety of statins.
Wagstaff LR, et al. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy. 2003 Jul;23(7):871-80.
Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ. 2007 Sep 22;335(7620):599. Epub 2007 Sep 13. The proposed strategy of screening children and parents for familial hypercholesterolaemia could have considerable impact in preventing the medical consequences of this disorder in two generations simultaneously.
Walldius G, Aastveit AH, Jungner I. Stroke mortality and the apoB/apoA-I ratio: results of the AMORIS prospective study. J Intern Med. 2006 Mar;259(3):259-66.
Wang Z, Zhang Y, Gao M, et al. Statin Therapy for the Prevention of Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials. Pharmacotherapy. 2011 Nov;31(11):1051-62.
Waters DD, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (Treating to New Targets) study. J Am Coll Cardiol. 2006 Nov 7;48(9):1793-9. Epub 2006 Oct 17.
Waters, David D., Ho, Jennifer E., DeMicco, David A., et al. Predictors of New-Onset Diabetes in Patients Treated With Atorvastatin: Results From 3 Large Randomized Clinical Trials (Ideal, TNT,Sparcl). J Am Coll Cardiol 2011 57: 1535-1545.
Watkins Jack L, Atkinson Bradley J, Pagliaro Lance C. Rhabdomyolysis in a Prostate Cancer Patient Taking Ketoconazole and Simvastatin: Case Report and Review of the Literature. 1 February 2011, DOI 10.1345/aph.1P433. Ann Pharmacother ;45:e9.
Waubant E, Pelletier D, Mass M, et al. behalf of the ITN STAyCIS Study Group; ITN020AI Study Management Team. Randomized controlled trial of atorvastatin in clinically isolated syndrome: The STAyCIS study. Neurology. 2012 Apr 10;78(15):1171-1178.
Welsh JA, Sharma A, Abramson JL, et al. Caloric sweetener consumption and dyslipidemia among us adults. *JAMA* 2010; 303:1490-1497.
West AM, Anderson JD, Meyer CH, et al. The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline. Atherosclerosis 2011; DOI:10.1016/j.atherosclerosis.2011.04.005.
Westover M. Brandon; Bianchi Matt T.; Eckman Mark H.; et al. Statin Use Following Intracerebral Hemorrhage: A Decision Analysis. *Arch Neurol.* 2011;0(2011):archneurol.2010.356.
Wiegman A, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. JAMA. 2004 Jul 21;292(3):331-7.
Winchester DE, Wen X, Xie L, et al. Evidence of pre-procedural statin therapy (PCI, CABG) a meta-analysis of randomized trials. J Am Coll Cardiol. 2010 Sep 28;56(14):1099-109. Epub 2010 Aug 31.
Wojnicz R, et al. Usefulness of atorvastatin in patients (n=74) with heart failure due to inflammatory dilated cardiomyopathy and elevated cholesterol levels. Am J Cardiol. 2006 Mar 15;97(6):899-904. Epub 2006 Feb 3.
Wolk A, et al. Long-term fatty fish consumption and renal cell carcinoma incidence in women. JAMA. 2006 Sep 20;296(11):1371-6. Our study suggests that consumption of fatty fish may reduce the occurrence of renal cell carcinoma in women.
Wongwiwatthananukit S, et al. Efficacy and Safety of Rosuvastatin 10mg Every Other Day Compared with 10mg Once Daily in Patients with Hypercholesterolemia (November). Ann Pharmacother. 2006 Sep 26; [n=80 8week]
Wyman M, Lenoard M, Morledge T. Coenzyme Q10: A therapy for hypertension and statin-induced myalgia? Cleveland Clinic Journal of Medicine 2010; 77(7):435-442; doi:10.3949/ccjm.77a.09078
Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q(10) 200mg/d supplementation on simvastatin-induced myalgia. Am J Cardiol. 2007 Nov 1;100(9):1400-3. Epub 2007 Aug 16. n=44 12weeks In conclusion, coenzyme Q(10) supplementation did not improve statin tolerance or myalgia, although further studies are warranted.
Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011; DOI:10.1016/ S0140-6736(11)61215-4.
Zhao YY, Weir MA, Manno M, et al. New fibrate use and acute renal outcomes in elderly adults: a population-based study. Ann Intern Med. 2012 Apr 17;156(8):560-9.
Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. Am Heart J. 2006 Feb;151(2):273-81. (InfoPOEMs: The overall effectiveness of statin therapy on the most important outcomes -- decreasing mortality, heart attacks, and strokes -- is not different among the 3 major statins. These are the results from a meta-analysis; no study has directly compared equivalent doses of 2 statins. (LOE = 1a))

TOP

References: RxFiles Post-MI

[1] Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (STEMI); A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004 Aug 4;44(3):E1-E211. http://www.acc.org/clinical/guidelines/stemi/index.pdf
Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). *Circulation* 2007; DOI: 10.1161/CIRCULATIONAHA.107.188209. Available at: http://circ.ahajournals.org. *J Am Coll Cardiol* 2007: DOI:10.1016/j.jacc.2007.10.001. Available at: http://content.onlinejacc.org. http://content.onlinejacc.org/cgi/content/full/j.jacc.2007.10.001v1
Kushner, Frederick G., Hand, Mary, Smith, Sidney C., et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009 0: j.jacc.2009.10.015 http://content.onlinejacc.org/cgi/reprint/j.jacc.2009.10.015v1.pdf

[2] Yusuf S, Sleight P, Pogue J, et al., The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, Effects of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. N Engl J Med 2000 342: 145-153.

[3] Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993 Oct 2;342(8875):821-8.

[4] Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995 Dec 21;333(25):1670-6.

[5] GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet. 1994 May 7;343(8906):1115-22.

[6] Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999 Dec 7;100(23):2312-8.

[7] The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003; 362: 782-88.

[8] Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) N Engl J Med. 1992 Sep 3;327(10):678-84.

[9] Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992 Sep 3;327(10):669-77.

[10] ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet. 1995 Mar 18;345(8951):669-85.

[11] Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.

[12] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan in Acute Myocardial Infarction Trial Investigators (VALIANT). Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003 Nov 13;349(20):1893-906. Epub 2003 Nov 10. (McMurray J, et al. The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol. 2006 Feb 21;47(4):726-33. Epub 2006 Jan 26.) (McMurray J, et al. The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol. 2006 Feb 21;47(4):726-33. Epub 2006 Jan 26.)
Califf RM, Lokhnygina Y, Velazquez EJ, McMurray JJ, et al. Usefulness of beta blockers in high-risk patients after myocardial infarction in conjunction with captopril and/or valsartan (from the VALsartan In Acute Myocardial Infarction [VALIANT] trial). Am J Cardiol. 2009 Jul 15;104(2):151-7. Epub 2009 Jun 3. PubMed PMID: 19576338. In conclusion, no evidence was found of adverse interactions between the angiotensin-receptor blocker valsartan and beta blockers or of a negative effect of the combination of valsartan, captopril, and beta blockers.

[13] Granger CB, McMurray JJ, Yusuf S, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003 Sep 6;362(9386):772-6. (Granger BB, et al.; for the CHARM investigators. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet. 2005 Dec 10;366(9502):2005-2011.)

[14] McMurray JJ, Ostergren J, Swedberg K,et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003 Sep 6;362(9386):767-71. (McMurray JJ, Young JB, Dunlap ME, et al. **Relationship of dose** of background angiotensin-converting enzyme inhibitor to the benefits of candesartan in Candesartan in Heart failure: Assessment of reduction in Mortality and morbidity (CHARM)-added trial. American Heart Journal 2006;151: 992-998)

[15] Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes (IRMA II). Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. N Engl J Med 2001 Sep 20;345(12):870-8.

[16] Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes (IDNT); Collaborative Study Group. N Engl J Med 2001 Sep 20;345(12):851-60.

[17] Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy; RENAAL Study Investigators. N Engl J Med 2001 Sep 20;345(12):861-9.

[18] Cicardi M, Zingale LC, Bergamaschini L, et al. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med. 2004 Apr 26;164(8):910-3.

[19] Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan.; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Lancet 2002 Sep 7;360(9335):752-60.

[20] Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction: a double blind randomised trial. *Lancet* 1981;ii:823-7.

[21] Janosi A, Ghali JK, Herlitz J, et al.; MERIT-HF Study Group. Metoprolol CR/XL in postmyocardial infarction patients with chronic heart failure: experiences from MERIT-HF. Am Heart J. 2003 Oct;146(4):721-8.

[22] Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA. 2000 Mar 8;283(10):1295-302.

[23] Gullestad L, Wikstrand J, et al.; for the MERIT-HF Study Group. What resting heart rate should one aim for when treating patients with heart failure with a beta-blocker? Experiences from the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). J Am Coll Cardiol. 2005 Jan 18;45(2):252-9.

[24] Deedwania PC, et al. MERIT-HF Study Group. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. Am Heart J. 2005 Jan;149(1):159-67.

[25] Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet. 1986 Jul 12;2(8498):57-66.

[26] Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001 May 5;357(9266):1385-90.

[27] A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA. 1982 Mar 26;247(12):1707-14.

[28] Pedersen TR. The Norwegian Multicenter Study of Timolol after Myocardial Infarction. Circulation. 1983 Jun;67(6 Pt 2):I49-53.

[29] Boissel JP, Leizorovicz A, Picolet H, et al. Efficacy of acebutolol after acute myocardial infarction (APSI trial). The APSI Investigators. Am J Cardiol. 1990 Sep 25;66(9):24C-31C.

[30] Freemantle N, Cleland J, Young P, et al. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999 Jun 26;318(7200):1730-7.

[31] Which Beta-blocker. Med Lett 2001;43:9-11. & Drugs for Hypertension, Treatment Guidelines from the Medical Letter 2003; Vol 1 (Issue 6) 33-40.

[32] Ko DT, Hebert PR, Coffey CS, et al. Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. Arch Intern Med. 2004 Jul 12;164(13):1389-94.

[33] Chen ZM, Pan HC, Chen YP, et al.; **COMMIT** (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5;366(9497):1622-32. Second Chinese Cardiac Study COMMIT/CCS-2. Mean age 61, Fibrinolytic therapy 54%, Metoprolol 5mg IV over 2-3mins x 3 if HR & BP ok, then 15mins later 50mg po q6h Day 0-1, then 200mg controlled release od vs placebo x ~15days. ↓Reinfarction 2 vs 2.5%, ↓Ventricular fibrilation 2.5 vs 3 %, BUT ↑Cardiogenic shock 5 vs 3.9% (risk more with heart failure, systolic BP <120 & in the first 24hrs). INTERPRETATION: The use of early beta-blocker therapy in acute MI reduces the risks of reinfarction & ventricular fibrillation, but increases the risk of cardiogenic shock, esp. during the first day or so after admission. Consequently, it might generally be prudent to consider starting **beta-blocker therapy in hospital only when the haemodynamic condition after MI has stabilised**. (InfoPOEMs: The early use of metoprolol in patients with acute myocardial infarction who are also receiving thrombolytics and aspirin provides no short-term benefit compared with placebo. Since the early use, however, increases the risk of cardiogenic shock, it may be wise to delay starting metoprolol until the patient is hemodynamically stable. (LOE = 1b)).

[34] Borrello F, Beahan M, Klein L, et al. Reappraisal of beta-blocker therapy in the acute and chronic post-myocardial infarction period. Rev Cardiovasc Med. 2003;4 Suppl 3:S13-24.

[35] Poole-Wilson PA, Swedberg K, Cleland JG, et al.; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003 Jul 5;362(9377):7-13. (Metra M, Torp-Pedersen C, Swedberg K, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J. 2005 Nov;26(21):2259-68. Epub 2005 Jul 21.)

[36] Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.

[37] Heart Protection Study Group.MRC/BHF HPS study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-22.

[38] Peter S Sever, Björn Dahlöf et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial Lancet 2003; 361: 1149-58. Online April 2, 2003. {RxFiles Q&A Summary: http://www.rxfiles.ca/acrobat/Lipid-Q&A-ASCOT.pdf }

[39] Cannon C, Braunwald E, McCabe C, et al. Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE IT-TIMI 22). New Engl J Med 2004; 350. Online April 8, 2004. {RxFiles Q&A Summary: http://www.rxfiles.ca/acrobat/Lipid-Q&A-Prove-It.pdf }

[40] Schwartz G, Olsson A, Ezekowitz M, Ganz P, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes (MIRACL). JAMA 2001;285:1711-8.

[41] Long-Term Intervention with Pravastatin in Ischeamic Heart Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339:1349-1357.

[42] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels (CARE). N Engl J Med 1996;335:1001-9.

[43] Carswell CI, Plosker GL, Jarvis B. Rosuvastatin. Drugs. 2002;62(14):2075-85; discussion 2086-7.
Ridker PM, Danielson E, Fonseca FA, Genest J, et al. the JUPITER Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med. 2008 Nov 9. [Epub ahead of print] In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

[44] Rosuvastatin--a new lipid-lowering drug. Med Lett Drugs Ther. 2003 Oct 13;45(1167):81-3.

[45] Shepherd J, Blauw GJ, Murphy MB, et al.; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623-30.

[46] NCEP Expert Panel. Executive summary-3rd national cholesterol education program on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-97. Grundy SM, Cleeman JI, Merz CN, et al.; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13;110(2):227-39. http://www.acc.org/clinical/adoptions/ncep_report.pdf

[47] Bloomfield Rubins A, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol (VA-HIT). N Engl J Med 1998; 339:1349-57.

[48] Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet. 1988 Aug 13;2(8607):349-60. Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. BMJ. 1998 May 2;316(7141):1337-43.
Berger JS, Stebbins A, Granger CB, et al. Initial Aspirin Dose and Outcome Among ST-Elevation Myocardial Infarction Patients Treated With Fibrinolytic Therapy. Circulation. 2007 Dec 17; [Epub ahead of print] These data suggest that an initial dose of 162 mg aspirin may be as effective as and perhaps safer than 325 mg for the acute treatment of ST-elevation myocardial infarction.

[49] Hirsh J, Guyatt G, Albers GW, et al. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. Chest. 2004 Sep;126(3 Suppl):172S-3S. (see also ACCP Antithrombotic and Thrombolytic 8th Edition 2008).

[50] RxFiles Oral Antiplatelet & Antithrombotic Comparison Chart http://www.rxfiles.ca/acrobat/cht-AntiThrombotics.pdf

[51] Yusuf S et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation (Clopidogrel in unstable angina to prevent recurrent events (CURE). N Engl J Med 2001; 345: 494-502. Mean age 64, Major bleed 3.7 vs 2.7 %, (Budaj A, Yusuf S, Mehta SR, et al.; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation. 2002 Sep 24;106(13):1622-6.)

[52] CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel vs aspirin in patients at risk of ischemic events (CAPRIE). Lancet 1996; 348:1329-39.

[53] Sabatine MS, et al. Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation (CLARITY-TIMI 28). N Engl J Med. 2005 Mar 9; [Epub] (N=3491,Groups: Plavix 300mg x1 then 75mg od (median **4 doses** given) until angiography vs placebo had 30 day mortality of less than 5%, age <75yr Mean age 57, >2/3 of pts fibrin specific lytic, excluded high bleeding risk pts (1.9 vs 1.7% major bleeds), few CABG performed, thus select pts were studied, mechanism may be to prevent reocclusion) (InfoPOEMs: Adding clopidogrel to aspirin and fibrinolytic therapy during the first week in patients with ST- segment elevation myocardial infarction reduces the likelihood of recurrent myocardial infarction and ischemia leading to revascularization over a 30-day period (number needed to treat = 15). The short-term risk of major bleeding was low. This trial does not address how long patients should continue to take clopidogrel after the first week of treatment. (LOE = 1b)) (Sabatine MS, Cannon CP, Gibson CM, et al.; Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the **PCI-CLARITY** study. JAMA. 2005 Sep 14;294(10):1224-32. CONCLUSIONS: Clopidogrel pretreatment significantly reduces the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding. These data add further support to the early use of clopidogrel in STEMI and the strategy of routine clopidogrel pretreatment in patients undergoing PCI).

[54] Chen ZM, Jiang LX, Chen YP, et al. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5;366(9497):1607-21. COMMIT/CCS-2 trial (Mean age 61, n=45,852, <24hr since MI symptom onset, primary PCI or high risk bleeding were excluded, 54% rec'd thrombolysis (primarily non fibrin specific: urokinase) , & <5% went on to have angiography, Plavix 75mg od (no loading dose) + ASA162mg od vs ASA 162mg od for a **mean of 15 days**, Death/MI/stroke 9.2 vs 10.1%, Death 7.5 vs 8.1%, Major Bleeding both equal ~0.6%, Minor bleeds 3.6 vs 3.1%). INTERPRETATION: In a wide range of patients with acute MI, adding clopidogrel 75 mg daily to aspirin and other standard treatments (such as fibrinolytic therapy) safely reduces mortality and major vascular events in hospital, and should be considered routinely.

[55] Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. (WARIS-II) N Engl J Med. 2002 Sep 26;347(13):969-74.

[56] Antithrombotic Trialists' Collaboration (ATC). Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86.

[57] Hayden M, Pignone M, Phillips C, et al. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002 Jan 15;136(2):161-72.

[58] Diener HC, Bogousslavsky J, Brass LM, et al.; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004 Jul 24;364(9431):331-7.

[59] Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). Am J Cardiol. 1996 Oct 15;78(8):902-7.
Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999 Sep 2;341(10):709-17.
Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004 Aug 5;351(6):543-51.

[60] Pitt B, Remme W, Zannad F, et al.; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. (EPHESUS) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003 Apr 3;348(14):1309-21.

[61] Yusuf S., Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004 (online version published Sept 3,2004)

[62] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, & Treatment of High Blood Pressure (The JNC 7); JAMA. 2003 May;289(19):2560-72. (Complete report in Hypertension 2003;42:1206-1252)

TOP

[63] Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004 Sep 23;351(13):1285-95. (Anand IS, Kuskowski MA, Rector TS, et al. Anemia & change in hemoglobin over time related to mortality & morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation. 2005 Aug 23;112(8):1121-7. Epub 2005 Aug 15.) Silletta MG, Marfisi R, Levantesi G, et al.; on behalf of the GISSI-Prevenzione Investigators. Coffee Consumption and Risk of Cardiovascular Events After Acute Myocardial Infarction. Results From the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione Trial. Circulation. 2007 Dec 3; [Epub ahead of print] No association between moderate coffee intake and cardiovascular events was observed in post-myocardial infarction patients.

[64] The 2010 Canadian Hypertension Education Program Recommendations www.hypertension.ca (Khan NA, McAlister FA, Campbell NR, Feldman RD, et al.; Canadian Hypertension Education Program. The 2004 Canadian recommendations for the management of hypertension: Part II--Therapy. Can J Cardiol. 2004 Jan;20(1):41-54.)
Canadian Hypertension Education Program. 2011 CHEP recommendations for the management of hypertension. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf

[65] Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol. 2009 Oct;25(10):567-79. McPherson R, Frohlich J, Fodor G, Genest J. Canadian 2006 Cardiovascular Society position statement -- Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol. 2006 Sep;22(11):913-27. (Genest J, Frohlich J, Fodor G, et al.; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the Canadian 2003 update. CMAJ. 2003 Oct 28;169(9):921-4. http://www.cmaj.ca/cgi/data/169/9/921/DC1/1 Full Report.)
Canadian Hypertension Education Program. 2011 CHEP recommendations for the management of hypertension. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf

[66] **Canadian 2008 Guidelines (Sept 2008)**: http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
Canadian 2003 Diabetes Guidelines http://www.diabetes.ca/cpg2003/download.aspx Harris SB, Lank CN. Recommendations from the Canadian Diabetes Association. 2003 guidelines for prevention and management of diabetes and related cardiovascular risk factors. Can Fam Physician. 2004 Mar;50:425-33. (Meltzer S, Leiter L, Daneman D, et al 1998. Clinical practice guidelines for the management of diabetes in Canada. CMAJ 1998;159 (8 Suppl)).

NOTE: Additional RxFiles Related Materials & Drug Comparison Charts: see www.RxFiles.ca {eg. Lipid Landmark Trials; Comparison Charts: ACEI, Beta-Blocker, Antithrombotic, Lipid Lowering}

Additional refs:

ACCF/AHA 2011 Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011 0: j.jacc.2011.02.009. http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.02.009v1.pdf

Adabag AS, Therneau TM, Gersh BJ, Weston SA, Roger VL. Sudden death after myocardial infarction. JAMA. 2008 Nov 5;300(17):2022-9. The risk of sudden cardiac death following MI in community practice has declined significantly over the past 30 years. Sudden cardiac death is independently associated with heart failure but not with recurrent ischemia.

AHA Writing Group Members, Roger VL, Go AS, Lloyd-Jones DM, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Roger VL, Turner MB; On behalf of the American Heart Association Heart Disease and Stroke Statistics Writing Group. Executive Summary: Heart Disease and Stroke Statistics—2011 Update: A Report From the American Heart Association. Circulation. 2011 Feb 1;123(4):459-463.

Akpek M, Kaya MG, Lam YY, et al. Relation of Neutrophil/Lymphocyte Ratio to Coronary Flow to In-Hospital Major Adverse Cardiac Events in Patients With ST-Elevated Myocardial Infarction Undergoing Primary Coronary Intervention. Am J Cardiol. 2012 May 17.

Aldous SJ, Richards M, Cullen L et al. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. CMAJ. 2012 Mar 20;184(5):E260-8.

Alpert JS, Thygesen K, Jaffe A, White HD. The universal definition of myocardial infarction: a consensus document: ischaemic heart disease. Heart. 2008 Oct;94(10):1335-41.

Akesson A, Weismayer C, Newby PK, et al. Combined effect of low-risk dietary and lifestyle behaviors in primary prevention of myocardial infarction in women. Arch Intern Med 2007; 167:2122-2127.

Amin AP, Salisbury AC, McCullough PA, et al. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. Arch Intern Med. 2012;172(3):246-253.

Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs & risk of acute myocardial infarction. Circulation. 2006 Apr 25;113(16):1950-7. Epub 2006 Apr 17. Current use of etoricoxib was associated with a 2.09-fold (95% confidence interval [CI], 1.10 to 3.97) risk of AMI compared with no use of NSAIDs during the prior year. Current use of rofecoxib (RR=1.29; 95% CI, 1.02 to 1.63), celecoxib (RR=1.56; 95% CI, 1.22 to 2.00), and diclofenac (RR=1.37; 95% CI, 1.17 to 1.59) also significantly increased the AMI risk. For current use of valdecoxib, the RR was 4.60 (95% CI, 0.61 to 34.51). RRs appeared to increase with higher daily doses of COX-2 inhibitors and were also increased in patients without major cardiovascular risk factors.

Antman EM, et al. Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction. (EXTRACT-TIMI 25)N Engl J Med. 2006 Mar 20; [Epub ahead of print] Conclusions In patients receiving fibrinolysis for ST-elevation myocardial infarction, treatment with enoxaparin throughout the index hospitalization is superior to treatment with unfractionated heparin for 48 hours but is associated with an increase in major bleeding episodes. (InfoPOEMs: For every 1000 patients treated with enoxaparin instead of unfractionated heparin there were 15 fewer nonfatal myocardial infarctions (MIs), 7 fewer urgent revascularizations, and 6 fewer deaths, but there were 4 additional episodes of nonfatal major bleeding. (LOE = 1b))

Andraws R, Berger JS, Brown DL. Effects of antibiotic therapy on outcomes of patients with coronary artery disease. A meta-analysis of randomized controlled trials. JAMA 2005;293:2641-47. (InfoPOEMs: Antibiotic therapy is no more effective than placebo in reducing the morbidity or mortality in patients with acute coronary syndromes. (LOE = 1a-))

Apple FS. Edging closer to early optimal patient management with high-sensitivity cardiac troponin assay. Circulation. 2011 Jul 12;124(2):127-9.

Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. Eur Heart J. 2006 Jun 6; [Epub ahead of print]

Armstrong PW, Boden WE. Reperfusion Paradox in ST-Segment Elevation Myocardial Infarction. Ann Intern Med. 2011 Sep 20;155(6):389-91.

Antoniou T, Gomes T, Mamdani MM, et al. Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: nested case-control study. BMJ. 2011 Sep 12;343:d5228. doi: 10.1136/bmj.d5228.

Aslibekyan S, Levitan EB, Mittleman MA. Prevalent cocaine use and myocardial infarction. Am J Cardiol. 2008 Oct 15;102(8):966-9. Epub 2008 Aug 5.

Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet. 2006 Feb 18;367(9510):569-78.

Assmus B, et al. Transcoronary transplantation of progenitor cells after myocardial infarction. N Engl J Med. 2006 Sep 21;355(12):*1222-32.*

Atzema CL, Austin PC, Huynh T, Hassan A, Chiu M, Wang JT, Tu JV. Effect of marriage on duration of chest pain associated with acute myocardial infarction before seeking care. CMAJ. 2011 Jul 18.

Aversano T et al. Outcomes of PCI at hospitals with or without on-site cardiac surgery. (CPORT) N Engl J Med 2012 Mar 25.

Bandosz P, O'Flaherty M, Drygas W, et al. Decline in mortality from coronary heart disease in Poland after socioeconomic transformation: modelling study. BMJ 2012;344:d8136.

Banerjee A, Silver LE, Heneghan C, et al. Relative familial clustering of cerebral versus coronary ischemic events. Circ CardiovascGenet 2011; DOI:10.1161/CIRCGENETICS.110.959114. (for MI but not stroke)

Bangalore Sripal, Kumar Sunil, Wetterslev Jørn, et al. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147,020 patients from randomised trials. BMJ 2011;342:doi:10.1136/bmj.d2234 (26 April 2011). –no ↑ MI.

Bangalore S, Fonarow GC, Peterson ED, et al. Age and gender differences in quality of care and outcomes for patients with ST-segment elevation myocardial infarction. Am J Cardiol 2012.

Beavers Craig James, Dunn Steven P, Macaulay Tracy E. The Role of Angiotensin Receptor Blockers in Patients with Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema. Articles Ahead of Print published on 1 April 2011, DOI 10.1345/aph.1P630. Ann Pharmacother ;45:520-524.

Bell Alan D., Roussin André, Cartier Raymond, et al. The Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society (CCS) Guidelines. The Canadian journal of cardiology 1 May 2011 volume 27 issue 3 Pages S1-S59.

Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. JAMA 2009; 302:874-882. Sex-based differences existed in 30-day mortality among patients with ACS and vary depending on clinical presentation. However, these differences appear to be largely explained by clinical differences at presentation and severity of angiographically documented disease.

Berry JD et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012 Jan 26; 366:321.

Berton G, Cordiano R, Cavuto F, et al. Predictors of Ten-Year Event-Free Survival in Patients With Acute Myocardial Infarction (from the Adria, Bassano, Conegliano, and Padova Hospitals [ABC] Study on Myocardial Infarction). Am J Cardiol. 2012 Jan 3.

Bhaskaran K., Hajat S., Haines A., et al.. Short term effects of temperature on risk of myocardial infarction in England and Wales: time series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry. BMJ 2010;341:c3823, doi: 10.1136/bmj.c3823 (Published 10 August 2010).

Bhaskaran K, Hajat S, Armstrong B, Haines A, Herrett E, Wilkinson P, et al. The effects of hourly differences in air pollution on the risk of myocardial infarction: case crossover analysis of the MINAP database. BMJ 2011;343:d5531.

Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. N Engl J Med. 2006 Mar 12; (Charisma) [Epub ahead of print] (InfoPOEMs: The use of the combination of clopidogrel (Plavix) and aspirin should be limited to carefully defined groups of patients with acute coronary syndromes. It is not recommended for the broader group of patients with coronary disease, cerebrovascular disease, or multiple risk factors such as diabetes, hyperlipidemia, & hypertension. (LOE = 1b))

Bjorck Lena; Wallentin Lars; Stenestrand Ulf; et al. Medication in Relation to ST-Segment Elevation Myocardial Infarction in Patients With a First Myocardial Infarction: Swedish Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). Arch Intern Med. 2010;170(15):1375-1381.

Blackshear JL, Cutlip DE, Roubin GS, et al. for the CREST Investigators. Myocardial Infarction After Carotid Stenting and Endarterectomy: Results From the Carotid Revascularization Endarterectomy Versus Stenting Trial. Circulation. 2011 Jun 7;123(22):2571-2578.

Boden WE, O'rourke RA, Teo KK, Hartigan PM, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. COURAGE Trial Research Group. N Engl J Med. 2007 Mar 26; [Epub ahead of print] As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy. PCI does not lower the rates of myocardial infarction or death in patients with stable coronary artery disease who receive optimal medical treatment, a large trial concluded. The study, released early online by NEJM, randomized nearly 2300 patients either to PCI with optimal medical therapy (intensive pharmacologic treatment plus lifestyle intervention) or to optimal medical therapy alone. After a median follow-up of almost 5 years, 19% in the PCI group died or had MIs, compared with 18.5% who received medical therapy alone. PCI patients were more likely to be free of angina after 1 and 3 years, but there was no significant difference after 5 years. One-third of patients in the medical therapy group ultimately required revascularization, while 21% in the PCI group needed additional revascularization. An editorialist concludes: "Patients whose condition is clinically unstable, who have left main coronary artery disease, or in whom medical therapy has failed to control symptoms remain candidates for revascularization, but PCI should not play a major role as part of a secondary prevention strategy."

Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol. 2011 Sep 20;58(13):1332-9.

Boersma E; The Primary Coronary Angioplasty vs. Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J. 2006 Apr;27(7):779-88. Epub 2006 Mar 2.

Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 2011; published online Nov 14. DOI:10.1016/S0140- 6736(11)61590-0.

Bolland Mark J, Avenell Alison, Baron John A, et al, Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691, doi: 10.1136/bmj.c3691 (Published 29 July 2010).

Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011; DOI: doi:10.1136/bmj.d2040.

Bonaca MP, Wiviott SD, Braunwald E, et al. American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation Universal Definition of Myocardial Infarction Classification System and the Risk of Cardiovascular Death: Observations From the TRITON-TIMI 38 Trial (Trial to Assess Improvement *in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38). Circulation. 2012 Jan 31;125(4):577-83.*

Bonnefoy E, Steg PG, Boutitie F, et al. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. Eur Heart J. 2009 Jul;30(13):1598-606. Epub 2009 May 8. The 5-year follow-up is consistent with the 30-day outcomes of the trial, showing similar mortality for primary percutaneous coronary intervention and a policy of pre-hospital lysis followed by transfer to an interventional center. In addition, for patients treated within 2 h of symptom onset, 5-year mortality was lower with pre-hospital lysis.

Bradley EH, et al. Strategies for Reducing the Door-to-Balloon Time in Acute Myocardial Infarction. N Engl J Med. 2006 Nov 13; [Epub ahead of print]

Bradley EH, Curry LA, Spatz ES, et al. Hospital strategies for reducing risk-standardized mortality rates in acute myocardial infarction. Ann Intern Med. 2012;156:618-26.

Bradshaw PJ, et al. Validity of the GRACE (Global Registry of Acute Coronary Events) acute coronary syndrome prediction model for six month post-discharge death in an independent data set. Heart. 2006 Jul;92(7):905-9. Epub 2005 Dec 30.

Brauer R, Douglas I, Smeeth L. The association between antipsychotic agents and the risk of myocardial infarction: a systematic review. Br J Clin Pharmacol. 2011 Dec;72(6):871-8. doi: 10.1111/j.1365-2125.2011.04043.x.

Brener SJ, Mehran R, Dressler O et al. Diabetes Mellitus, Myocardial Reperfusion, and Outcome in Patients With Acute ST-Elevation Myocardial Infarction Treated With Primary Angioplasty (from HORIZONS AMI). Am J Cardiol. 2012 Jan 12.

Bretler DM, Hansen PR, Sørensen R, et al. Discontinuation of hormone replacement therapy after myocardial infarction and short term risk of adverse cardiovascular events: nationwide cohort study. BMJ. 2012 Mar 27;344:e1802.

Briffa T, Hickling S, Knuiman M, et al. Long term survival after evidence based treatment of acute myocardial infarction and revascularisation: follow-up of population based Perth MONICA cohort, 1984-2005. BMJ. 2009 Jan 26;338:b36. doi: 10.1136/bmj.b36. The improving trends in 12 year survival after a definite acute myocardial infarction are associated with progressive use of evidence based treatments during the initial admission to hospital and in the 12 months after the event. These changes in the management of acute myocardial infarction are probably contributing to the continuing decline in mortality from coronary heart disease in Australia.

Brugts JJ, Knetsch AM, Mattace-Raso FU, Hofman A, Witteman JC. **Renal function and risk of myocardial infarction** in an elderly population: the Rotterdam Study. Arch Intern Med. 2005 Dec 12-26;165(22):2659-65.

Bucholz EM, Rathore SS, Gosch K, et al. Effect of living alone on patient outcomes after hospitalization for acute myocardial infarction. Am J Cardiol. 2011 Oct 1;108(7):943-8.

Burns JD, Rabinstein AA, Roger VL. Incidence and predictors of myocardial infarction after transient ischemic attack: A population-based study. Stroke. 2001; DOI:10.1161/STROKEAHA.110.593723

Cabello JB, Burls A, Emparanza JI, et al. Oxygen therapy for acute myocardial infarction. Cochrane Database Syst Rev 2010; 6: CD007160.

Canto J G, Rogers W J, Goldberg R J et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA 2012; 307:813-822. (Women under 55 having an MI are more likely to present without chest pain)

Cantor WJ et al. for the TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med 2009 Jun 25; 360:2705. These findings support making every effort to transfer STEMI patients who have received fibrinolytic therapy to a PCI-capable hospital and perform angiography promptly, rather than delaying such action. Critics will wonder (as do the authors) what might have been achieved with a strategy of routine early transfer followed by selective use of angiography, as opposed to the routine transfer-for-angiography strategy studied in this trial. (Verheugt, Freek W.A. Routine Angioplasty after Fibrinolysis -- How Early Should "Early" Be? N Engl J Med 2009 360: 2779-2781)

Canto JG, Kiefe CI, Roger WJ, et al; NRMI Investigators. Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. JAMA. 2011;306(19):2120-2127.

Chan Paul S., Patel Manesh R., Klein Lloyd W., et al. Appropriateness of Percutaneous Coronary Intervention (PCI). JAMA. 2011;306(1):53-61.doi:10.1001/jama.2011.916.

Chen Jersey; Krumholz Harlan M.; Wang Yun; et al. Differences in Patient Survival After Acute Myocardial Infarction by Hospital Capability of Performing Percutaneous Coronary Intervention: Implications for Regionalization. Arch Intern Med. 2010;170(5):433-439.

Chen YL, Chang CL, et al. Major Adverse Upper Gastrointestinal Events in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Coronary Intervention and Dual Antiplatelet Therapy. Am J Cardiol. 2011 Sep 14. (Major GI 10.4% over 4yr)

Cheung NW, Wong VW, McLean M. The hyperglycemia: intensive insulin infusion in infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care. 2006 Apr;29(4):765-70.

Cleland JG, et al.; Cardiac Resynchronization-Heart Failure (CARE-HF) Study. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005 Apr 14;352(15):1539-49. Epub 2005 Mar 7.

Chen J et al. Recent declines in hospitalizations for acute myocardial infarction for Medicare fee-for-service beneficiaries: Progress and continuing challenges. Circulation 2010 Mar 23; 121:1322.

Cheung NW, et al. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care. 2006 Apr;29(4):765-70.

Choudhry NK, Singh JM, Barolet A, Tomlinson GA, Detsky AS. How should patients with unstable angina and non-ST-segment elevation myocardial infarction be managed? A meta-analysis of randomized trials. Am J Med. 2005 May;118(5):465-74 & ACP Journal Club .

Choudhry NK, Patrick AR, Antman EM, et al. Cost-effectiveness of providing full drug coverage to increase medication adherence in post-myocardial infarction Medicare beneficiaries. Circulation 2008; DOI: 10.1161/CIRCULATIONAHA.107.735605.

Choudhry NK, Avorn J, Glynn RJ, et al. Full coverage for preventive medications after myocardial infarction (MI FREE). N Engl J Med 2011. DOI: 10.1056/NEJMsa1107913.

Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007 Dec 15;370(9604):2011-9.

Claessen B, Dangas G, Weisz, et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. Eur Heart J 2012.

TOP

Claeys Marc J.; de Meester Antoine; Convens Carl; et al. Contemporary Mortality Differences Between Primary Percutaneous Coronary Intervention and Thrombolysis in ST-Segment Elevation Myocardial Infarction. Arch Intern Med. 2011;171(6):544-549.

Clifford DM, Fisher SA, Brunskill SJ,et al. Stem cell treatment for acute myocardial infarction. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD006536. DOI: 10.1002/14651858.CD006536.pub3. Despite the high degree of heterogeneity observed, the results of this systematic review suggest that moderate improvement in global heart function is significant and sustained long-term.

Codner P, Vaduganathan M, Rechavia E, et al. Clopidogrel Response Up to Six Months After Acute Myocardial Infarction. Am J Cardiol. 2012 Apr 23.

Collet JP, Montalescot et al. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. J Am Coll Cardiol. 2006 Oct 3;48(7):1326-35. Epub 2006 Sep 14.

Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. (OASIS-5) N Engl J Med. 2006 Mar 14; [Epub ahead of print] Conclusions Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long term mortality and morbidity.

Cooper WO, et al Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med. 2006 Jun 8;354(23):2443-51.

Cristell N, Cianflone D, Durante A, et al. High-sensitivity C-reactive protein (CRP) is within normal levels at the very onset of first ST-segment elevation acute myocardial infarction in 41% of case. J Am Coll Cardiol 2011; 58: 2654-2661.

Crowe E, Lovibond K, Gray H, et al. on behalf of the Guideline Development Group. Early management of unstable angina and non-ST segment elevation myocardial infarction: summary of NICE guidance. BMJ. 2010 Mar 24;340:c1134. doi: 10.1136/bmj.c1134.

Curry Leslie A., Spatz Erica, Cherlin Emily, et al. What Distinguishes Top-Performing Hospitals in Acute Myocardial Infarction Mortality Rates?: A Qualitative Study. *Ann Intern Med* March 15, 2011 154:384-390; doi:10.1059/0003-4819-154-6-201103150-00003

DAD study group. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007; 356: 1723-1735. Increased exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia. We found no evidence of such an association for nonnucleoside reverse-transcriptase inhibitors; however, the number of person-years of observation for exposure to this class of drug was less than that for exposure to protease inhibitors. (23,437 pts followed for a median of 4.5yrs, there were 345 MIs).

Dahabreh Issa J., Paulus Jessica K.. Association of Episodic Physical and Sexual Activity With Triggering of Acute Cardiac Events: Systematic Review and Meta-analysis. JAMA. 2011;305(12):1225-1233.doi:10.1001/jama.2011.336

Dangas George D., Caixeta Adriano, Mehran Roxana, et al., and for the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial Investigators. Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention in Acute Myocardial Infarction. Circulation 123: 1745-1756.

Dangas GD, Caixeta A, Mehran R, et al. Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention (PCI) in Acute Myocardial Infarction. Circulation. 2011 Apr 26;123(16):1745-1756.

Das SR, Alexander K, Chen AY, et al. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50 149 patients with ST-segment elevation myocardial infarction: Results from the NCDR. J Am Coll Cardiol 2011; 58:2642-50.

De Felice Francesco, Fiorilli Rosario, Parma Antonio, et al. Comparison of One-Year Outcome of Patients Aged <75 Years Versus >=75 Years Undergoing 'Rescue' Percutaneous Coronary Intervention, The American Journal of Cardiology, online 24 July 2011.

De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109(10):1223-1225.

De Luca G, Dirksen MT, Spaulding C, et al; DrugEluting Stent in Primary Angioplasty (DESERT) Cooperation. Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Arch Intern Med. 2012;172(8):611-621.

Digoxin (Ahmed A, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J. 2006 Jan;27(2):178-86. Epub 2005 Dec 8. & Adams KF Jr, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol. 2005 Aug 2;46(3):497-504.

De Luca G, Biondi-Zoccai G, Marino P. Transferring patients with ST-segment elevation myocardial infarction for mechanical reperfusion: a meta-regression analysis of randomized trials. Ann Emerg Med. 2008 Dec;52(6):665-76.

de Winter RJ, Windhausen F, Cornel JH, et al. Invasive vs Conservative Treatment in Unstable Coronary Syndromes (ICTUS) Investigators. Early invasive vs selectively invasive management for acute coronary syndromes. N Engl J Med. 2005 Sep 15;353(11):1095-104. (InfoPOEMs: An intensive medical program with selective use of angiography and percutaneous coronary interventions is at least as good as a more aggressive strategy of catheterizing everyone. (LOE = 1b))

Devereaux P.J., Xavier Denis, Pogue Janice, et al, on behalf of the POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and Short-Term Prognosis of Perioperative Myocardial Infarction in Patients Undergoing Noncardiac Surgery: A Cohort Study. Ann Intern Med April 19, 2011 154:523-528.

Diagnosis and Management of Chronic Heart Failure in the Adult: ACC/AHA 2005 Guideline Update for the (J Am Coll Cardiol 2005) http://www.acc.org/clinical/guidelines/failure/index.pdf

Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(suppl):169-73S.

Deyell MW, Buller CE, Miller LH, et al. Impact of national clinical guideline recommendations for revascularization of persistently occluded infarctrelated arteries (OAT trial) on clinical practice in the United States. Arch Intern Med. doi:10.1001/archinternmed.2011.315.

Dodson J,Wang Y, Sarwat C et al. Bleeding Avoidance Strategies and Outcomes in Patients ≥80 Years of Age With ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention (NCDR CathPCI Registry). Am. J Cardiology 2012 2012 Apr 5.

Dunlay SM, Weston SA, Killian JM, et al. Thirty-day rehospitalizations after acute myocardial infarction. A cohort study. Ann Intern Med 2012; 157:11-18.

Dzavik V, et al. Randomized Trial of Percutaneous Coronary Intervention for Subacute Infarct-Related Coronary Artery Occlusion to Achieve Long-Term Patency and Improve Ventricular Function. The Total Occlusion Study of Canada (TOSCA)-2 Trial. Circulation. 2006 Nov 14; [Epub ahead of print] PCI with stenting of a persistently occluded IRA in the subacute phase after MI effectively maintains long-term patency but has no effect on LV ejection fraction. On the basis of these findings and the lack of clinical benefit in the main Occluded Artery Trial, routine PCI is not recommended for stable patients with a persistently occluded IRA after MI.

Edwards M, Chang AM, Matsuura AC, Green M, Robey JM, Hollander JE. Relationship between pain severity and outcomes in patients presenting with potential acute coronary syndromes. Ann Emerg Med. 2011 Dec;58(6):501-7.

Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction: The OASIS-6 Randomized Trial. JAMA. 2006 Mar 14; [Epub ahead of print] CONCLUSION: In patients with STEMI, particularly those not undergoing primary percutaneous coronary intervention, fondaparinux significantly reduces mortality and reinfarction without increasing bleeding and strokes.

Eikelboom JW, et al. Unfractionated & **low-molecular-weight heparin** as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute MI: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67. Epub 2005 Dec 12.

Eisenberg, Afilalo J, Lawler P, et al. Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction. CMAJ 2011. DOI:10.1503/cmaj.100463.

Ekerstad N et al. Frailty Is Independently Associated With Short-Term Outcomes for Elderly Patients With Non-ST-Segment Elevation Myocardial Infarction. Circulation. 2011 Nov 29;124(22):2397-404.

Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L,et al. FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med. 2008 May 22;358(21):2205-17. Neither facilitation of PCI with reteplase plus abciximab nor facilitation with abciximab alone significantly improved the clinical outcomes, as compared with abciximab given at the time of PCI, in patients with ST-segment elevation myocardial infarction.

Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction. The SWISSI II Randomized Controlled Trial. JAMA 2007; 297:1985-1991. Among patients with recent MI, silent myocardial ischemia verified by stress imaging, and 1- or 2-vessel coronary artery disease, PCI compared with anti-ischemic drug therapy reduced the long-term risk of major cardiac events.

Epstein Andrew J., Polsky Daniel, Yang Feifei, et al. Coronary Revascularization Trends in the United States, 2001-2008. JAMA. 2011;305(17):1769-1776.doi:10.1001/jama.2011.551.

Fox KA, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (**GRACE**). BMJ. 2006 Oct 10; [Epub ahead of print]

Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet. 2005 Sep 10-16;366(9489):914-20. (InfoPOEMs: In this study, patients with acute coronary syndromes when managed according to arteriography experience slightly better 5-year mortality rates (P=.054) than those managed conservatively. (LOE = 2b))

Fox KA, Steg PG, Eagle KA, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA. 2007 May 2;297(17):1892-900. In this multinational observational study, GRACE, improvements in the management of patients with ACS were associated with significant reductions in the rates of new heart failure and mortality and in rates of stroke and myocardial infarction at 6 months. In patients with STEMI, hospital deaths decreased by 18 percentage points (95% CI, -5.3 to -1.9) and cardiogenic shock by -24 percentage points (95% CI, -4.3 to -0.5.)

Fox CS, Muntner P, Chen AY, et al. Short-term Outcomes of Acute Myocardial Infarction in Patients with Acute Kidney Injury: A Report from the National Cardiovascular Data Registry. Circulation. 2011 Dec 16.

García Rodriguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. BMJ 2011;343:d4094.

Gast GCM, Pop VJM, Samsioe GN, et al. Vasomotor menopausal symptoms are associated with increased risk of coronary heart disease. Menopause 2011; 18:146-151.

Gelfand JM, et al. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006 Oct 11;296(14):1735-41. Psoriasis may confer an independent risk of MI. The RR was greatest in young patients with severe psoriasis.

Gerber Y, Rosen LJ, Goldbourt U, et al. Smoking status and long-term survival after first acute myocardial infarction. J Am Coll Cardiol 2009; 54:2382-2387.

Gerber Y, Melton LJ, Weston SA, et al. Association between myocardial infarction and fractures. An emerging phenomenon. Circulation 2011;

Gershlick AH, Stephens-Lloyd A, Hughes S, et al.; REACT Trial Investigators. **Rescue angioplasty after failed thrombolytic therapy** for acute myocardial infarction. N Engl J Med. 2005 Dec 29;353(26):2758-68.

Gharacholou S. Michael; Lopes Renato D.; Alexander Karen P.; et al. Age and Outcomes in ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Findings From the APEX-AMI Trial. Arch Intern Med. 2011;171(6):559-567.

Gluckman TJ, Sachdev M, Schulman SP, Blumenthal RS. A simplified approach to the management of non-ST-segment elevation acute coronary syndromes. JAMA 2005; 293:349-57.

Goldberger JJ, Bonow RO, Cuffe M, Dyer A, Rosenberg Y, O'Rourke R, Shah PK, Smith SC Jr; PACE-MI Investigators. beta-Blocker use following myocardial infarction: Low prevalence of evidence-based dosing. Am Heart J. 2010 Sep;160(3):435-442.e1.

Go AS, et al. Atherosclerotic Disease, Vascular Function & Genetic Epidemiology (ADVANCE) Study. Statin & beta-blockers & the initial presentation of coronary heart disease. Ann Intern Med. 2006 Feb 21;144(4):229-38.

Go AS, Yang J, Gurwitz JH, Hsu J, Lane K, Platt R. Comparative effectiveness of different beta-adrenergic antagonists on mortality among adults with heart failure in clinical practice. Arch Intern Med. 2008 Dec 8;168(22):2415-21. Compared with atenolol, the adjusted risks of death were slightly higher with shorter-acting metoprolol tartrate but did not significantly differ for carvedilol in adults with heart failure. Our results should be interpreted cautiously and they suggest the need for randomized trials within real-world settings comparing a broader spectrum of beta-blockers for heart failure.

Goldberg A, Hammerman H, Petcherski S, Nassar M, Zdorovyak A, Yalonetsky S, Kapeliovich M, Agmon Y, Beyar R, Markiewicz W, Aronson D. **Hyponatremia** and Long-term Mortality in Survivors of Acute ST-Elevation Myocardial Infarction. Arch Intern Med. 2006 Apr 10;166(7):781-6.

Goodacre S, Bradburn M, Cross E, Collinson P, Gray A, Hall A. The randomised assessment of treatment using panel assay of cardiac markers (RATPAC) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. Heart 2010; 97: 190–96.

Goto K, Nikolsky E, Lansky AJ, et al. Impact of Smoking on Outcomes of Patients With ST-Segment Elevation Myocardial Infarction (from the HORIZONS-AMI Trial). Am J Cardiol. 2011 Aug 23.

Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. JAMA. 2012;307(2):157-164.

Gu YL, Kampinga MA, Wieringa WG, et al. Intracoronary versus intravenous administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: the comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial. Circulation. 2010 Dec 21;122(25):2709-17.

Gulliksson Mats; Burell Gunilla; Vessby Bengt; et al. Randomized Controlled Trial of Cognitive Behavioral Therapy vs Standard Treatment to Prevent Recurrent Cardiovascular Events in Patients With Coronary Heart Disease: Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM). *Arch Intern Med*. 2011;171(2):134-140.

Haaf P, Drexler B, Reichlin T, et al. High Sensitivity Cardiac Troponin in the Distinction of Acute Myocardial Infarction from Acute Cardiac Non-Coronary Artery Disease. Circulation. 2012 May 23.

Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Sep 21.

Hanna EB, Glancy DL. ST-segment depression and T-wave inversion: Classification, differential diagnosis, and caveats Cleveland Clinic Journal of Medicine 2011; 78(6):404-414; doi:10.3949/ccjm.78a.10077

Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med 2005; 352: 2174-83. (InfoPOEMs: Coronary artery bypass grafting (CABG) is associated with lower long-term mortality than percutaneous coronary interventions (PCI) with stenting for most anatomic groups in patients with multivessel disease, and a lower risk of requiring revascularization in the 3 years following intervention. Of course, this was an observational study and the groups were quite different at baseline, so we must be cautious about drawing firm treatment conclusions, even with appropriate statistical adjustments. Stenting is less invasive and is associated with lower unadjusted in-hospital mortality, so it remains a good option for many patients. (LOE = 2b))

Hannan EL, Racz M, Walford G. Out-of-Hospital Deaths Within 30 Days Following Hospitalization Where Percutaneous Coronary Intervention Was Performed. Am J Cardiol. 2011 Sep 29.

Hardoon SL, Morris RW, Whincup PH, et al. Rising adiposity curbing decline in the incidence of myocardial infarction: 20-year follow-up of British men and women in the Whitehall II cohort. Eur Heart J 2011.

Heer T, et al. Acute Coronary Syndromes Registry Investigators. Beneficial effects of abciximab in patients with primary percutaneous intervention for acute ST segment elevation myocardial infarction in clinical practice. Heart. 2006 Oct;92(10):1484-9. Epub 2006 Apr 10.

Held C, Iqbal R, Lear SA, et al. Physical activity levels, ownership of goods promoting sedentary behavior and risk of myocardial infarction: results of the INTERHEART study. Eur Heart J 2012

Helin-Salmivaara A, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. Eur Heart J. 2006 Jul;27(14):1657-63. Epub 2006 May 26.

Held C, Iqbal R, Lear SA, et al. Physical activity levels, ownership of goods promoting sedentary behavior and risk of myocardial infarction: results of the INTERHEART study. Eur Heart J 2012

Herrin J, Miller LE, Turkmani DF. National performance on door-in to door-out time among patients transferred for primary percutaneous coronary intervention. Arch Intern Med. 2011;171(21):1879-1886.

Hess EP, Agarwal D, Chandra S, et al. Diagnostic accuracy of the TIMI risk score in patients with chest pain in the emergency department: a meta-analysis. CMAJ. 2010 Jun 7.

Hirakawa Y, et al. Effect of emergency percutaneous coronary intervention on in-hospital mortality of very elderly (80+ years of age) patients with acute myocardial infarction. Int Heart J. 2006 Sep;47(5):663-9.

Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med 2006; 166: 1842-1847.

Hoebers LP, Damman P, Claessen BE, et al. Predictive Value of Plasma Glucose Level on Admission for Short and Long Term Mortality in Patients With ST-Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention. Am J Cardiol. 2011 Sep 23.

Hochman JS, et al. Coronary Intervention for Persistent Occlusion after Myocardial Infarction. (OAT) N Engl J Med. 2006 Nov 14; [Epub ahead of print] PCI did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction during 4 years of follow-up in stable patients with occlusion of the infarct-related artery 3 to 28 days after myocardial infarction.

Hochman JS, et al.; SHOCK Investigators. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA. 2006 Jun 7;295(21):2511-5.

Hochman JS, Reynolds HR, Dzavík V, et al. for the Occluded Artery Trial Investigators. Long-Term Effects of Percutaneous Coronary Intervention of the Totally Occluded Infarct-Related Artery in the Subacute Phase After Myocardial Infarction. (OAT) Circulation. 2011 Oct 24.

Hoenig MR, Doust JA, Aroney CN, et al. Early invasive versus conservative strategies for unstable angina and non-ST-elevation myocardial infarction in the stent era. *Cochrane Database Syst Rev* 2006; 3:CD004815.

Hohnloser SH, Kuck KH, Dorian P, Roberts RS, et al; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004 Dec 9;351(24):2481-8.

Honkola J, Hookana E, Malinen S, et al. Psychotropic medications (antipsychotics & antidepressants) and the risk of sudden cardiac death during an acute coronary event. Eur Heart J. 2012 Mar;33(6):745-51.

Hsia J, Larson JC, Ockene JK, Sarto GE, Allison MA, et al.; Women's Health Initiative Research Group. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. BMJ. 2009 Feb 3;338:b219. doi: 10.1136/bmj.b219. Resting heart rate, a low tech and inexpensive measure of autonomic tone, independently predicts myocardial infarction or coronary death, but not stroke, in women.

Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: a community study. Circulation. 2011;123:2094-100.

Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation 2008; DOI: 10.1161/CIRCULATIONAHA.107.706820.

Janszky I, Ljung R. Shifts to and from daylight saving time and incidence of myocardial infarction. N Engl J Med. 2008 Oct 30;359(18):1966-8.

Jernberg T, Johanson P, Held C, Svennblad B, Lindba¨ ck J, Wallentin L; SWEDEHEART, RIKS-HIA. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction, 1996-2007. JAMA. 2011; 305(16):1677-1684.

Jensen LO et al. Influence of Diabetes Mellitus on Clinical Outcomes Following Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2011 Dec 5.

Jollis J, Al-Khalidi HR, Monk L, et al. Expansion of a regional ST-segment elevation myocardial infarction system to an entire state.Circulation 2012.

Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005; 352: 1951-58. (InfoPOEMs: This study showed that a higher resting heart rate was associated with an increased risk of sudden death. We do not know whether any exercise or pharmacologic intervention in patients with an elevated heart rate would modify their risk. (LOE = 1b))

Kaehler J, Koester R, Billmann W, et al. 13-year follow-up of the German **angioplasty bypass surgery** investigation. Eur Heart J. 2005 Oct;26(20):2148-53. Epub 2005 Jun 23.

Kaikkonen KS, et al. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. Circulation. 2006 Oct 3;114(14):1462-7. Epub 2006 Sep 25.

Kastrati A, et al. Abciximab in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention After Clopidogrel Pretreatment: The ISAR-REACT 2 Randomized Trial. JAMA. 2006 Mar 13; [Epub ahead of print] CONCLUSIONS: Abciximab reduces the risk of adverse events in patients with non-ST-segment elevation ACS undergoing PCI after pretreatment with 600 mg of clopidogrel. The benefits provided by abciximab appear to be confined to patients presenting with an elevated troponin level.

Kastrati A et al. for the ISAR-REACT 4 Trial Investigators. Abciximab and heparin versus bivalirudin for non–ST-elevation myocardial infarction. N Engl J Med 2011 Nov 13;

Kaya MG, Uyarel H, Akpek M et al. Prognostic Value of Uric Acid in Patients With ST-Elevated Myocardial Infarction Undergoing Primary Coronary Intervention. Am J Cardiol. 2011 Nov 17.

Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003 Jan 4;361(9351):13-20.

Keeley EC, Boura JA, et al. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. Lancet. 2006 Feb 18;367(9510):579-88. Erratum in: Lancet. 2006 May 20;367(9523):1656.

Keller, Till, Zeller, Tanja, Peetz, Dirk, et al. Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction. N Engl J Med 2009 361: 868-877. The use of a sensitive assay for troponin I improves early diagnosis of acute myocardial infarction and risk stratification, regardless of the time of chest-pain onset.

Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay (3hrs after)and early diagnosis of myocardial infarction.JAMA 2011; 306:2684-2693.

Kharazmi Elham, Dossus Laure, Rohrmann Sabine, et al. Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). Heart hrt.2010.202226Published Online First: 1 December 2010 doi:10.1136/hrt.2010.202226.

Khawaja FJ, Shah ND, Lennon RJ, et al. Factors associated with 30-day readmission rates after percutaneous coronary intervention [published online November 28, 2011]. Arch Intern Med. doi:10.1001/archinternmed.2011.569.

Kim HW, Klem I, Shah DJ, et al. Unrecognized non-Q-wave myocardial infarction: prevalence and prognostic significance in patients with suspected coronary disease. PLoS Med. 2009 Apr 21;6(4):e1000057. Epub 2009 Apr 21. In patients with suspected coronary disease, the prevalence of non-Q-wave UMI is more than 3-fold higher than Q-wave UMI. The presence of non-Q-wave UMI predicts subsequent mortality, and is incremental to LVEF.

Kim JH, Malhotra R, Chiampas G et al, Cardiac arrest during long-distance running races. N Engl J Med 2012; 366:130-140.

Kloner RA, et al. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. Eur Heart J. 2006 Oct;27(20):2400-5. Epub 2006 Jun 16.

Kociol RD, Lopes RD, Clare R, et al. International variation in and factors associated with hospital readmission after myocardial infarction (APEX-AMI). JAMA 2012; 307:66-74.

Koek HL, et al. Short- and long-term prognosis after acute myocardial infarction in men versus women. Am J Cardiol. 2006 Oct 15;98(8):993-9. Epub 2006 Aug 17. In conclusion, our findings in an unselected cohort (n=21,565) covering a complete nation indicate that the worse short- and long-term prognoses after an AMI in women compared with men may largely be explained by differences in age, whereas differences in co-morbidity, origin, infarct location, and reperfusion therapy seem to contribute little.

Koeth O, et al; PREMIR Investigators. Fate of Patients With Prehospital Resuscitation for ST-Elevation Myocardial Infarction and a High Rate of Early Reperfusion Therapy (Results from the PREMIR [Prehospital Myocardial Infarction Registry]). Am J Cardiol. 2012 Mar 31.

Kosiborod M, Inzucchi SE, Goyal A, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA. 2009 Apr 15;301(15):1556-64.

Kovoor P, Lee AK, Carrozzi F, Wiseman V, Byth K, Zecchin R, Dickson C, King M, Hall J, Ross DL, et al. **Return to full normal activities** including work at two weeks after acute myocardial infarction. Am J Cardiol. 2006 Apr 1;97(7):952-8. Epub 2006 Feb 13.

Kramer JM, Curtis LH, Dupree CS, Pelter D, Hernandez A, Massing M, Anstrom KJ. Comparative effectiveness of beta-blockers in elderly patients with heart failure. Arch Intern Med. 2008 Dec 8;168(22):2422-8; discussion 2428-32. This elderly population, the comparative effectiveness of EBBBs vs non-EBBBs was similar for 1-year survival, whereas the rehospitalization rate was higher for patients receiving EBBBs.

Kromhout D, Gitay EJ, Geleijnse JM, et al. N-3 fatty acids and cardiovascular events after myocardial infarction. (Alpha Omega Trial)N Engl J Med 2010; DOI:10.1056.NEJM0a.1003603.

Krumholz HM,; American College of Cardiology; American Heart Association Task Force on Performance Measures; Writing Committee to Develop Performance Measures on ST-Elevation and Non-ST-Elevation Myocardial Infarction. ACC/AHA clinical performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures on ST-Elevation and Non-ST-Elevation Myocardial Infarction). J Am Coll Cardiol. 2006 Jan 3;47(1):236-65.

Krumholz Harlan M.; Wang Yun; Chen Jersey; et al. Reduction in Acute Myocardial Infarction Mortality in the United States: Risk-Standardized Mortality Rates From 1995-2006. JAMA. 2009;302(7):767-773. Between 1995 and 2006, the risk-standardized hospital mortality rate for Medicare patients discharged with AMI showed a significant decrease, as did between-hospital variation.

Krumholz HM, Herrin J, Miller LE, et al. Improvements in Door-to-Balloon Time in the United States, 2005 to 2010. Circulation. 2011 Aug 30;124(9):1038-45.

Kumbhani DJ, Shishehbor MH, Willis JM et al. Influence of Gender on Long-Term Mortality in Patients Presenting With Non-ST-Elevation Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention. Am J Cardiol. 2012 Apr 15;109(8):1087-91

Kuo H-K, Fujise K. Human papillomavirus and cardiovascular disease among US women in the National Health and Nutrition Examination Survey, 2003 to 2006. J Am Coll Cardiol 2011; 58: 2001-2006.

Kurth T, et al. Migraine and risk of cardiovascular disease in women. JAMA. 2006 Jul 19;296(3):283-91. Erratum in: JAMA. 2006 Jul 19;296(3):1 p following 291. In this large, prospective cohort of women, active migraine with aura was associated with increased risk of major CVD, myocardial infarction, ischemic stroke, and death due to ischemic CVD, as well as with coronary revascularization and angina.

Laarman GJ, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. (Passion trial)N Engl J Med. 2006 Sep 14;355(11):1105-13.

Lahoud R, Howe M, Krishnan SM, et al. Effect of Use of Combination Evidence-Based Medical Therapy After Acute Coronary Syndromes on Long-Term Outcomes. Am J Cardiol. 2011 Oct 17.

Lambert Laurie; Brown Kevin; Segal Eli; et al. Association Between Timeliness of Reperfusion Therapy and Clinical Outcomes in ST-Elevation Myocardial Infarction. JAMA. 2010;303(21):2148-2155.

Lane JR, Ben-Shachar G. Myocardial infarction in healthy adolescents. Pediatrics. 2007 Oct;120(4):e938-43.

Larsen KK, Agerbo E, Christensen B, Søndergaard J, Vestergaard M. Myocardial infarction and risk of suicide: a population-based case-control study. Circulation. 2010 Dec 7;122(23):2388-93.

Larson DM, Menssen KM, Sharkey SW, Duval S, Schwartz RS, Harris J, Meland JT, Unger BT, Henry TD. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. JAMA. 2007 Dec 19;298(23):2754-60.

Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the Risk of Acute Myocardial Infarction: A Population Study. Circulation. 2011 Oct 24.

Lavie C, Milani R, Ventura H, et al. Impact of obesity on outcomes in myocardial infarction. J Am Coll Cardiol 2011; 58:2651-53.

Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. Am Heart J. 2011 Oct;162(4):571-584.e2.:

Lawler PR, Afilalo J, Eisenberg MJ, Pilote L. Exposure to Low-Dose Ionizing Radiation from Cardiac Imaging Among Patients With Myocardial Infarction. Am J Cardiol. 2011 Sep 29.

Le May MR, So DY, Dionne R, et al. A citywide (Ottawa) protocol for primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2008 Jan 17;358(3):231-40.

León H, Shibata MC, Dorgan M, et al. Effect of fish oil on arrhythmias and mortality: systematic review. BMJ 2008; DOI: 10.1136/bmj.a2931. Fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. Evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes is insufficient. Fish oils are a heterogeneous product, and the optimal formulations for DHA and EPA remain unclear.

Levesque LE, Brophy JM, Zhang B. Time variations in the risk of myocardial infarction among elderly users of COX-2 inhibitors. CMAJ. 2006 May 23;174(11):1563-9. Epub 2006 May 2. A small proportion of patients using rofecoxib for the first time had their first MI shortly after starting the drug. This risk did not increase with the length of treatment and returned to baseline shortly after treatment was discontinued. More research is needed to identify those most susceptible to cardiotoxicity mediated by COX-2 inhibitor therapy.

Levine DA, Funkhouser EM, Houston TK, et al. Improving care after myocardial infarction using a 2-year Internet-delivered intervention: the Department of Veterans Affairs Myocardial Infarction–Plus cluster randomized trial. Arch Intern Med. 2011;171(21):1910-1917.

Liew R. Implantable cardioverter defibrillators (ICD) after acute myocardial infarction. BMJ. 2010 Nov 19;341:c5741. doi: 10.1136/bmj.c5741.

Lightwood JM, Glantz SA. Declines in Acute Myocardial Infarction After Smoke-Free Laws and Individual Risk Attributable to Secondhand Smoke. Circulation. 2009 Sep 21. [Epub ahead of print]

Lindau ST, Abramsohn E, Gosch K, et al. Patterns and Loss of Sexual Activity in the Year Following Hospitalization for Acute Myocardial Infarction (a United States National Multisite Observational Study). Am J Cardiol. 2012 May 15;109(10):1439-44.

Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011 Jun;70(6):929-34.

Lunde K, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med. 2006 Sep 21;355(12):1199-209. With the methods used, we found no effects of intracoronary injection of autologous mononuclear BMC on global left ventricular function.

Madjid M, Miller CC, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34 892 subjects. Eur Heart J. 2007 Apr 17; [Epub ahead of print]

Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. Circulation. 2011 Nov 22;124(21):2350-4.

Malmberg K, Ryden L, Wedel H; DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J. 2005 Apr;26(7):650-61. Epub 2005 Feb 23. (Malmberg K, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol. 1995 Jul;26(1):57-65. & Van den Berghe G, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med. 2003 Feb;31(2):359-66.) Diaz R, Goyal A, Mehta S, et al. Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. JAMA 2007; 298: 2399-2405.

Masoudi FA, Bonow RO, Brindis RG, et al. ACC/AHA 2008 Statement on Performance Measurement and Reperfusion Therapy. A Report of the ACC/AHA Task Force on Performance Measures (Work Group to Address the Challenges of Performance Measurement and Reperfusion Therapy). Circulation. 2008 Nov 10. [Epub ahead of print]

Mathews R, Peterson ED, Li S, et al. Use of Emergency Medical Service Transport Among Patients With ST-Segment-Elevation Myocardial Infarction: Findings From the National Cardiovascular Data Registry Acute Coronary Treatment Intervention Outcomes Network Registry-Get With the Guidelines. Circulation. 2011 Jul 12;124(2):154-63.

Makkar RR, Smith RR, Cheng K, et al. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): A prospective, randomised phase 1 trial. Lancet 2012. (stem cells)

Mauri L, Silbaugh TS, Garg P,et al. Drug-eluting or bare-metal stents for acute myocardial infarction. N Engl J Med. 2008 Sep 25;359(13):1330-42. In patients presenting with acute myocardial infarction, treatment with drug-eluting stents is associated with decreased 2-year mortality rates and a reduction in the need for repeat revascularization procedures as compared with treatment with bare-metal stents.

McCabe JM, et al. Prevalence and Factors Associated With False-Positive ST-Segment Elevation Myocardial Infarction Diagnoses at Primary Percutaneous Coronary Intervention-Capable Centers: A Report From the Activate-SF Registry. Arch Intern Med. 2012 May 7.

McCord J, Jneid H, et al. Management of Cocaine-Associated Chest Pain and Myocardial Infarction. A Scientific Statement From the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation online Mar 17,2008.

McNamara RL, et al. NRMI Investigators. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2006 Jun 6;47(11):2180-6. Epub 2006 May 15. InfoPOEMs: Mortality resulting from ST-segment elevation myocardial infarction (STEMI) is independently related to the time it takes to administer percutaneous coronary intervention (PCI) following presentation to the emergency department. The relationship is still seen in patients who present several hours after symptoms begin. If you have a choice of hospitals, find out their door-to-balloon times and send patients to the faster one. (LOE = 2b))

Mega JL et al. for the ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome.N Engl J Med 2011 Nov 13. (but at baseline only 66% on BB, & 39% on ACEI)

Mehta RH, et al. Recent Trends in the Care of Patients With Non-ST-Segment Elevation Acute Coronary Syndromes: Insights From the CRUSADE Initiative. Arch Intern Med. 2006 Oct 9;166(18):2027-34.

Mehta SR, Yusuf S, Diaz R, et al.; CREATE-ECLA Trial Group Investigators. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA. 2005 Jan 26;293(4):437-46. CONCLUSION: In this large, international randomized trial, high-dose GIK infusion had a neutral effect on mortality, cardiac arrest, and cardiogenic shock in patients with acute STEMI.

Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA. 2005 Jun 15;293(23):2908-17 & ACP Journal Club .

Mehta RH, Stebbins AS, Lopes RD, et al. Comparison of Incidence of Bleeding and Mortality of Men Versus Women With ST-Elevation Myocardial Infarction Treated With Fibrinolysis. Am J Cardiol. 2011 Nov 10.

Mehta RH, et al.; National Registry of Myocardial Infarction (NRMI) Investigators. Association of Bleeding & In-Hospital Mortality in Black & White Patients With ST-Segment-Elevation Myocardial Infarction Receiving Reperfusion. Circulation. 2012 Apr 10;125(14):1727-1734.

Miedema MD, Newell MC, Duval S, et al. Causes of delay and associated mortality in patients transferred with ST-segment-elevation myocardial infarction. Circulation 2011; DOI: 10.1161/CIRCULATIONAHA.111.033118.

Mills Nicholas L., Churchhouse Antonia M. D., Lee Kuan Ken, et al. Implementation of a Sensitive Troponin I Assay and Risk of Recurrent Myocardial Infarction and Death in Patients With Suspected Acute Coronary Syndrome. JAMA. 2011;305(12):1210-1216.

Mills NL, Lee KK, McAllister DA et al. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. BMJ. 2012 Mar 15;344:e1533.

Mir Arshid, Obafemi Adebisi, Young Amy, et al. Myocardial Infarction Associated With Use of the Synthetic Cannabinoid K2. Pediatrics 2011; peds.2010-3823; published ahead of print November 7, 2011

Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. Lancet. 2011 Aug 20;378(9792):693-703.

Moradkhan R, Sinoway LI. Revisiting the role of oxygen therapy in cardiac patients. J Am Coll Cardiol. 2010 Sep 21;56(13):1013-6.

Morrow DA, de Lemos JA, Blazing MA, et al.; A to Z Investigators. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. JAMA. 2005 Dec 14;294(22):2866-71.

Mostofsky E, Maclure M, Sherwood JB, et al. Risk of acute myocardial infarction after the death of a significant person on one's life be (bereavement). The determinants of myocardial infarction onset study. Circulation 2012.

Motivala, Apurva A., Cannon, Christopher P., Srinivas, Vankeepuram S., et al. Changes in Myocardial Infarction Guideline Adherence as a Function of Patient Risk: An End to Paradoxical Care? J Am Coll Cardiol 2011 58: 1760-1765.

Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J. 2008 Mar;155(3):465-70. These preliminary results suggest possible hazards of marijuana for patients who survive acute myocardial infarction.

Mustafic H, Jabre P, Caussin C, et al. Main air pollutants and myocardial infarction: A systematic review and meta-analysis. JAMA2012; 307:713-721.

Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. N Engl J Med. 2008 Nov 20;359(21):2245-53.

Myerson M, Coady S, Taylor H, et al. Declining severity of myocardial infarction from 1987 to 2002. The Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2009; 119:503-514.

Najjar SS, Rao SV, Melloni C, et al. REVEAL Investigators. Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction (STEMI): REVEAL: a randomized controlled trial. JAMA. 2011 May 11;305(18):1863-72.

Nakagawa S, et al. Antipsychotics and risk of first-time hospitalization for myocardial infarction: a population-based case-control study. J Intern Med. 2006 Nov;260(5):451-8.

Navarese EP, De Luca G, Castriota F, et al. Low-molecular-weight heparins vs unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: A meta-analysis. J Thromb Haemost 2011.

Nawrot TS, Perez L, Künzli N, et al. Public health importance of triggers of myocardial infarction: A comparative risk assessment. Lancet 2011; DOI: 10.1016/S0140-6736(10)62296-9. A comparative risk assessment of various triggers for MI suggests that cocaine is most likely to trigger an event in an individual, but traffic and exposure to air pollution has the greatest effect on triggering an MI at the population level.

Ng FH, Tunggal P, Chu WM, et al. Esomeprazole compared with famotidine in the prevention of upper gastrointestinal bleeding in patients with acute coronary syndrome or myocardial infarction. Am J Gastroenterol. 2012 Mar;107(3):389-96.

NICE Guidelines May 2007 Secondary prevention in primary and secondary care for patients following a myocardial infarction. http://guidance.nice.org.uk/CG48

Nikolsky E, Mehran R, Dangas GD, et al. Outcomes of Patients Treated With Triple Antithrombotic Therapy After Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction (from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] Trial). Am J Cardiol. 2011 Dec 21. In conclusion, in the setting of STEMI treated with primary PCI, the combination of aspirin, thienopyridine, and VKA results in an excess of bleeding complications.

Novack V, Pencina M, Cohen DJ, et al. Troponin criteria for myocardial infarction after percutaneous coronary intervention. Arch Intern Med. 2012; 72(4):ioi110026.

O'Donnell CJ et al. Genome-wide association study for coronary artery calcification with follow-up in myocardial infarction. Circulation. 2011 Dec 20;124(25):2855-64.

O'Donoghue M, et al. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trial.Circulation. 2006 Apr 11;113(14):1745-52. Epub 2006 Mar 14.

O'Driscoll BR, Howard LS, Davison AG; British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008 Oct;63 Suppl 6:vi1-68.

O'Keefe JH Jr, et al. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. Am J Cardiol. 2006 Apr 15;97(8):1127-30. Epub 2006 Mar 3.

Olsen Anne-Marie Schjerning, Fosbøl Emil L., Lindhardsen Jesper, et al. Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction: A Nationwide Cohort Study. Circulation published May 9, 2011, doi:10.1161/CIRCULATIONAHA.110.004671

Page, Maude, Doucet, Michel, Eisenberg, Mark J., et al. Temporal trends in revascularization and outcomes after acute myocardial infarction among the very elderly. CMAJ 2010 182: 1415-1420.

Pai JK, Mukamal KJ, Rimm EB. Long-term alcohol consumption in relation to all-cause and cardiovascular mortality among survivors of myocardial infarction: the Health Professionals Follow-up Study. Eur Heart J 2012.

Palmerini T, Mehran R, Dangas G, et al. Impact of leukocyte count (WBC) on mortality and bleeding in patients with myocardial infarction undergoing primary percutaneous coronary interventions: analysis from the harmonizing outcome with revascularization and stent in acute myocardial infarction trial. Circulation. 2011 Jun 21;123(24):2829-37.

Parashar S, et al. Time course of depression and outcome of myocardial infarction. Arch Intern Med. 2006 Oct 9;166(18):2035-43.

Pariente A, Fourrier-Réglat A, Ducruet T, Farrington P, et al. Antipsychotic use and myocardial infarction in older patients with treated dementia [published online Mar 26, 2012]. Arch Intern Med doi:10.1001/archinternmed.2012.28.

Patel, MR, Smalling RW, Thiele H, et al. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: The CRISP AMI randomized trial. JAMA 2011. (Not result in reduced infarct size)

Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular

Tomography. J Am Coll Cardiol 2012
Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. Circulation. 2011 Apr 19;123(15):1622-32.
Patti G, Bárczi G, Orlic D, et al. Outcome comparison of 600- and 300-mg loading doses of clopidogrel in patients undergoing primary PCI for STEMI. Results from the ARMYDA-6 MI (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty—Myocardial Infarction) randomized study. J Am Coll Cardiol 2011; 58:1592-1599.
Peberdy M, Ornato JP. Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. JAMA 2008; 299:785-792.
Perez MI, Musini VM, Wright JM. Effect of early treatment with anti-hypertensive drugs on short and long-term mortality in patients with an acute cardiovascular event. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006743.
Pinto DS et al. for the National Registry of Myocardial Infarction Investigators. Benefit of Transferring ST-Segment-Elevation Myocardial Infarction Patients for Percutaneous Coronary Intervention Compared With Administration of Onsite Fibrinolytic Declines as Delays Increase. Circulation. 2011 Dec 6;124(23):2512-2521.
Podolecki T, Lenarczyk R, Kowalczyk J, et al. Effect of Type of Atrial Fibrillation on Prognosis in Acute Myocardial Infarction Treated Invasively. Am J Cardiol. 2012 Mar 20.
Prasad Abhiram, Herrmann Joerg. Myocardial Infarction Due to Percutaneous Coronary Intervention (PCI). N Engl J Med 2011; 364:453-464.
Puymirat E, Aissaoui N, Coste P, et al. Comparison of efficacy and safety of a standard versus a loading dose of clopidogrel for acute myocardial infarction in patients >/= 75 years of age (from the FAST-MI registry). Am J Cardiol. 2011 Sep 15;108(6):755-9.
Qian F, Ling FS, Deedwania P, et al. Care and outcomes of Asian acute myocardial infarction patients: findings from the American Heart Association Get With The Guidelines—Coronary Artery Disease program (GWTG-CAD). Circ Cardiovasc Qual Outcomes 2012.
Rao SV, Kaltenbach LA, Weintraub WS, et al. Prevalence and outcomes of same-day discharge after elective percutaneous coronary intervention among older adults. JAMA 2011; 306: 1461-1467.
Rathore SS, Curtis JP, Chen J, et al. National Cardiovascular Data Registry. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ. 2009 May 19;338:b1807. doi: 10.1136/bmj.b1807.
Rauch Bernhard, Schiele Rudolf, Schneider Steffen, et al., and for the OMEGA Study Group OMEGA, a Randomized, Placebo-Controlled Trial to Test the Effect of Highly Purified Omega-3 Fatty Acids on Top of Modern Guideline-Adjusted Therapy After Myocardial Infarction Circulation published November 8, 2010, doi:10.1161/CIRCULATIONAHA.110.948562
Reichlin, Tobias, Hochholzer, Willibald, Bassetti, Stefano, et al. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009 361: 858-867. The diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain.
Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation. 2011 Jul 12;124(2):136-45.
Reiter M, Twerenbold R, Reichlin T, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J. 2011 Jun;32(11):1379-89.
Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation. 2011;124:1414 –1425
Ridker PM, Danielson E, Fonseca FA, Genest J, et al. the JUPITER Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med. 2008 Nov 9. [Epub ahead of print] In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.
Rodríguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. BMJ. 2011 Jul 19;343:d4094.
Roger VL, Weston SA, Gerber Y, et al. Trends in Incidence, Severity, and Outcome of Hospitalized Myocardial Infarction. Circulation. 2010 Feb 8.
Romaguera R, Wakabayashi K, Laynez-Carnicero A, et al.. Association Between Bleeding Severity and Long-Term Mortality in Patients Experiencing Vascular Complications After Percutaneous Coronary Intervention. Am J Cardiol. 2011 Sep 29.
Rosamond WD, Chambless LE, Heiss G, et al. Twenty-Two-Year Trends in Incidence of Myocardial Infarction, Coronary Heart Disease Mortality, and Case Fatality in 4 US Communities, 1987-2008. Circulation. 2012 Apr 17;125(15):1848-57.
Rosenbloom JI, Mukamal KJ, Frost LE, Mittleman MA. Alcohol Consumption Patterns, Beverage Type, and Long-Term Mortality Among Women Survivors of Acute Myocardial Infarction. Am J Cardiol. 2011 Oct 17.
Rosenbloom JI, Wilker EH, Mukamal KJ, et al. Residential proximity to major roadway and 10-year all-cause mortality after myocardial infarction. Circulation. 2012 May 8;125(18):2197-203.
Ross, Joseph S., Normand, Sharon-Lise T., Wang, Yun, et al. Hospital Volume and 30-Day Mortality for Three Common Medical Conditions. N Engl J Med 2010 362: 1110-1118.
Rossignol P, Ménard J, Fay R, et al. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects: insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. J Am Coll Cardiol 2011; 58:1958-1966.
Rothberg MB, Celestin C, Fiore LD, et al. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. Ann Intern Med. 2005 Aug 16;143(4):241-50. (InfoPOEMs: Adding warfarin to aspirin prophylaxis does not affect overall death rates, though the combination decreases subsequent myocardial infarction risk ([NNT = 56) and, to a lesser degree, ischemic stroke risk (NNT = 221). As one might expect, major bleeding episodes occur more often with the added warfarin, though only in a small number of patients (1.5% vs 0.56%). (LOE = 1a))
Salisbury AC, Reid KJ, Alexander KP, et al. Diagnostic Blood Loss From Phlebotomy and Hospital-Acquired Anemia During Acute Myocardial Infarction. Arch Intern Med. 2011 Aug 8.
Salisbury AC, Amin AP, Reid KJ et al. Red Blood Cell Indices and Development ofHospital-Acquired Anemia During Acute Myocardial Infarction. Am J Cardiol. 2012 Jan 18.
Schachinger V, et al. REPAIR-AMI Investigators. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med. 2006 Sep 21;355(12):1210-21.
Scherrer JF, Chrusciel T, Garfield LD et al. Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction. Br J Psychiatry. 2012 Feb;200:137-42.
Schjerning Olsen AM, Fosbøl EL, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Circulation. 2011;123: 2226-35.
Schmidt M, Jacobsen JB, et al. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. BMJ 2012;344:e356.
Schomig A, Mehilli J, Mechanical Reperfusion in Patients with Acute Myocardial Infarction Presenting more than 12 Hours from Symptom Onset (BRAVE-2). JAMA. 2005 June 15;293:2865-2872.
Schulman SP, et al. **L-arginine** therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. JAMA. 2006 Jan 4;295(1):58-64.
Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. Circulation. 2010 Dec 14;122(24):2558-69.
Secemsky EA, Lange D, Ho JE, et al. Improvement in revascularization time after creation of a coronary catheterization laboratory at a public hospital. Arch Intern Med. doi:10.1001/archinternmed.2011.564.
Selker HP, Beshansky JR, Sheehan PR, et al. Out-of-hospital administration of intravenous-insulin-potassium in patients with suspected acute coronary syndromes. (Immediate) JAMA 2012.
Senecal EL, Rosenfield K, Caldera AE, et al. Case 36-2011 — A 93-Year-Old Woman with Shortness of Breath and Chest Pain. (Takosubo cardiomyopathy). N Engl J Med 2011; 365:2021-2028.
Shen YC, Hsia RY. Association between ambulance diversion and survival among patients with acute myocardial infarction. JAMA. 2011 Jun 15;305(23):2440-7.
Shiomi H, et al; CREDO-Kyoto AMI investigators. Association of onset to balloon and door to balloon time with long term clinical outcome in patients with ST elevation acute myocardial infarction having primary percutaneous coronary intervention: observational study. BMJ. 2012 May 23;344:e3257.
Silletta MG, Marfisi R, Levantesi G, et al. R; GISSI-Prevenzione Investigators. Coffee consumption and risk of cardiovascular events after acute myocardial infarction: results from the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial. Circulation. 2007 Dec 18;116(25):2944-51. Epub 2007 Dec 3. Coffee consumption does not increase the risk of cardiovascular events following acute myocardial infarction (AMI). (LOE = 1b)
Silva D, Cortez-Dias N, Jorge C et al. Cystatin C as Prognostic Biomarker in ST-Segment Elevation Acute Myocardial Infarction. Am J Cardiol. 2012 Feb 20.
Silvain J, Beygui F, Barthelemy O, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ. 2012 Feb 3;344:e553.
Sims Michelle, Maxwell Roy, Bauld Linda, Gilmore Anna. Short term impact of smoke-free legislation in England: retrospective analysis of hospital admissions for myocardial infarction. BMJ 2010;340:c2161
Siriwardena AN, Gwini SM, Coupland C. Influenza vaccination, pneumococcal vaccination and risk of AMI: Matched case-control study. CMAJ 2010; DOI:10.1503/cmaj.091891.
Skolnick AH et al. Comparison of Late Results of Percutaneous Coronary Intervention Among Stable Patients ≤65 Versus >65 Years of Age With an Occluded Infarct Related Artery (from the Occluded Artery Trial). Am J Cardiol. 2011 Dec 13 –no indication for routine PCI.
Smith SC Jr, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006 May 16;113(19):2363-72. http://circ.ahajournals.org/cgi/reprint/113/19/2363
Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. BMJ 2012;344:d8059.
Sode BF, Dahl M, Nordestgaard BG. Myocardial infarction and other co-morbidities in patients with chronic obstructive pulmonary disease: a Danish Nationwide Study of 7.4 million individuals. Eur Heart J. 2011 Aug 29.
Solomon SD, Zelenkofske S, McMurray JJ, et al, for the Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med 2005; 352: 2581-8. (InfoPOEMs: Sudden death occurs in 1.4% of patients during the first month after an acute myocardial infarction (AMI), & in approximately 0.14% per month after 2 years. Sudden death is more likely in patients with a lower ejection fraction. Although this suggests that early implantation of a cardiac defibrillator may be helpful, a previous trial did not find such a benefit, perhaps because this outcome is relatively rare and a larger, longer study would be needed to detect a statistically significant benefit. (LOE = 1b))
Solomon SD, Hee Shin S, Shah A, et al. Effect of the direct rennin inhibitor aliskiren on left ventricular remodelling following myocardial infarction *with systolic dysfunction.(ASPIRE) Eur Heart J 2011; 32: 1227–34.*
Spaulding C, et al. TYPHOON Investigators. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med. 2006 Sep 14;355(11):1093-104.
Steinbeck G, Andresen D, Seidl K, et al. the IRIS Investigators. Defibrillator Implantation Early after Myocardial Infarction. N Engl J Med. 2009 Oct 8;361(15):1427-1436.
Stenestrand U, Lindback J, Wallentin L; RIKS-HIA Registry. Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. JAMA. 2006 Oct 11;296(14):1749-56.
Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease. Arch Intern Med 2012; 172:312-319.
Stone GW, Witzenbichler B, Guagliumi G, et al.; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008 May 22;358(21):2218-30. In patients with ST-segment elevation myocardial infarction who are undergoing primary PCI, anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in significantly reduced 30-day rates of major bleeding and net adverse clinical events.
Stone GW et al. for the HORIZONS-AMI Trial Investigators. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009 May 7; 360:1946.
Stone GW, Witzenbichler B, Guagliumi G, et al, on behalf of the HORIZONS AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011; DOI:10.1016/S0140-6736(11)60764-2.
Stone GW et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: The INFUSE-AMI randomized trial. JAMA 2012 Mar 25.
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Effects of Homocysteine-Lowering With Folic Acid Plus Vitamin B12 vs Placebo on Mortality and Major Morbidity in Myocardial Infarction Survivors: A Randomized Trial. JAMA. 2010;303(24):2486-2494.
Sumner MD, Elliott-Eller M, Weidner G,et al. Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. Am J Cardiol. 2005 Sep 15;96(6):810-4.
Svensson L, et al. Comparison of very early treatment with either fibrinolysis or percutaneous coronary intervention facilitated with abciximab with respect to ST recovery & infarct-related artery epicardial flow in patients with acute ST-segment elevation myocardial infarction: the Swedish Early Decision (SWEDES) reperfusion trial. Am Heart J. 2006 Apr;151(4):798.e1-7. CONCLUSIONS: Despite much shorter time delay to start of fibrinolysis than PCI, this did not result in signs of superior myocardial reperfusion. Epicardial flow in the infarct-related artery was better after invasive therapy, and there was a trend toward better clinical outcome after this treatment compared with after fibrinolysis.
Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA 2010; 304: 763-771.
Terkelsen CJ, Jensen LO, Tilsted HH, et al. Health Care System Delay and Heart Failure in Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Follow-up of Population-Based Medical Registry Data. Ann Intern Med. 2011 Sep 20;155(6):361-7.
Than M, Cullen L, Reid CM, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacifi c region (ASPECT): a prospective observational validation study. Lancet 2011; published online March 23. DOI:10.1016/S0140-6736(11)60310-3.
Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker. The ADAPT trial. J Am Coll Cardiol 2012.
Thiele H, et al. Leipzig Prehospital Fibrinolysis Group. ST-Segment Recovery and Prognosis in Patients With ST-Elevation Myocardial Infarction Reperfused by Prehospital Combination Fibrinolysis, Prehospital Initiated Facilitated Percutaneous Coronary Intervention, or Primary Percutaneous Coronary Intervention. Am J Cardiol. 2006 Nov 1;98(9):1132-9. Epub 2006 Sep 1.
Thiele H, Wöhrle J, Hambrecht R, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST elevation myocardial infarction: a randomised trial. Lancet 2012; online Feb 21.
Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation* 2007; DOI: 10.1161/CIRCULATIONAHA.107.187397. Available at: http://circ.ahajournals.org.
Thune JJ, Hoefsten DE, Lindholm MG, et al.; Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI)-2 Investigators. Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. Circulation. 2005 Sep 27;112(13):2017-21.
Towfighi A, Markovic D, Ovbiagele B. National Gender-Specific Trends in Myocardial Infarction Hospitalization Rates Among Patients Aged 35 to 64 Years. Am J Cardiol. 2011 Aug 2.
Traverse JH, Henry TD, Ellis SG, et al. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: LateTIME randomized trial [Nov 14, 2011]. JAMA. 2011;306(19):2110-2119.
Tricoci P et al for the TRACER Investigators. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med2011 Nov 13
Tu Jack V., Nardi Lorelei, Jiming Fang, et al., for the Canadian Cardiovascular Outcomes Research Team, National trends in rates of death and hospital admissions related to acute myocardial infarction, heart failure and stroke, 1994-2004. CMAJ 2009 180: E118-125.
Vaccarino Viola; Parsons Lori; Peterson Eric D.; et al. Sex Differences in Mortality After Acute Myocardial Infarction: Changes From 1994 to 2006. Arch Intern Med. 2009;169(19):1767-1774.
Valgimigli M, et al. STRATEGY Investigators. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA. 2005 May 4;293(17):2109-17.
Van't Hof AW, Ten Berg J, Heestermans T, et al. Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet. 2008 Aug 16;372(9638):537-46. (n=491) or placebo (N=493) in addition to aspirin (500 mg), heparin (5000 IU), and clopidogrel (600 mg). Our finding that routine prehospital initiation of high-bolus dose tirofiban improved ST-segment resolution and clinical outcome after PCI, emphasises that further platelet aggregation inhibition besides high-dose clopidogrel is mandated in patients with STEMI undergoing PCI.
Van de Werf F. Drug-eluting stents in acute myocardial infarction. N Engl J Med. 2006 Sep 14;355(11):1169-70.
Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC): Eur Heart J. 2008 Nov 12. [Epub ahead of print] http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/acs-st-segment-elevation.aspx
Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. Circulation 2008; DOI: 10.1161/CIRCULATIONAHA.108.784215.
Voors AA, Belonje AM, Zijlstra F, et al. A single dose of erythropoietin in ST-elevation myocardial infarction. Eur Heart J 2010; DOI:10.1093/eurheartj/ehq304.
Waqar S, Sarkar PK. Exacerbation of psoriasis with beta-blocker therapy. CMAJ. 2009 Jul 7;181(1-2):60.
Wang OJ, Wang Y, Lichtman JH, et al.. "America's Best Hospitals" in the treatment of acute myocardial infarction. Arch Intern Med. 2007 Jul 9;167(13):1345-51. On average, admission to a ranked hospital for AMI was associated with a lower risk of 30-day mortality, although about one-third of the ranked hospitals fell outside the best performing quartile based on RSMR. Although ranked hospitals were much more likely to have an SMR significantly less than 1, many more nonranked hospitals had this distinction.
Wang OJ, Wang Y, Chen J, Krumholz HM. Recent trends in hospitalization for acute myocardial infarction. Am J Cardiol. 2012 Jun 1;109(11):1589-93.
Wang Tracy Y.; Fonarow Gregg C.;. Hernandez Adrian F; et al. The Dissociation Between Door-to-Balloon Time (DIDO) Improvement and Improvements in Other Acute Myocardial Infarction Care Processes and Patient Outcomes. Arch Intern Med. 2009;169(15):1411-1419.
Wang Tracy Y., Nallamothu Brahmajee K., Krumholz Harlan M., et al. Association of Door-In to Door-Out Time With Reperfusion Delays and Outcomes Among Patients Transferred for Primary Percutaneous Coronary Intervention. JAMA. 2011;305(24):2540-2547
Wang Y, Peterson E, et al. Door-to-balloon times for patients with STsegment elevation myocardial infarction requiring interhospital transfer for primary percutaneous coronary intervention: a report from the national cardiovascular data registry. Am Heart J. 2011;161(1):76-83.
Wang Y, Wu B, Shu X. Meta-Analysis of Randomized Controlled Trials Comparing Intracoronary and Intravenous Administration of Glycoprotein IIb/IIIa Inhibitors in Patients With ST-Elevation Myocardial Infarction. Am J Cardiol. 2012 Jan 13.
Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al. Comparative effectiveness of revascularization strategies (PCI vs CABG). N Engl J Med2012.

TOP

West RR, Jones DA, Henderson AH. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. Heart. 2011 Dec 22
Widimsky P, Wijns W, Fajadet J, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J 2010; 31:943-957.
Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction. A meta-analysis of randomized trials. J Am Coll Cardiol 2007; 49:422-30. Rescue PCI is associated with improved clinical outcomes for STEMI patients after failed fibrinolytic therapy, but these benefits must be interpreted in the context of potential risks. On the other hand, repeat fibrinolytic therapy is not associated with significant clinical improvement and may be associated with increased harm.
Witt BJ, Brown RD Jr, Jacobsen SJ, et al. A community-based study of stroke incidence after myocardial infarction. Ann Intern Med. 2005 Dec 6;143(11):785-92.
Wiviott SD, Morrow DA, Frederick PD, Antman EM, Braunwald E; National Registry of Myocardial Infarction. Application of the thrombolysis in myocardial infarction risk index in non-ST-segment elevation myocardial infarction: evaluation of patients in the National Registry of Myocardial Infarction. J Am Coll Cardiol. 2006 Apr 18;47(8):1553-8. Epub 2006 Mar 29.
Wong CK, et al. HERO-2 Investigators. Initial Q waves accompanying ST-segment elevation at presentation of acute myocardial infarction and 30-day mortality in patients given streptokinase therapy: an analysis from HERO-2. Lancet. 2006 Jun 24;367(9528):2061-7.
Wood FO, Leonowicz NA, Vanhecke TE, et al. Mortality in Patients With ST-Segment Elevation Myocardial Infarction Who Do Not Undergo Reperfusion. Am J Cardiol. 2012 May 23.
Yeh Robert W.; Go Alan S. Rethinking the Epidemiology of Acute Myocardial Infarction: Challenges and Opportunities. Arch Intern Med. 2010;170(9):759-764.
Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 10 Jun 2010;362(23):2155-65.
Yerman T, Gan WQ, Sin DD. The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Med 2007; 5:29.
Yusuf S, Mehta SR, Xie C, et al. CREATE Trial Group Investigators. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. JAMA. 2005 Jan 26;293(4):427-35. CONCLUSIONS: In patients with acute ST-segment elevation or new left bundle-branch block MI, reviparin reduces mortality and reinfarction, without a substantive increase in overall stroke rates. There is a small absolute excess of life-threatening bleeding but the
Zaman T, Agarwal S, Anabtawi AG, Patel NS, Ellis SG, Tuzcu EM, Kapadia SR. Angiographic Lesion Severity and Subsequent Myocardial Infarction. Am J Cardiol. 2012 Apr 10.
Zhang Z, Fang J, Gillespie C, et al. Age-Specific Gender Differences in In-Hospital Mortality by Type of Acute Myocardial Infarction. Am J Cardiol. 2012 Jan 13.
Zhao YT, Weng CL, Chen ML, et al. Comparison of glucose-insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials. Heart. 2010 Oct;96(20):1622-6. Current evidence suggests that GIK with insulin does not reduce mortality in patients with AMI. However, studies of glycaemia are inconclusive and it remains possible that glycaemic control is beneficial.

TOP

6. Crouch M et al. Clinical relevance & management of drug-related QT interval prolongation. Pharmacotherapy 2003; 23(7):881-908.
7. Witchel H et al. Psychotropic drugs, cardiac arrhythmia, & sudden death. J Clin Psychopharmacol 2003; 23(1):58-77.
8. Brown et al. Cardiovascular effects of anti-psychotics. Clin Pharmacokinet 2004; 43(1): 38-56 (see Roden NEJM'08)
9. Gowda RM, et al. Torsade de pointes: the clinical considerations. Int J Cardiol. 2004;96:1
10. Sudden Arrhythmia Death Syndromes Foundation The long QT syndrome. SADS Foundation http://www.sads.org/LQTflyer.pdf (Cardiac Arrhythmia Reasearch & Education Foundation www.longqt.org)
11. Ray WA, et al. Oral erythromycin & the risk of sudden death from cardiac causes. N Engl J Med. 2004 Sep 9;351(11):1089-96.
12. Liu BA, Juurlink DN. Drugs and the QT interval - caveat doctor. N Engl J Med. 2004 Sep 9;351(11):1053-6.
13. Woeffel JA. Drug-Induced Long QT Interval & Sudden Cardiac Death. Pharmacist's Letter Nov 2004;20:201111
14. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA. 2003 Apr 23-30;289(16):2120-7. Review. Erratum in: JAMA. 2003 Sep 10;290(10):1318.
15. Astrôm-Lilja et al. Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database. Pharmacoepidemiol Drug Saf.2008 Jun;17(6):587-92.

QT PROLONGATION and TORSADES DE POINTES: DRUGS and SUDDEN DEATH

Additional references:

Abrams DJ, Perkin MA, Skinner JR. **Long QT syndrome**. BMJ. 2010 Jan 8;340:b4815. doi: 10.1136/bmj.b4815.

AHA/ACCF-**Prevention of Torsade de Pointes in Hospital Settings**, Scientific Statement From American Heart Association and the American College of Cardiology Foundation. 2010. http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192704

Arking DE, Pfeufer A, Post W, et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. Nat Genet 2006; DOI: 10.1038/ng1790. Available at: http://www.nature.com/ng.

Barsheshet A, Goldenberg I, O-Uchi J, et al. **Mutations in cytoplasmic loops of the KCNQ1** channel and the risk of life-threatening events: implications for mutation-specific response to Beta-blocker therapy in type 1 long-QT syndrome. Circulation. 2012;125:1988 –1996.

Basavarajaiah S, Wilson M, Whyte G, et al. Prevalence and significance of an isolated long QT interval in **elite athletes**. Eur Heart J. 2007 Dec;28(23):2944-9. Epub 2007 Oct 18. The prevalence of prolonged QTc in elite athletes is 0.4%. A QTc of >500 ms is highly suggestive of LQTS. A QTc of <500 ms in the absence of symptoms or familial disease is unlikely to represent LQTS in elite athletes.

Blaufox AD, Tristani-Firouzi M, Seslar S, et al. Congenital Long **QT 3 in the Pediatric** Population. Am J Cardiol. 2012 Feb 21.

Boyce MJ, Baisley KJ,Warrington SJ. Pharmacokinetic Interaction between **domperidone and ketoconazole** leads to QT prolongation in healthy volunteers: randomized, placebo-controlled, double-blind, crossover study. Br J Clin Pharmacol 2012;73:411–21.

Buber J, Mathew J, Moss AJ, et al. Risk of Recurrent Cardiac Events **After Onset of Menopause** in Women With Congenital Long-QT Syndrome Types 1 and 2. Circulation. 2011 Jun 21;123(24):2784-91.

Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, Mariani R, Gunson K, Jui J. Determinants of Prolonged QT Interval and Their Contribution to Sudden Death Risk in Coronary Artery Disease. The Oregon Sudden Unexpected Death Study. Circulation. 2009 Jan 26. [Epub ahead of print] Diabetes mellitus and QTc-affecting drugs determined QTc prolongation and were predictors of SCD in coronary artery disease. However, idiopathic abnormal QTc prolongation was associated with 5-fold increased odds of SCD. A continued search for novel determinants of QTc prolongation such as genomic factors is likely to enhance risk stratification for SCD in coronary artery disease.

Djeddi D, Kongolo G, Lefaix C, Mounard J, Léké A. Effect of **domperidone** on QT interval in neonates. J Pediatr. 2008 Nov;153(5):663-6. Epub 2008 Jun 27. This study shows a significant association between oral domperidone therapy and QTc prolongation. Two risk factors identified: advanced gestational age & serum potassium at the upper limit of normal.

Ehret GB, et al. Drug-Induced Long QT **Syndrome** in Injection Drug Users Receiving **Methadone**: High Frequency in Hospitalized Patients and Risk Factors. Arch Intern Med. 2006 Jun 26;166(12):1280-7.

FDA Feb/10 notified healthcare professionals and patients that it is reviewing clinical trial data about a potentially serious effect on the heart from the use of Invirase (saquinavir) in combination with Norvir (ritonavir), antiviral medications given together to treat HIV infection. The data suggest that together the two drugs may affect the electrical activity of the heart, known as prolonged QT or PR intervals.

FDA Nov/10 is requesting that manufacturers of the painkiller **propoxyphene** pull the drug from the market because of concerns over cardiotoxicity. (Propoxyphene is marketed alone as Darvon & combined with acetaminophen as Darvocet.) The agency's request is based on data showing that, even when taken at therapeutic doses, the drug can lead to potentially dangerous changes in the heart's electrical activity, including prolonged PR & QT intervals & widened QRS complex. FDA advises clinicians to stop prescribing propoxyphene and to ask current users to discontinue the drug. FDA's MedWatch alert

FDA Dec/10 The injectable form of dolasetron mesylate (Anzemet) should not be used to prevent nausea or vomiting related to chemotherapy because the drug increases the risk for torsade de pointes, the FDA announced on Friday. The FDA recommends against using Anzemet injections in patients with congenital long-QT syndrome. The warning does not apply to Anzemet tablets because the risks for developing an abnormal heart rhythm are not as high as with the injections. FDA MedWatch alert (Free)

FDA July/11 FDA has added a warning to the label of the atypical antipsychotic quetiapine (Seroquel) cautioning about potential increases in the QT interval. Postmarketing cases of QT prolongation have been reported in some 17 patients, according to the *New York Times.* These patients had overdosed on quetiapine, had other illnesses, or were taking other medications that can cause electrolyte imbalance or QT prolongation.

FDA Aug/11 The antidepressant citalopram (marketed as Celexa) should not be prescribed at doses above 40 mg/day because higher dosages can cause arrhythmias, the FDA has warned.

FDA Sep/11 The U.S. Food and Drug Administration (FDA) is informing the public of an ongoing safety review of the anti-nausea drug Zofran (ondansetron, ondansetron hydrochloride and their generics). Ondansetron may increase the risk of developing abnormal changes(QT prolongation & torsades) in the electrical activity of the heart.

Health Canada Aug/10 **Droperidol** Injection USP is associated with severe arrhythmia (eg. QT) and the Canadian Monograph of this product has been updated to reflect this risk.

Health Canada Nov/10 **Darvon-N (dextropropoxyphene) - Recall and Withdrawal in Canada** - Paladin Labs Inc. Paladin Labs Inc. in collaboration with Health Canada would like to inform healthcare professionals of the voluntary recall and withdrawal of the opioid analgesic Darvon-N (dextropropoxyphene) in Canada. (widen the QRS complex, prolong the QT interval and therefore increase the risk of serious abnormal heart rhythms.)

Health Canada Feb/12 has recently approved vandetanib (CAPRELSA) to treat medullary thyroid cancer in adult patients where either the tumour cannot be removed by surgery or it has spread from the thyroid gland to other parts of the body. CAPRELSA can cause serious QT heart rhythm changes which may result in sudden death, if left untreated.

Health Canada Mar/12: **Domperidone** should be used at the lowest possible dose. The risk of serious ventricular arrhythmias and sudden cardiac death may be higher in patients taking daily doses greater than 30 mg, and in patients over 60 years old.

Hough DW, Natarajan J, Vandebosch A, et al. Evaluation of the effect of **paliperidone** extended release and **quetiapine** on corrected QT intervals: a randomized, double-blind, placebo-controlled study. Int Clin Psychopharmacol. 2010 Sep 28.

Hunt K, Hughes CA, Hills-Nieminen C. **Protease Inhibitor**-Associated QT Interval Prolongation. Ann Pharmacother. 2011 Dec;45(12):1544-50.

Jackson H, Huisman LA, Sanatani S, Arbour LT. **Long QT syndrome**. CMAJ. 2011 Aug 9;183(11):1272-5.

Kao WHL, Arking DE, Post W, et al. Genetic variations in nitric oxide synthase 1 adaptor protein are associated with sudden cardiac death in US white community-based populations. Circulation 2009; 119:940-951.

Kaufman ES, McNitt S, Moss AJ, Zareba W, et al. Risk of death in the long QT syndrome when a **sibling has died**. Heart Rhythm. 2008 Jun;5(6):831-6. Epub 2008 Mar 4.

Krantz MJ, Martin J, et al. QTc Interval Screening in **Methadone** Treatment. Ann Intern Med. 2009 Jan 19. [Epub ahead print]
450 Recommendation 1 (Disclosure): Clinicians should inform patients of arrhythmia risk when they prescribe methadone. Recommendation 2 (Clinical History): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope. Recommendation 3 (Screening): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures. Recommendation 4 (Risk Stratification): If the QTc interval is greater than ms but less than 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy. Recommendation 5 (Drug Interactions): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone.

Leitch A, McGinness P, Wallbridge D. Calculate the QT interval in patients taking drugs for dementia. BMJ. 2007 Sep 15;335(7619):557.

Medical Letter –Treatment Guidelines: Drugs for Cardiac Arrhythmias. June 2007.

MHRA Dec/11 **Citalopram and escitalopram** are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval. ECG measurements should be considered for patients with cardiac disease, and electrolyte disturbances should be corrected before starting treatment. For citalopram, new restrictions on the maximum daily doses now apply: 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment. For escitalopram, the maximum daily dose for patients older than 65 years is now reduced to 10 mg/day; other doses remain unchanged.

Miceli JJ, Tensfeldt TG, Shiovitz T, et al. Effects of **Oral Ziprasidone and Oral Haloperidol** on QTc interval in patients with Schizophrenia or Schizoaffective disorder. Pharmacotherapy. 2010 Feb;30(2):127-35.

Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of **beta-blocker** therapy in congenital long-QT syndrome.Circulation. 2000 Feb 15;101(6):616-23.

Moretti A, Bellin M, et al. Patient-specific induced **pluripotent stem-cell models** for long-QT syndrome. N Engl J Med 2010.

Morganroth J, et al; CAPRIE Study Group. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. Chest. 2005 Nov;128(5):3398-406.

Morita H, Wu J, Zipes DP. The **QT syndromes**: long and short. Lancet. 2008 Aug 30;372(9640):750-63.

Napolitano C, et al. **Genetic testing** in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA. 2005 Dec 21;294(23):2975-80.

Newton-Cheh C, Eijgelsheim M, Rice KM, et al. **common variants** at ten loci influence QT interval duration in the QTGEN Study. Nature Genetics 2009; DOI:10.1038/ng.364.

Newton-Cheh Christopher, Lin Angela E., Baggish Aaron L., et al. Case 11-2011 — A 47-Year-Old Man with Systemic Lupus Erythematosus and Heart Failure. N Engl J Med 2011; 364:1450-1460. (Infiltrative cardiomyopathy & possible long-QT syndrome due to hydroxychloroquine)

Nuttall GA, Eckerman KM, Jacob KA, et al. Does Low-dose **Droperidol** Administration Increase the Risk of Drug-induced QT Prolongation and Torsade de Pointes in the General Surgical Population? Anesthesiology. 2007 Oct;107(4):531-536. This indicates that the Food and Drug Administration black box warning for low dose droperidol is excessive and unnecessary.

Phillips Mark; Sullivan B; Snyder B; et al. Effect of **Enzyte** on QT and QTc Intervals. Arch Intern Med. 010;170(15):1402-1404.

Roden DM. Clinical practice. **Long-QT syndrome**. N Engl J Med. 2008 Jan 10;358(2):169-76.

Sauer AJ, Newton-Cheh C. Clinical and genetic determinants of **torsade de pointes risk**. Circulation. 2012 Apr 3;125(13):1684-94.

Schwartz PJ, Priori SG, Cerrone M, et al. **Left cardiac sympathetic denervation** in the management of high-risk patients affected by the long-QT syndrome. Circulation. 2004 Apr 20;109(15):1826-33. Epub 2004 Mar 29.

Schwartz PJ, Spazzolini C, Priori SG, et al. Who are the long-QT syndrome patients who receive an **implantable cardioverter-defibrillator** and what happens to them?: data from the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry. Circulation. 2010 Sep 28;122(13):1272-82.

Siddique SM, Shariff N, Vesuwala N, et al. **Metoclopramide** as a possible cause of prolonged QT syndrome and torsade de pointes in

RxFiles: Q&A Summary © www.RxFiles.ca May, 2012 S. Downey BSP, B. Jensen BSP, L.Regier BSP, BA

PROMOTING OPTIMAL DRUG THERAPY www.RxFiles.ca

a patient with heart failure and renal insufficiency. Ann Intern Med. 2009 Apr 7;150(7):502-4.

Stahlmann R, Lode H. Safety considerations of **fluoroquinolones in the elderly**: an update. Drugs Aging 27 (3): 193-209, 2010.

Stollberger C, Huber JO, Finsterer J. **Antipsychotic drugs** and QT prolongation. Int Clin Psychopharmacol. 2005 Sep;20(5):243-51.

Sugiyama A, Nakamura Y, Nishimura S, et al. Comparison of the effects of **levofloxacin** on QT/QTc interval assessed in both healthy Japanese and Caucasian subjects. Br J Clin Pharmacol 2012; 73: 455–9.

Sy RW, van der Werf C, Chatta IS, et al. Derivation and validation of a simple **exercise-based algorithm** for prediction of genetic testing in relatives of LQTS probands. Circulation. 2011;124:2187–2194.

Takaya T, Okamoto M, et al. Torsades de Pointes with QT prolongation related to **donepezil** use. J Cardiol. 2009 Dec;54(3):507-11.

Taubel J, Naseem A, Wang D, et al. Repeated supratherapeutic dosing of **strontium** ranelate 4g/d over 15 days does not prolong QTc interval in healthy volunteers. Br J Clin Pharmacol. 2012 Jan 29.

Thottathil P, Acharya J, Moss AJ, et al. International Long QT Syndrome Investigative Group. Risk of cardiac events in patients with asthma and long-QT syndrome treated with **beta(2) agonists**. Am J Cardiol. 2008 Oct 1;102(7):871-4. Epub 2008 Jul 17.

Van Dorn CS et al. **QTc Values Among Children and Adolescents** Presenting to the Emergency Department. Pediatrics. 2011 Dec;128(6):e1395-401.

van Gorp F, Whyte IM, et al. Clinical and ECG effects of **escitalopram** overdose. Ann Emerg Med. 2009 Sep;54(3):404-8.

van Gorp F, Duffull S, Hackett LP, Isbister GK. Population pharmacokinetics and pharmacodynamics of **escitolapram** in overdose and the effect of activated charcoal. Br J Clin Pharmacol 2012; 73: 402–10.

Viskin S, Postema PG, Bhuiyan ZA, et al. The response of the QT interval to the brief **tachycardia provoked by standing. A bedside test** for diagnosing long-QT syndrome. J Am Coll Cardiol 2010

Wang NC, Maggioni AP, Konstam MA, et al. Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Clinical implications of QRS duration in patients hospitalized with worsening **heart failure** & reduced left ventricular ejection fraction. JAMA. 2008 Jun 11;299(22):2656-66. A prolonged QRS duration appears common in patients with reduced LVEF who are hospitalized for heart failure and is an independent predictor of high postdischarge morbidity and mortality.

Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-Interval Effects of Methadone, Levomethadyl, and Buprenorphine in a Randomized Trial. Arch Intern Med. 2007 Dec 10;167(22):2469-75. **Buprenorphine is associated with less** QTc prolongation than levomethadyl or methadone and may be a safe alternative.

Weinberg G, Di Gregorio G, Hiller D, et al. Reversal of haloperidol-induced cardiac arrest by using lipid emulsion. Ann Intern Med. 2009 May 19;150(10):737-8.

Zhang Y, Post WS, Dalal D, et al.. **QT-interval duration and mortality**: results from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2011;171(19):1727-1733.

TOP

Other acne drugs

	Salicylic Acid = SA▼x Oxy, Clearasil, Neutrogena, others Gels, lotions, toners, cleansers, sticks, pads, washes & astringents 0.5, 1, 2 & 3.5%	Common: less irritating than BP, burning, stinging, pruritius & erythema Serious: rare systemic salicylate toxicity: nausea, vomiting, diarrhea, dizziness, loss of hearing, lethargy, psychic disturbances & hyperpnea ?protect from sun 8-12 weeks for noted improvement	√Used with topical retinoids to treat mild comedonal acne or 2nd line monotherapy agent[3] (also for seborrhea & psoriasis) ☒Not commonly recommended (less potent than equal strength BP) DI: ↑ skin irritation or drying effect: Abrasive or medicated soaps or cleansers; Acne preps (e.g., BP, Resorcinol, Sulfur, Tretinoin); alcohol-containing topicals (After-shave lotions, perfumed toiletries, cosmetics/soaps with a strong drying effect); Isotretinoin OD or BID, 3-6% is keratolytic , OTC: $10-15

References (ACNE – www.RxFiles.ca) :

[1] Abbas S, Goldberg JW, and Massaro M. Personal cleanser technology and clinical performance. Derm Ther 2004;17:35-42
[2] Magin P, Pond D, Smith W & Watson A. A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight. Family Practice 2005;22:62-70
[3] Katsambas AD, Stefanaki C, and Cunliffe WJ. Guidelines for Treating Acne. Clin Derm 2004;22:439-44
[4] Russell JJ. Topical therapy for Acne. American Family Physician. 2000;61(2):357-66
[5] Repchinsky, C. Patient Self-Care Helping Patients make therapeutic choices. 2002;Chapter 43:529-45.
[6] Layton AM. A review on the treatment of acne vulgaris. Int J clin Pract. 2006;60(1):64-72.
[7] Neely C et al. Health Care Guideline: Acne Management. 3rd ed. Institute for clinical systems improvement. 2006;May:1-33
[8] Poulin Y. Practical approach to the hormonal treatment of acne. J Cutan Med Surg 2005;8(4):16-21
[9] Work Group:; Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007 Feb 2; [Epub ahead of print]
[10] Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol. 2003 Sep;49(3 Suppl):S200-10.
[11] Agency for Healthcare Research and Quality, 2001
[12] Gray J, ed. Therapeutic Choices. 2003; 4th ed.
[13] AHFS, 2008 online, Micromedex 2010.
[14] Elliott R. Patient Self-Care Helping patients make therapeutic choices. 2002;1st ed.
[15] Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.
[16] James WD. Clinical practice. Acne. N Engl J Med. 2005 Apr 7;352(14):1463-72.
[17] Dreno B. Topical Antibacterial Therapy for Acne Vulgaris. Drugs 2004;64(21):2389-97
[18] Cunliffe WJ, Holland KT, Bojar R, et al. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. Clin Ther 2002;24:1117-33
[19] Eady Ea, Cove JH, Holland KT, et al. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. Br J Dermatol 1989;121:51-7
[20] Simonart T & Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. Br J Derm 2005153:395-403.
[21] Ozolins M, Eady EA, Avery AJ, et al. comparison of five antimicrobial regimens for treatment of mild to moderate inflammation facial acne vulgaris in the community: randomized controlled trial. Lancet 2004;364:2188-95
[22] Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. J Am Acad Dermatol 1997;37:590-5.
[23] Wolf JE Jr, Kaplan D, Kraus SJ, et al. A multicenter, randomized, investigator-blinded study. J Am Acad Dermatol 2003;49:Suppl:S211-S217
[24] Leyden JJ, Hickman JG, Jarratt MT, et al. The efficacy and safety of a combination benzoyl peroxide/clindamycin topical gel compared with benzoyl perosixde alone and a benzoyl peroxide/erythromycin combiantion product. J Cutan Med Surg 2001;5:37-42
[25] Bikowski JB. Clinical experience results with clindamycin 1% benzoyl peroxide 5% gel (Duac) as monotherapy and in combination. J Drugs Dermatol. 2005 Mar-Apr;4(2):164-71.
[26] Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. Med J Aust. 1990 Oct 15;153(8):455-8.
[27] Purdy S, de Berker D. Acne. BMJ. 2006 Nov 4;333(7575):949-53.
[28] Braathen LR. Topical clindamycin versus oral tetracycline and placebo in acne vulgaris. Scand J Infect Dis Suppl 1984;43:71-5
[29] Samuelson JS. An accurate photographic method for grading acne: initial use in adouble-blind clinical comparison of minocycline and tetracycline. J Am Acad Dermatol 1985;12:461-7
[30] Harrison PV. A comparison of doxycycline and minocycline in the treatment of acne vulgaris. Clin Exp Dermatol 1988;13:242-4
[31] Harcup JW, Cooper J. The treatment of acne vulgaris in general practice: a double-blind assessment of co-trimoxazole and tetracycline. Practitioner 1980;224:747-50
[32] Leyden JJ, Kaidbey K, Gans EH. The antimicrobial effects in vivo of minocycline, doxycycline and tetracycline in humans. J Dermatol Treat. 1996;7:223-5
[33] Gammon WR, Meyer C, Lantis S, et al. Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris. J Am Acad Dermatol. 1986;14:183-6
[34] van Vloten WA, Sigurdsson V. Selecting an oral contraceptive agent for the treatment of acne in women. Am J Clin Dermatol. 2004;5(6):435-41.
[35] Arowojolu AO, Gallo MF, Grimes DA, Garner SE. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2004;(3):CD004425.
[36] Thorneycroft H. Gollnick H. Schellschmidt I. Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] Cutis. 74(2):123-30, 2004 .
[37] van Vloten WA. van Haselen CW. van Zuuren EJ. Gerlinger C. Heithecker R. The effect of 2 combined oral Contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] Cutis. 69(4 Suppl):2-15, 2002 Apr.
[38] Healy E, Simpson N. Acne vulgaris. BMJ. 1994 Mar 26;308(6932):831-3.
[39] McLane, J. Analysis of common side effects of isotretinoin. J Am Acad Dermatol 2001;45:S188-94
[40] Marqueling AL & Zane LT. Depression and Suicidal Behavior in Acne Patients Treated with isotretinoin: A systematic review. Semin Cutan Med Surg 2005;24:92-102
Azoulay L, Blais L, Koren G, LeLorier J, Bérard A. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. J Clin Psychiatry. 2008 Apr;69(4):526-32. This is the first controlled study to find a statistically significant association between isotretinoin and depression. Because depression could have serious consequences, close monitoring of isotretinoin users is indicated.
Sundström Anders, Alfredsson Lars, Sjölin-Forsberg Gunilla, et al. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. BMJ 341:doi:10.1136/bmj.c5812 (Published 11 November 2010)
[41] Katsambas A & Papakonstantinou A. Acne: Systemic Treatment. Clin Derm. 2004;22:412-8
[42] Cunliffe WJ, van de Kerkhof PCM, Caputo R, et al. Roaccutane treatment guidelines: results of an international survey. Dermatology 1997;194:351-7
[43] Layton AM, Knaggs H, Taylor J, et al. Isotretinoin for acne vulgaris 10 years later: a safe and successful treatment. Br J Dermatol 1993;129:292-6
[44] Wessels F, Anderson AN, Kropman K. The cost-effectiveness of isotretinoin in the treatment of acne. S Afr Med J 1999;89:780-4
[45] Gollnick H. Current Concepts of the Pathogenesis of Acne Implications for Drug Treatment. Drugs 2003;63(15):1579-96.
[46] Cunliffe WJ, Layton AM. Oral isotretinoin: Patient selection and management. J Dermatol Treat 1993;4(suppl 2):S10-5
[47] Katsambas A, Papkonstantinou A. Acne: Systemic Treatment. Clin Derm 2004;22:412-8
[48] Goldsmith LA, bolognia JL, Callen JP, et al. American Academy of Dermatology Consensus Conference on the Safe and Optimal Use of Isotretinoin: Summary and recommendations. J Am Acad Dermatol 2004;50:900-6.
[49] Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol. 2006 Apr;54(4):644-6.
[50] Shalita A. The integral role of topical and oral retinoids in the early treatment of acne. J Eur Acad Derm Venereol 2001;15(Suppl 3):43-9
[51] Layton AM, Stainforth JM, Cunliffe WJ. 10 years' experience of oral isotretinoin for the treatment of acne vulgaris. J Dermatol Treat 1994;4(Suppl 2):S2-5
[52] Haroun M. Hormonal Therapy of Acne. J Cutan Med Surg 2005;6-10
[53] Simonart T, Dramaix M, De Maertelaer V. Efficacy of tetracyclines in the treatment of acne vulgaris: a review. Br J Dermatol. 2008 Feb;158(2):208-16. {InfoPOEMs 2008-Aug:There is no difference between tetracyclines regarding their efficacy in reducing lesion counts in acne. Although minocycline and doxycycline cost more, they require only once-daily dosing and may be better tolerated. There is no clear advantage to higher doses.}

Other References:

http://www.mayoclinic.com/health/acne/DS00169, accessed September 18, 2006
Haider A & Shaw JC. Treatment of Acne Vulgaris. JAMA. 2004;292:726-735
Phototoxic effects of topical azelaic acid, benzoyl peroxide and adapalene were not detected when applied immediately before UVB to normal skin. Eur J Dermatol. 2004 Jul-Aug;14(4):235-7.

Additional info:

AADA Nov/10 American Academy of Dermatology Association (AADA) updated its position statement on the use of isotretinoin. http://www.aad.org/forms/policies/Uploads/PS/PS-Isotretinoin.pdf

Arowojolu AO, Gallo MF, Lopez LM, Grimes DA, Garner SE. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004425. The three COCs evaluated in placebo-controlled trials are effective in reducing inflammatory and non-inflamm

TOP

lesions. Few differences were found between COC types in their effectiveness for treating acne.
Autret-Leca E, Kreft-Jais C, Elefant E, Cissoko H, Darrouzain F,Grimaldi-Bensouda L, Attia S, Jonville-Béra AP. Isotretinoin exposure during pregnancy: assessment of spontaneous reports in France. Drug Saf. 2010 Aug 1;33(8):659-65.
Bastawrous A, Silvester A, Batterbury M. Laser refractive eye surgery. BMJ2011;342:d2345. (20 April.) (CI: isotretinoin)
Benzoyl peroxide products: Adasept B.P. .5 acne gel; Clean & Clear Continuous Control = BP 5% lotion = WATER based; CLEAN & CLEAR PERSA-GEL = BP 5% gel = WATER BASED; OVERNIGHT ACNE CONTROL LOTION = BP 3% lotion = WATER based; CLEAR ACNE TREATMENT CREAM = BP 5% cream = WATER based; CLEAR PORE ON-THE SPOT ACNE TREATMENT, VANISHING = BP 2.5% lotion; CLEAR SKIN TREATMENT REPAIRING LOTION = BP 3.7% lotion; CLEAR ZONE ACNE SYSTEM SKIN PURIFYING MOISTURIZER = BP 3.5% lotion; CLEARASIL STAYCLEAR ACNE TREATMENT CREAM BP PLUS - VANISHING = BP 5% cream; CLEARZ - IT = BP 5% lotion; CLINIQUE ACNE SOLUTIONS CLEARING MOISTURIZER = BP 2.5% lotion; CLINIQUE ACNE SOLUTIONS EMERGENCY LOTION = BP 5% lotion; DERMACNE LOTION TRAITMENT 5% = BP 5% lotion; DERMALOGICA SPECIAL CLEARING BOOSTER = BP 5% lotion; LIFE ACNE MEDICATION = BP 5% gel; MEDICATED ACNE GEL 5% = BP 5% gel; NATURE'S CURE ACNE TREATMENT = BP 5% cream; OBAGI CLENZIDERM ACNE GEL = BP 5% gel; OXY 5 COVER UP FORMULA = BP 5% cream; OXY 5 SENSITIVE SKIN VANISHING LOTION = BP 2.5% lotion; OXY 5 VANISHING FORMULA = BP 5% lotion; OXYDERM LOT 20% = BP 20% lotion - Schedule F; OXYDERM LOTION 10% = BP 10% lotion - Schedule F; OXYDERM LOTION 5% = BP 5% lotion; PURE PEFECTION CLASSIC REPLENISHING CLEANSER = BP 2.5% cream; PURE PERFECTION CLASSIC RENEWING CREME = BP 2.5% cream; RODAN & FIELDS/PROACTIV SOLUTION:RENEWING CLEANSER = BP 2.5% lotion; RODAN & FIELDS/PROACTIV SOLUTION:REPAIRING LOTION = BP 2.5% lotion; SPECTRO ACNECARE DEEP PORE VANISHING LOTION = BP 5% lotion; SPECTRO ACNECARE VANISHING LOTION FOR SENSITIVE SKIN = BP 2.5% lotion; CLEAR ZONE ACNE SYSTEM SKIN PURIFYING WASH = BP 3.5% liquid (WASH); PANOXYL CREAMY WASH 4% = BP 4% (WASH)
Berard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br J Clin Pharmacol. 2007 Feb;63(2):196-205. Of the 90 women who became pregnant while on the drug, 76 terminated the pregnancy (84%), three had a spontaneous abortion (3%), two had trauma during delivery resulting in neonatal deaths (2%) and nine had a live birth (10%). Among the live births, only one had a congenital anomaly of the face and neck (11%).
Bernstein CN, et al. Isotretinoin Is Not Associated With Inflammatory Bowel Disease: A Population-Based Case-Control Study. Am J Gastroenterol. 2009 Jul 21. [Epub ahead of print]
Bozzo P, Chua-Gocheco A, Einarson A. Safety of skin care products during pregnancy. Can Fam Physician. 2011 Jun;57(6):665-7. (tretinoin & hydroquinone concern)
Bremner JD, Shearer KD, McCaffery PK. Retinoic acid (Isotretinoin) and affective disorders (depression): the evidence for an association. J Clin Psychiatry. 2011 Aug 23.
Crockett SD et al. Isotretinoin use and the risk of inflammatory bowel disease: A case–control study. Am J Gastroenterol 2010 Mar 30; [e-pub ahead of print].
Draelos ZD, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol. 2007 Mar;56(3):439.e1-10. Epub 2007 Jan 17. Dapsone gel 5% (Aczone) is marginally more effective than placebo (NNT = 13, 9-23) in the treatment of acne vulgaris. At 12 weeks of treatment, less than half the patients in the treatment group received acne assessment scores of "none" or "minimal". No serious adverse events were reported, but data from follow-up longer than 3 months is forthcoming. (LOE = 1b)
Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD.2011.
Fanelli Matthew; Kupperman Eli; Lautenbach Ebbing; et al. Antibiotics, Acne, and Staphylococcus aureus Colonization. Arch Dermatol. 2011;0(2011):archdermatol.2011.67.
Garner SE, Eady EA, Popescu C, Newton J, Li WA. Minocycline for acne vulgaris: efficacy and safety.Cochrane Database Syst Rev. 2003;(1):CD002086.
Goldgar C, Keahey DJ, Houchins J. Treatment options for acne rosacea. Am Fam Physician. 2009 Sep 1;80(5):461-8.
Goodfield MJ, Cox NH, Bowser A, et al. Advice on the safe introduction and continued use of isotretinoin in acne in the U.K. 2010. Br J Dermatol 2010;162:1172-9. http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Isotretinoin%20Guidelines%202010.pdf
Halvorsen JA, Vleugels RA, Bjertness E, Lien L. A population-based study of acne and body mass index in adolescents. Arch Dermatol. 2012 Jan;148(1):131-2.
Hamilton Fiona, Car Josip, Layton Alison. Acne vulgaris. BMJ 2009;338:a2738, doi: 10.1136/bmj.a2738 (Published 5 June 2009)
Health Canada Sept/07 is advising consumers not to use BuXie PaiDu XiaoDou Su is used as an acne treatment and was found to contain the prescription drug rifampicin (rifampin).
Health Canada Feb/10 Accutane has been associated with cases of severe skin reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme).
iPLEDGE (The iPLEDGE program is a computer-based risk management program designed to further the public health goal to eliminate fetal exposure to isotretinoin through a special restricted distribution program approved by the FDA. The program strives to ensure that: No female patient starts isotretinoin therapy if pregnant & No female patient on isotretinoin therapy becomes pregnant . This enhanced program is a SINGLE pregnancy risk management program for prescribing and dispensing all isotretinoin products (brand and generic products). The iPLEDGE program requires registration of all wholesalers distributing isotretinoin, all healthcare professionals prescribing isotretinoin, all pharmacies dispensing isotretinoin, and all male and female patients prescribed isotretinoin. This program is designed to create a verifiable link between the negative pregnancy test and the dispensing of the isotretinoin prescription to the female patient of childbearing potential. The iPLEDGE program requires that all patients meet qualification criteria and monthly program requirements. Before the patient receives his/her isotretinoin prescription each month, the prescriber must counsel the patient and document in the iPLEDGE system that the patient has been counseled about the risks of isotretinoin. There are also additional qualification criteria and monthly requirements for female patients of childbearing potential. As part of the ongoing risk management of isotretinoin products, it is crucial that a female of childbearing potential selects and commits to use two forms of effective contraception simultaneously for one month before, during, and for one month after isotretinoin therapy. She must have 2 negative urine or blood (serum) pregnancy tests with a sensitivity of at least 25 mIU/ml before receiving the initial isotretinoin prescription. The first pregnancy test is a screening test and can be conducted in the prescriber's office. The second pregnancy test must be done in a CLIA-certified laboratory according to the package insert. Each month of therapy, the patient must have a negative result from a urine or blood (serum) pregnancy test conducted by a CLIA-certified laboratory prior to receiving each prescription. https://www.ipledgeprogram.com/
Lesens O, Haus-Cheymol R, Dubrous P, et al; Working Group on Cutaneous Infections in the Army. Methicillin-susceptible, doxycycline-resistant Staphylococcus aureus, Coˆte d'Ivoire. Emerg Infect Dis. 2007;13(3):488-490.
Kraft, John, Freiman, Anatoli. Management of acne. CMAJ 2011 0: cmaj.090374
Maloney JM, Dietze P Jr, Watson D, et al. Treatment of Acne Using a 3-Milligram Drospirenone/20-Microgram Ethinyl Estradiol Oral Contraceptive Administered in a 24/4 Regimen: A Randomized Controlled Trial. Obstet Gynecol. 2008 Oct;112(4):773-781.
Margolis David J.; Fanelli Matthew; Kupperman Eli; et al. Association of Pharyngitis With Oral Antibiotic Use for the Treatment of Acne: A Cross-sectional and Prospective Cohort Study. Arch Dermatol. 2011;0(2011):archdermatol.2011.355.
McKeage K, Keating GM. Clindamycin/benzoyl peroxide gel (BenzaClin): a review of its use in the management of acne. Am J Clin Dermatol. 2008;9(3):193-204.
Medical Letter Nov 20/06. Extended release minocycline od (Solodyn) for acne
Medical Letter Nov,2008. Treatment Guidelines: Drugs for Acne, Rosacea and Psoriasis.
Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R, American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol 2009 Apr;60(4):643-59.
Neudorfer M, Goldshtein I, Shamai-Lubovitz O, et al. Ocular Adverse Effects of Systemic Treatment With Isotretinoin. Arch Dermatol. 2012 Apr 16.
November 8, 2006 -- Medicis and Dow Pharmaceutical Sciences, Inc. announced that the U.S. Food and Drug Administration ("FDA") has approved Ziana(TM) (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel. Ziana(TM) Gel is the first and only combination of clindamycin and tretinoin approved for once daily use for the topical treatment of acne vulgaris in patients 12 years or older.
November 8, 2006 -- QLT Inc. announced positive results of a Phase IV clinical trial of Aczone(TM) dapsone in more than 50 patients with G6PD deficiency that was performed to meet a post-approval commitment requested by the FDA. Mar/08 FDA removes G6PD screening & labeling requirements from the label. June 6/08 /CNW/ - QLT Inc. (NASDAQ: QLTI; TSX: QLT) announced today that Health Canada has completed its review of QLT USA, Inc.'s labeling supplement (SNDS) for Aczone(R) and has removed the glucose-6-phosphate dehydrogenase (G6PD) screening and blood monitoring requirements.
Perera E, Massie J, Phillips RJ. Treatment of Acne with Oral Isotretinoin in Patients with Cystic Fibrosis. Arch Dis Child. 2009 May 21. [Epub ahead of print] PubMed PMID: 19465582. Adolescents with cystic fibrosis and acne can be treated with oral isotretinoin. Oral isotretinoin should be considered for adolescents with cystic fibrosis who have acne associated with scarring, acne not clearing with topical and antibiotic treatment, acne associated with depression, or severe cystic acne.
Pickett H, Wiltz S. Adapelene/Benzoyl peroxide (Epiduo/Tactuo) for acne vulgaris. Am Fam Physician. 2011 Jun 15;83(12):1486-91.
Piette WW, Taylor S, Pariser D, Jarratt M, Sheth P, Wilson D. Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. Arch Dermatol. 2008 Dec;144(12):1564-70. After treatment with dapsone gel, 5%, no clinical or laboratory evidence of drug-induced hemolytic anemia was noted in G6PD-deficient subjects with acne vulgaris.
Rehn L, Merirınne E, et al. Depressive symptoms & suicidal ideation during isotretinoin treatment: a 12-week follow-up study of male Finnish military conscripts. J Eur Acad Dermatol Venereol. 2009 Jun 11. [Epub ahead of print] On group level, isotretinoin seems not to be typically associated with treatment-emergent depression or suicidal ideation among young men. However, the possibility that individual patients may be susceptible for mood effects of isotretinoin as a rare idiosyncratic reaction can not be excluded.
Scope A, Agero AL, Dusza SW, Myskowski PL, Lieb JA, Saltz L, Kemeny NE, Halpern AC. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. J Clin Oncol. 2007 Dec 1;25(34):5390-6. Prophylaxis with oral minocycline may be useful in decreasing the severity of the acneiform rash during the first month of cetuximab treatment. Topical tazarotene is not recommended for management of cetuximab-related rash.
Smith RN, Braue A, Varigos GA, Mann NJ. The effect of a low glycemic load diet on acne vulgaris and the fatty acid composition of skin surface triglycerides. J Dermatol Sci. 2008 Apr;50(1):41-52.
Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al.; American Academy of Dermatology/American Academy of Dermatology Association. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007 Apr;56(4):651-63. Epub 2007 Feb 5.
Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: Assessment of efficacy and safety in 2813 patients. J Am Acad Dermatol. 2008 Sep 19.
Clindamycin-BPO 2.5% provides statistically significant greater efficacy than individual active ingredients and vehicle with a highly favorable safety and tolerability profile.
Turowski CB, James WD. The efficacy and safety of amoxicillin, trimethoprim-sulfamethoxazole, and spironolactone for treatment-resistant acne vulgaris. Adv Dermatol. 2007;23:155-63.
Weinstock MA, Bingham SF, Lew RA, et al. Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial Group. Topical tretinoin therapy and all-cause mortality. A total of 1131 veterans were randomized. Their mean age was 71 years. Patients with a very high estimated short-term risk of death were excluded. Interventions Application of tretinoin, 0.1%, or vehicle control cream twice daily to the face and ears. Arch Dermatol. 2009 Jan;145(1):18-24. We observed an association of topical tretinoin therapy with death, but we do not infer a causal association that current evidence suggests is unlikely.
Williams Hywel C, Dellavalle Robert P, Garner Sarah. Acne vulgaris. www.thelancet.com Published online August 30, 2011

TOP

For more information, topics and products see: **www.RxFiles.ca**

Web sites:
American Academy of Dermatology www.skincarephysicians.com/acnenet/FAQ.html www.aad.org/public/publications/pamphlets/common_acne.html?media=print
Medline Plus www.nlm.nih.gov/medlineplus/tutorials/acne/htm/index.htm
National Institute of Arthritis and Musculoskeletal and Skin Diseases www.niams.nih.gov/Health_Info/Acne/default.asp

TOP

EXTRAS:

Eczema in Children – NICE guideline approach http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11636

Tx Escalator ⇳			
			Systemic treatment
			Phototherapy
		Bandages	Bandages
		Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Mild potency corticosteroids	Mild potency corticosteroids	Mild potency corticosteroids
	emolliants	emolliants	emolliants
	Mild	**Moderate**	**Severe**
	Atopic ezema severity		

Ridd M, Purdy S. Exacerbation of atopic eczema in children. BMJ. 2009 Aug 25;339:b2997.

Relative Absorption

Forearm	***1.0***
Sole	***0.14***
Back	***1.7***
Scalp	***3.5***
Forehead	***6.0***
Cheek	***13.0***
Scrotum	***42.0***

Cushing Syndrome (pituitary-adrenal axis suppression)**:**
- 50g of 0.05% clobetasol/wk or
- 500g of 1% hydrocortisone/wk
- in infants: a little as 1g/day x several days may ↓ HPA

Topical Corticosteroids: Comparison Chart

[1] American Hospital Formulary System (AHFS) Drug Information 2009.
[2] Merck Manual of Diagnosis and Therapy 1999 (http://www.merck.com/pubs/mmanual/tables/110tb1.htm access verified May 27, 2003)
[3] WHO Model Prescibing Information: Drugs Used Dermatology, draft 1995.
[4] Stoughton R. The vasoconstrictor assay in bioequivalence testing: practical concerns and recent developments. Int J Dermatol 1992; Suppl 1:26-28.
[5] Brazzini B, Pimpinelli N. New & established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. Am J Clin Dermatol. 2002;3(1):47-58.
[6] Korting HC, Unholzer A, Schafer-Korting M, Tausch I, Gassmueller J, Nietsch KH. Different skin thinning potential of equipotent medium-strength glucocorticoids. Skin Pharmacol Appl Skin Physiol. 2002 Mar-Apr;15(2):85-91.
[7] FDA Issues Public Health Advisory Informing Health Care Providers of Safety Concerns Associated with the Use of Two Eczema Drugs, Elidel and Protopic Mar 10,2005 http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html April/05 Health Canada http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_31.html **CDA response:** http://www.dermatology.ca/public-patients/atopic-dermatitis/calcineurin_e.php

Additional References:

Alabdulrazzaq F, Koren G. Topical corticosteroid use **during pregnancy**. Can Fam Physician. 2012 Jun;58(6):643-4.

Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. BMJ 2005; 330:516-25**.** (InfoPOEMs: In comparison studies to date, tacrolimus is as effective as steroids in adults and is more effective in the higher concentration (0.1%) than weak corticosteroids in children. Pimecrolimus was less effective than potent steroids in adults, and has not been studied compared with weak corticosteroids. Neither has been studied in patients with corticosteroid-resistant lesions. These are expensive alternatives to corticosteroids. The Unites States Food and Drug Administration has issued a caution linking these drugs to cancer, and does not recommend them for children younger than 2 years. (LOE = 1a))

Arellano FM, Arana A, Wentworth CE, et al. **Lymphoma** among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom. J Allergy Clin Immunol. 2009 May;123(5):1111-6, 116.e1-13. Epub 2009 Apr 10. We did not find any cases of lymphoma in TCI users; however, the number of patients exposed to (topical calcineurin inhibitors) TCI was insufficient to study any possible association between lymphoma and these drugs. Our results show an association between lymphoma-especially skin lymphoma-and use of TCS. The risk increased with duration of exposure and potency of (topical corticosteroids) TCS.

Baumer JH. Guideline review: **atopic eczema** in children, NICE. Arch Dis Child. 2008 Apr 1; [Epub ahead of print]

Bieber T, Cork M, Ellis C, Girolomoni G, Groves R, Langley R, Luger T,Meurer M, Murrell D, Orlow S, Paller A, de Prost Y, Puig L, Ring J, Saurat JH, Schwarz T, Shear N, Stingl G, Taieb A, Thestrup-Pedersen K; Pediatric Advisory Committee of the Food and Drug Administration. Consensus statement on the safety profile of topical calcineurin inhibitors. Dermatology. 2005;211(2):77-8.

Breneman D, Fleischer AB Jr, Abramovits W, et al.; for the Tacrolimus Ointment Study Group. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: A randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. J Am Acad Dermatol. 2008 Mar 20; [Epub ahead of print]

Breuer K, Werfel T, Kapp A. Safety and efficacy of topical calcineurin inhibitors in the treatment of childhood atopic dermatitis. Am J Clin Dermatol. 2005;6(2):65-77. (Topical calcineurin inhibitors have been proven to be effective and have a good safety profile during short-term and long-term use for up to 1 year with pimecrolimus and up to 4 years with tacrolimus. Given the lack of extensive experience with use of topical calcineurin inhibitors over longer periods, regular use of these agents, particularly in children, should be undertaken only after careful consideration of individual cases. Sun protection should also be advised.)

Chi CC, Kirtschig G, Baldo M, et al. Topical interventions for **genital lichen sclerosus**. Cochrane Database Syst Rev. 2011 Dec 7;12:CD008240. The current limited evidence demonstrates the efficacy of clobetasol propionate, mometasone furoate, and pimecrolimus in treating genital lichen sclerosus.

Cook BA, Warshaw EM. Role of topical **calcineurin inhibitors** in the treatment of **seborrheic dermatitis**: a review of pathophysiology, safety, and efficacy. Am J Clin Dermatol. 2009;10(2):103-18. doi: 10.2165/00128071-200910020-00003.

Dalziel K, Shaw S. **Lichen sclerosus**. BMJ. 2010 Feb 15;340:c731. doi: 10.1136/bmj.c731.

Drugs for acne, rosacea and psoriasis. Treat Guidel Med Lett. 2005 Jul;3(35):49-56.

Ference J, Last A. Choosing Topical Corticosteroids. Am Fam Phys **2009**;79(2): 135-140.

Forsyth EL, Millard TP. Diagnosis and pharmacological treatment of **chronic actinic dermatitis** in the elderly: an update. Drugs Aging. 2010 Jun 1;27(6):451-6.

Fraser, Lisa-Ann, Van Uum, Stan. Work-up for **Cushing** syndrome. CMAJ 2009 0: cmaj.090250.

Green C, Colquitt JL, Kirby J, Davidson P. Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use. Br J Dermatol 2005; 152:130-41. (InfoPOEMs: Patients should begin with once-daily dosing of topical corticosteroids for atopic eczema, increasing to twice or 3 times per day only if symptoms are not well controlled. (LOE = 1a-))

TOP

Haeck IM, Rouwen TJ, Timmer-de Mik L, et al. Topical corticosteroids in atopic dermatitis and the risk of **glaucoma and cataracts.** J Am Acad Dermatol. 2011 Feb;64(2):275-81.

Kelso JM. Application of topical corticosteroids to sites of **positive immediate-type allergy skin tests** to relieve itching: results of a double-blind, placebo-controlled trial. Ann Allergy Asthma Immunol. 2007 Feb;98(2):182-4. The application of corticosteroid cream to sites of positive immediate-type allergy skin tests does not provide relief of itching; therefore, this practice should be abandoned. Instead, patients should be informed that any itching they may be experiencing will substantially resolve during the next 30 minutes and that application of such topical treatment will not hasten the relief of itching.

Kirtschig G, Middleton P, Bennett C, et al. Interventions for **bullous pemphigoid**. Cochrane Database Syst Rev. 2010 Oct 6;10:CD002292. Very potent topical steroids are effective and safe treatments for BP, but their use in extensive disease may be limited by side-effects and practical factors. Milder regimens (using lower doses of steroids) are safe and effective in moderate BP. Starting doses of prednisolone greater than 0.75 mg/kg/day do not give additional benefit, lower doses may be adequate to control disease and reduce the incidence and severity of adverse reactions. The effectiveness of adding plasma exchange, azathioprine or mycophenolate mofetil to corticosteroids, and combination treatment with tetracycline and nicotinamide needs further investigation.

Knight AK, Boxer M, Chandler MJ. **Alcohol**-induced rash caused by topical **tacrolimus**. Ann Allergy Asthma Immunol. 2005 Sep;95(3):291-2.

Kreuter A, et al. 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of **intertriginous psoriasis**: a double-blind, randomized controlled study. Arch Dermatol. 2006 Sep;142(9):1138-43. The 1% **pimecrolimus was shown to be less potent than 0.1% betamethasone** in the treatment of IP. Considering the adverse-effect profile of long-term application of corticosteroids, occasional or intermittent rescue therapy with short-term topical corticosteroids and maintenance with a less potent agent, such as 1% pimecrolimus or 0.005% calcipotriol, might be appropriate for patients with IP in general practice. (InfoPOEMs: For intertriginous psoriasis (IP), betamethasone is more effective than calcipotriol; calcipotriol is more effective than placebo; & pimecrolimus is mimimally, if at all, effective. (LOE = 1b))

Lebrun-Vignes B, Le Cleach L, Giraudeau B, Chosidow O. Safety of **topical corticosteroid use during pregnancy**. Arch Dermatol. 2012 Apr;148(4):525-7.

Liu C, Zhou Z, Liu G, et al. Efficacy and safety of **dexamethasone ointment on recurrent aphthous ulceration**. Am J Med. 2012 Mar;125(3):292-301.

Lowther A, McCormick T, Nedorost S. Systemic contact dermatitis from propylene glycol. Dermatitis. 2008 Mar-Apr;19(2):105-8.

Medical Letter. Treatment Guidelines. Drugs for **Allergic Disorders**. Aug 2007.

National Institute for Clinical Excellence (NICE). **Tacrolimus and pimecrolimus** for atopic eczema. London (UK): National Institute for Clinical Excellence (NICE); 2004 Aug. 45 p. (Technology appraisal; no. 82). http://www.nice.org.uk/pdf/TA082guidance.pdf

National Institute for Clinical Excellence (NICE). Frequency of application of **topical corticosteroids for atopic eczema**. London (UK): National Institute for Clinical Excellence (NICE); 2004 Aug. 34 p. (Technology appraisal guidance; no. 81).

National Institute for Clinical Excellence (NICE). **Atopic eczema in children**: Management of atopic eczema in children from birth up to the age of 12 years. http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11901

Medscape Mar 18, 2010 - Drugs for eczema made by Novartis AG and Astellas Pharma may need their warning labels expanded after dozens of new reported cases of cancer and infection in children, U.S. Food and Drug Administration staff said in documents released on Thursday. Agency scientists said **46 cancer cases and 71 infection** cases have been reported in patients aged 16 and younger from 2004 to 2008 with Novartis' Elidel and Astellas' Protopic. Both drugs -- also known as pimecrolimus and tacrolimus respectively -- already carry strong warnings about cancer and infection, but officials should consider expanding them to include the new post-marketing reports, they wrote.

Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R, American Academy of Dermatology. Guidelines of care for the management of **psoriasis and psoriatic arthritis**. Section 3. Guidelines of care for the management and treatment of psoriasis with **topical** therapies. J Am Acad Dermatol 2009 Apr;60(4):643-59.

Paller AS, Lebwohl M, Fleischer AB, and the US/Canada Tacrolimus Ointment Study Group. **Tacrolimus** ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: Results from 3 randomized, comparative studies. J Am Acad Dermatol 2005; 52:810-22.
(InfoPOEMs: Tacrolimus ointment is slightly more effective for the treatment of atopic dermatitis (AD) than pimecrolimus cream in pediatric and adult patients with moderate to severe disease. Adverse events are similar with both treatments. However, there is recent concern about the potential for an increased risk of skin cancer with prolonged use of either product. (LOE = 1b))

Paul C, et al. Safety and tolerability of 1% **pimecrolimus** cream among infants: experience with 1133 patients treated for up to 2 years. Pediatrics. 2006 Jan;117(1):e118-28. Epub 2005 Dec 15.

Reitamo S, Ortonne JP, Sand C, et al.; European Tacrolimus Ointment Study Group. A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% **tacrolimus** ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol. 2005 Jun;152(6):1282-9.

Reitamo S, Rustin M, Harper J, et al. the 0·1% Tacrolimus Ointment Long-term Follow-up Study Group. A **4-year follow-up** study of atopic dermatitis therapy with 0.1% **tacrolimus** ointment in children and adult patients. Br J Dermatol. 2008 Jul 15. [Epub ahead of print] n=782. The safety profile of intermittent or continuous long-term application of 0.1% tacrolimus ointment for up to 4 years was consistent with that which has been established from shorter studies and gave no reason for concern. In addition, 0.1% tacrolimus ointment demonstrated sustained efficacy as reflected by the expression of high satisfaction with treatment by both patients and investigators.

Rigopoulos D, et al. Tacrolimus ointment 0.1% in pityriasis alba: an open-label, randomized, placebo-controlled study. Br J Dermatol. 2006 Jul;155(1):152-5. (InfoPOEMs: **Tacrolimus is an option for the treatment of pityriasis alba** (PA). Note that this drug has not been approved for use in children younger than 2 years and should be used in all patients for as short a time as possible since long-term use has been associated with an increased risk of lymphoma and skin cancer. Since PA is a self-limiting condition, with patients in the control group improving throughout the study, this expensive and potentially harmful agent should only be used after a careful discussion of the risks and benefits with patients and their parents. Moisturizers, sun block, and low-dose corticosteroids are first-line treatments. (LOE = 1b))

Rustin MH. The safety of **tacrolimus** ointment for the treatment of atopic dermatitis: a review. Br J Dermatol. 2007 Nov;157(5):861-73. Epub 2007 Sep 13.

Schwarz T, Kreiselmaier I, Bieber T, et al. A randomized, double-blind, vehicle-controlled study of 1% pimecrolimus cream in adult patients with **perioral dermatitis**. J Am Acad Dermatol. 2008 Jul;59(1):34-40. Epub 2008 May 7. Adults with perioral dermatitis clinically improve faster with 1% pimecrolimus cream (Elidel) compared with inactive placebo, but after 1 month there is no longer any significant difference in response rates between active and control therapy. In this study, the subgroup of patients with a history of topical corticosteroid use received significantly more benefit from pimecrolimus cream. (LOE = 1b-)

SIGN: Scottish Intercollegiate Guidelines Network, 2011. Management of atopic eczema in primary care – a national clinical guideline [online]. Available: http://www.sign.ac.uk/pdf/sign125.pdf [Accessed 19 May 2011].

TOP

Usatine RP, Tinitigan M. Diagnosis and Treatment of **Lichen Planus**. Am Fam Physician. 2011;84(1):53-60.

van Velsen SGA et al. **Bone mineral density** in children with moderate to severe atopic dermatitis. J Am Acad Dermatol 2010 Nov; 63:824.

Useful tables from Canadian Glaucoma Guidelines 2009:

Table 19—Staging each eye for glaucoma damage

Suspect	One or two of the following: IOP >21 mm Hg; suspicious disc or cup to disc (C/D) asymmetry of >0.2; suspicious 24-2 (or similar) VF defect
Early	Early glaucomatous disc features (e.g. C/D* <0.65) and (or) mild VF defect not within 10° of fixation (e.g. MD better than –6 dB on HVF 24-2)
Moderate	Moderate glaucomatous disc features (e.g. vertical C/D* 0.7–0.85) and (or) moderate VF defect not within 10° of fixation (e.g. MD from –6 to –12 dB on HVF 24-2)
Advanced	Advanced glaucomatous disc features (e.g. C/D* >0.9) and (or) VF defect within 10° of fixation† (e.g. MD worse than –12 dB on HVF 24-2)

Adapted from Damji et al.[160]

Please refer to text in order to decide whether a nerve exhibits characteristics of glaucomatous damage.
*Refers to vertical C/D ratio in an average size nerve. If the nerve is small, then a smaller C/D ratio may still be significant; conversely, a large
nerve may have a large vertical C/D ratio and still be within normal limits.
†Also consider baseline 10-2 VF (or similar)
Note: MD, mean deviation; HVF, Humphrey Visual Field Analyzer.

Table 20—Suggested upper limit of initial target IOP for each eye

Stage	Suggested upper limit of target IOP. Modify based on longevity, QOL and risk factors for progression	Evidence
Suspect in whom a clinical decision is made to treat	24 mm Hg with at least 20% reduction from baseline	OHTS,[47] EGPS[325]
Early	20 mm Hg with at least 25% reduction from baseline	EMGTS,[48] CIGTS[326]
Moderate	17 mm Hg with at least 30% reduction from baseline	CNTGS,[12] AGIS[11]
Advanced	14 mm Hg with at least 30% reduction from baseline	AGIS,[11] Odberg[327]

Adapted from Damji et al.[160]

Note: Target IOP may need to be adjusted during the course of follow-up. Extremes of CCT may be helpful in the setting of target IOP. For example, if the cornea is very thin, this may encourage a more aggressive approach with more frequent follow-up.[161]

Table 21—Advantages and disadvantages of single and combined cataract and glaucoma procedures

Procedure	Advantages	Disadvantages
Phacoemulsification alone	Quick procedure with more rapid visual recovery	Postoperative IOP spike is a potential risk, particularly in patients with advanced VF loss
	Improved vision, which benefits QOL	Not regarded as a consistent or powerful means of lowering IOP
	May lower IOP a small amount in some patients	IOP should be watched closely in both the early postoperative period and later
Trabeculectomy alone	Quicker than combined procedure	Will not improve vision
	May achieve superior long-term IOP lowering than combined procedure or cataract alone	May cause or worsen cataract
Combined procedure	Minimizes anesthetic risk by combining 2 procedures in 1	May not be as effective at long-term IOP control as trabeculectomy alone
	Convenience to patient with 1 trip to operating room rather than 2	Increased risk of complications with 2 procedures rather than 1
	Cost savings	Slower visual recovery than doing cataract alone
	May blunt potentially damaging postoperative IOP spikes in patients with advanced VF loss	
	Opportunity to improve IOP control and improve vision at the same time with enhanced QOL	

References: *RxFiles* - Glaucoma

[1] Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. *Pharmacotherapy: a pathophysiologic approach*. Fourth ed. Stamford, CT: Appleton and Lange; 1999:1470-75.

[2]Boucher M. Glaucoma: Keeping a close eye on your patients. *Pharmacy Practice* 2000; 16(2): 61-66

[3] Tsao S. The use of drugs in glaucoma patients. *CPJ* 2000; 133(7): 30-34.
[4] Micromedex 2010
[5] Khaw PT, Shah P, Elkington AR. Glaucoma--1: Diagnosis. BMJ. 2004 Jan 10;328(7431):97-9.
[6] Khaw PT, Shah P, Elkington AR. Glaucoma--2: Treatment. BMJ. 2004 Jan 17; 328(7431): 156-8.
[7] van der Valk R, Webers CA, Schouten JS, et al. Intraocular Pressure-Lowering Effects of All Commonly Used Glaucoma Drugs A **Meta-analysis** of Randomized Clinical Trials. Ophthalmology. **2005** May 24; [Epub ahead of print] Conclusion: This meta-analysis suggests that bimatoprost, travoprost, latanoprost, and timolol are the most effective intraocular pressure-reducing agents in POAG and OH patients.
[8] Reis R, dos Santos LC, Vila MP, Magacho L. Effects of travoprost 0.004% ophthalmic solution, six weeks after its laminated packaging had been removed, in primary open-angle glaucoma: a randomized, controlled, investigator-blinded study. Clin Ther. 2004 Dec;26(12):2121-7.
[9] Simmons ST, Dirks MS, Noecker RJ. Bimatoprost versus latanoprost in lowering intraocular pressure in glaucoma and ocular hypertension: results from parallel-group comparison trials. Adv Ther. 2004 Jul-Aug;21(4):247-62. Konstas AG, Hollo G, Irkec M, Tsironi S, Durukan I, Goldenfeld M, Melamed S. Diurnal IOP control with bimatoprost versus latanoprost in exfoliative glaucoma: a crossover, observer-masked, three-centre study. Br J Ophthalmol. 2007 Jun;91(6):757-60. Epub 2006 Nov 23. This crossover study suggests that better diurnal IOP control is obtained with bimatoprost than with latanoprost in patients with XFG. N=129. Curran MP. Bimatoprost: a review of its use in open-angle glaucoma and ocular hypertension. Drugs Aging. 2009;26(12):1049-71. doi: 10.2165/11203210-000000000-00000.
[10] Doi LM, Melo LA Jr, Prata JA Jr. Effects of the combination of bimatoprost and latanoprost on intraocular pressure in primary open angle glaucoma: a randomised clinical trial. Br J Ophthalmol. 2005 May;89(5):547-9.
[11] Garcia-Sanchez J, Rouland JF, Spiegel D, et al. A comparison of the fixed combination of latanoprost and timolol with the unfixed combination of brimonidine and timolol in patients with elevated intraocular pressure. A six month, evaluator masked, multicentre study in Europe. Br J Ophthalmol. 2004 Jul;88(7):877-83.
[12] Johnson SM, Martinez M Freedman S. Management of glaucoma in pregnancy and lactation. Surv Opthalmol 2001;45:449-54.

AAO- American Academy of Ophthalmology Glaucoma Panel. **Primary open-angle glaucoma**. San Francisco (CA): American Academy of Ophthalmology; 2010. http://one.aao.org/ce/practiceguidelines/ppp_content.aspx?cid=93019a87-4649-4130-8f94-b6a9b19144d2

AAO-American Academy of Ophthalmology Glaucoma Panel. **Primary open-angle glaucoma suspect**. San Francisco (CA): American Academy of Ophthalmology; 2010. http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=e2387c8a-e51c-4c21-be20-c30fbf4f3260

Alm A, Grunden JW, Kwok KK. **Five-year**, Multicenter Safety Study of Fixed-combination Latanoprost/Timolol (**Xalacom**) for Open-angle Glaucoma and Ocular Hypertension. J Glaucoma. 2010 May 29.

Alvan G, Calissendorff B, Seideman P, et al. **Absorption of ocular timolol**. Clin Pharmacokinet. 1980 Jan-Feb;5(1):95-100.

American Optometric Association. Care of the patient with open angle glaucoma. St. Louis (MO): American Optometric Association; **2010**. http://www.aoa.org/documents/CPG-9.pdf

American Optometric Association. Care of the patient with open angle glaucoma. 2nd ed. St. Louis (MO): American Optometric Association; 2002 Aug 17. http://www.aoa.org/documents/CPG-9.pdf

Aptel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandin analogs: a meta-analysis of randomized controlled clinical trials. J Glaucoma. 2008 Dec;17(8):667-73. The findings suggest a greater efficacy of bimatoprost compared with latanoprost and travoprost, although the incidence of hyperemia was lower with the latter 2 agents.

Arici MK, et al. The effect of **latanoprost**, bimatoprost, & **travoprost** on intraocular pressure after cataract surgery. J Ocul Pharmacol Ther. 2006 Feb;22(1):34-40. Our findings show that a single-dose topical of latanoprost and travoprost can prevent early postoperative IOP elevation after phacoemulsification surgery without any side effects.

Barnett EM, Fantin A, Wilson BS, Kass MA, Gordon MO; **Ocular Hypertension Treatment Study** Group. The Incidence of Retinal Vein Occlusion in the Ocular Hypertension Treatment Study. Ophthalmology. 2010 Mar;117(3):484-488.

Becker ML, Huntington N, Woolf AD. **Brimonidine tartrate poisoning** in children: frequency, trends, and use of naloxone as an antidote. Pediatrics. 2009 Feb;123(2):e305-11. Epub 2009 Jan 5. All children < or =5 years of age with confirmed brimonidine ingestions should be medically evaluated and monitored for an extended period. Indications for the use of naloxone in brimonidine poisoning remain uncertain.

Bournias TE, Lai J. Brimonidine Tartrate 0.15%, Dorzolamide Hydrochloride 2%, and Brinzolamide 1% Compared as Adjunctive Therapy **to Prostaglandin Analogs**. Ophthalmology. 2009 Jul 8. [Epub ahead of print] The addition of brimonidine to a PGA provided greater IOP lowering than the addition of either dorzolamide or brinzolamide.

Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee; Canadian Ophthalmological Society. **Canadian Ophthalmological Society** evidence-based clinical practice guidelines for the management of **glaucoma** in the adult eye. Can J Ophthalmol. 2009;44 Suppl 1:S7-93.

Cantor LB, Hoop JS, Morgan L. IOP-Lowering Efficacy of Bimatoprost 0.03% and Travoprost 0.004% in Patients with Glaucoma or Ocular Hypertension. Br J Ophthalmol. 2006 Jul 6; [Epub ahead of print]

Centofanti M, Oddone F, Gandolfi S, et al. Comparison of **Travoprost and Bimatoprost plus Timolol** Fixed Combinations in Open-Angle Glaucoma Patients Previously Treated with Latanoprost plus Timolol Fixed Combination.Am J Ophthalmol.2010 Aug 3.

Chauhan BC; Mikelberg FS; Balaszi AG; et al.; for the Canadian Glaucoma Study Group. Canadian Glaucoma Study: 2. **Risk Factors** for the Progression of Open-angle Glaucoma. *Arch Ophthalmol*. 2008;126(8):1030-1036.

Chauhan BC, Mikelberg FS, Artes PH, Balazsi AG, Leblanc RP, Lesk MR, Nicolela MT, Trope GE; for the Canadian Glaucoma Study Group. Canadian Glaucoma Study: 3. Impact of Risk Factors and Intraocular Pressure Reduction on the Rates of Visual Field Change. Arch Ophthalmol. 2010 Aug 9. Patients with abnormal anticardiolipin antibody levels and increasing age had faster visual field change. Modest IOP reduction in progressing patients significantly ameliorated the rate of visual field decline.

TOP

Cheng JW, Cai JP, Li Y, Wei RL. A meta-analysis of topical **prostaglandin analogs** in the treatment of chronic angle-closure glaucoma. J Glaucoma. 2009 Dec;18(9):652-7.

Chiba T, et al. Effect of non-steroidal anti-inflammatory ophthalmic solution on intraocular pressure reduction by latanoprost in patients with primary open angle glaucoma or ocular hypertension. Br J Ophthalmol. 2006 Mar;90(3):314-7.

De Moraes CG, Juthani VJ, Liebmann JM, Teng CC, Tello C, Susanna R Jr, Ritch R. **Risk factors** for visual field progression in treated glaucoma. Arch Ophthalmol. 2011 May;129(5):562-8. (Especially peak IOP)

Dirks MS, et al. A 3-Month Clinical Trial Comparing the IOP-Lowering Efficacy of **Bimatoprost** and Latanoprost in Patients With Normal-Tension Glaucoma. Adv Ther. 2006 May-Jun;23(3):385-94. Bimatoprost was found to be more effective than latanoprost in lowering IOP in the patient with normal-tension glaucoma. Both drugs were efficacious and well tolerated.

Etminan M, Mikelberg FS, Brophy JM. Selective **Serotonin Reuptake Inhibitors** and the Risk of Cataracts A Nested Case-Control Study. Ophthalmology. 2010 Mar 6.

Fahim A, Morice AH. Heightened **cough** sensitivity secondary to **latanoprost**. Chest. 2009 Nov;136(5):1406-7.

FDA: Nov/07 Cosmetic Eyelash-Lengthener Seized The FDA says U.S. marshals have seized more than 12,000 applicator tubes of Age Intervention Eyelash, a cosmetic promoted to increase eyelash growth, because of concerns it may cause eye damage. In a press release the agency said that the product is an "adulterated cosmetic" because it contains bimatoprost (Lumigan), used to treat elevated intraocular pressure. In patients taking the prescription drug, the agency said the extra dose of bimatoprost may decrease the treatment's effectiveness, leading to optic nerve damage. Other side effects could include macular edema and uveitis.The cosmetic's maker, Jan Marini Skin Research, responded that no cases of eye damage have been reported. It said it reformulated the product last year to remove bimatoprost and that "several other companies have copied [Marini's] discontinued product and continue to market their competing products with 'drug' claims for eyelash growth."

Glaucoma Panel, Preferred Practice Patterns Committee. Primary open-angle glaucoma suspect. San Francisco (CA): American Academy of Ophthalmology (AAO); 2005. http://one.aao.org/asset.axd?id=2e86ca2e-9db0-43c9-b605-c004a82b6ea5

Goldberg I, Moloney G, McCluskey P. Topical ophthalmic medications: what potential for **systemic side effects** and interactions with Other medications. Med J Aust 2008;189:356-7.

Good TJ, Kimura AE, Mandava N, Kahook MY. Sustained elevation of intraocular pressure after intravitreal injections of **anti-VEGF** agents. Br J Ophthalmol. 2010 Aug 11.

Hatanaka M, Grigera DE, Barbosa WL, Jordao M, Susanna R Jr. An eight-week, multicentric, randomized, interventional, open-label, phase 4, parallel comparison of the efficacy and tolerability of the fixed combination of timolol maleate 0.5%/brimonidine tartrate 0.2% versus fixed combination of timolol maleate 0.5%/dorzolamide 2% in patients with elevated intraocular pressure. J Glaucoma. 2008 Dec;17(8):674-9. Both fixed combinations were capable of significantly reducing the mean diurnal IOP, mean diurnal peak, and mean WDT peak after 8 weeks of treatment. Also, both fixed combinations are well tolerated with few side effects.

Honrubia F, Garcia-Sánchez J, Polo V, Martinez-de-la-Casa JM, Soto J. **Conjunctival hyperemia** with the use of **latanoprost** versus other prostaglandin analogues in patients with ocular hypertension or glaucoma: a meta-analysis of randomized clinical trials. Br J Ophthalmol. 2008 Nov 19. [Epub ahead of print] According to available data, the use of latanoprost is associated with a lower incidence of conjunctival hyperemia when compared to travoprost and bimatoprost in the treatment of patients with ocular hypertension or glaucoma.

Hodge WG, Lachaine J, Steffensen I, Murray C, et al. The efficacy and harm of **prostaglandin analogues** for IOP reduction in Glaucoma patients compared to dorzolamide and brimonidine: a **systematic review**. Br J Ophthalmol. 2008 Jan;92(1):7-12. Latanoprost was found to be significantly superior to dorzolamide but not brimonidine. However, ocular adverse events were significantly fewer in latanoprost users than in brimonide users. Neither travoprost nor bimatoprost was compared to dorzolamide or brimonidine in the present literature.

Kass MA, Gordon MO, Gao F, et al. for the Ocular Hypertension Treatment Study Group. Delaying Treatment of Ocular **Hypertension**: The Ocular Hypertension Treatment Study. Arch Ophthalmol. 2010 Mar;128(3):276-287.

Katz LJ, Cohen JS, Batoosingh AL, et al. Twelve-month, randomized, controlled trial of **bimatoprost 0.01%,** 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. Am J Ophthalmol. 2010 Apr;149(4):661-671.e1.

Kenigsberg PA. Changes in medical and surgical treatments of glaucoma between 1997 and 2003 in France. Eur J Ophthalmol. 2007 Jul-Aug;17(4):521-7. Between 1997 and 2003, new glaucoma drugs, primarily prostaglandins, improved intraocular pressure control and delayed surgery, reducing glaucoma surgery by 22%.

Konstas AG, Mikropoulos D, Dimopoulos AT, et al. Second line therapy with dorzolamide/timolol or latanoprost/timolol fixed combination versus adding dorzolamide/timolol fixed combination to latanoprost monotherapy. Br J Ophthalmol. 2008 Aug 14. [Epub ahead of print] This study showed DTFC, LTFC and the addition of DTFC to latanoprost significantly decrease the IOP compared to latanoprost alone, but the latter therapy regime obtains the greatest IOP reduction.

Konstas AG, Katsimbris JM, Lallos N, et al. Latanoprost 0.005% versus bimatoprost 0.03% in primary open-angle glaucoma patients. Ophthalmology. 2005 Feb;112(2):262-6.

Kurtz S, Mann O. Incidence of hyperemia associated with bimatoprost treatment in naïve subjects and in subjects previously treated with latanoprost. Eur J Ophthalmol. 2009 May-Jun;19(3):400-3. The above findings suggest that patients already on prostaglandin therapy may be less likely to experience an increase in conjunctival hyperemia induced by bimatoprost.

Kwon YH, Fingert JH, et al. **Primary open-angle glaucoma**. (Mechanism of Disease) N Engl J Med. 2009 Mar 12;360(11):1113-24.

Landers J, Martin K, Sarkies N, Bourne R, Watson P. A Twenty-Year Follow-up Study of **Trabeculectomy**: Risk Factors and Outcomes. Ophthalmology. 2011 Dec 23.

Leske MC, et al.; Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003 Jan;121(1):48-56.

Levy J, et al. **Topiramate**-induced bilateral angle-closure glaucoma. Can J Ophthalmol. 2006 Apr;41(2):221-5.

Liu JH, Medeiros FA, Slight JR, Weinreb RN. Diurnal and Nocturnal Effects of Brimonidine Monotherapy on Intraocular Pressure. Ophthalmology. 2010 Jul 20. [Epub ahead of print]

Lin HC, Kang JH, Jiang YD, et al. **Hypothyroidism** and the Risk of Developing Open-Angle **Glaucoma** A Five-Year Population-

TOP

Based Follow-Up Study. Ophthalmology. 2010 Jun 15. Hypothyroid patients had a significantly increased risk of OAG development during the 5-year follow-up period. Levothyroxine seemed to be protective.

Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. BMJ. 2005 Jul 1; [Epub ahead of print] CONCLUSIONS: Lowering intraocular pressure in patients with ocular hypertension or manifest glaucoma is beneficial in reducing the risk of visual field loss in the long term.

Marquis RE, Whitson JT. Management of glaucoma: focus on pharmacological therapy. Drugs Aging. 2005;22(1):1-21.

Moroi SE. **Eyelash Preservation** During Chemotherapy & Topical Prostaglandin Therapy.Arch Intern Med.2010;170(14):1269-1270.

Muller ME, van der Velde N, Krulder JW, van der Cammen TJ. Syncope and falls due to timolol eye drops. BMJ. 2006 Apr 22;332(7547):960-1.

NICE April 2009 -- The National Institute for Health and Clinical Excellence (NICE) and the National Clinical Guideline Centre will issue a guideline to improve the diagnosis and management of chronic open angle glaucoma (COAG) and ocular hypertension (OHT). People who have COAG, who are suspected of having COAG or who have OHT should be offered a suite of tests including assessments of the eye pressure, the thickness of the cornea, the drainage area in the eye and field of vision, and an assessment and image of the appearance of the optic nerve heads. People at risk of developing glaucoma should be monitored regularly using tests similar to those used to diagnose glaucoma. The frequency of these tests will depend on how high the risk is of developing glaucoma. Clarity on monitoring intervals for testing people who have glaucoma or are at risk of developing it, and recommendations on follow-up of patients who turn out not to have glaucoma after a period of careful monitoring. Treatment with prostaglandins or beta-blockers to reduce high eye pressure in people with glaucoma or those at risk of the condition. After previous treatment switches, earlier consideration of alternative treatments for worsening glaucoma, such as surgery or laser treatment to avoid disease progression. The guidance will be available at http://www.nice.org.uk/CG85

Nouri-Mahdavi K, Zarei R, Caprioli J. Influence of Visual Field **Testing Frequency** on Detection of Glaucoma Progression With Trend Analyses. Arch Ophthalmol. 2011 Aug 8.

Parikh R, et al. Choroidal drainage in the management of acute angle closure after **topiramate** toxicity. J Glaucoma. 2007 Dec;16(8):691-3.

Pasquale LR, et al. Prospective study of type 2 **diabetes mellitus** and risk of primary open-angle glaucoma in women. Ophthalmology. 2006 Jul;113(7):1081-6. Epub 2006 Jun 6.

Pasquale LR, Willett WC, Rosner BA, Kang JH. **Anthropometric measures** and their relation to incident primary open-angle glaucoma. Ophthalmology. 2010 Aug;117(8):1521-9. Epub 2010 Apr 10.

Passo MS, Palmer EA, Van Buskirk EM. **Plasma timolol** in glaucoma patients. Ophthalmology. 1984 Nov;91(11):1361-3.

Patil AJ, Vajaranant TS, Edward DP. **Bimatoprost** - a review. Expert Opin Pharmacother. 2009 Nov;10(16):2759-68.

Pelletier AL, Thomas J, Shaw FR. **Vision loss** in older persons. Am Fam Physician. 2009 Jun 1;79(11):963-70.

Pharmacist's Letter. Moving On Up: **Altitude** and Your Cardiac Patients. Feb 2010.

Pharmacist's Letter. **Systemic Effects of Ophthalmic Beta-Blockers**. Mar, 20101.

Quigley Harry A. **Glaucoma**. www.thelancet.com Published online March 30, 2011 DOI:10.1016/S0140-6736(10)61423-7.

Rahman MQ, Montgomery DM, Lazaridou MN. Surveillance of Glaucoma Medical Therapy in a Glasgow Teaching Hospital: 26 Years Experience. Br J Ophthalmol. 2009 Jul 23. [Epub ahead of print] Bimatoprost had a higher rate of discontinuation due to adverse effects (25%) than travoprost (16.3%), or latanoprost (12.4%), but this was only statistically significant between latanoprost and bimatoprost (p=0.0038).

Sherwood MB, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combo therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol. 2006 Sep;124(9):1230-8.

Smith S, Fagien S, Whitcup SM, et al. **Eyelash growth** in subjects treated with **bimatoprost**: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. J Am Acad Dermatol. 2012 May;66(5):801-6.

Sonty S, Donthamsetti V, Vangipuram G, Ahmad A. Long-term IOP lowering with bimatoprost in open-angle glaucoma patients poorly responsive to latanoprost. J Ocul Pharmacol Ther. 2008 Oct;24(5):517-20. Significant additional long-term IOP lowering may be achieved by switching to **bimatoprost** in patients with open-angle glaucoma who are not at target IOP with latanoprost.

Sorkhabi R, Alipanahi R, Eftakhari-Milani A, Ghojazadeh L. The Influence of Topical **Diclofenac** Sodium on the Ocular Hypotensive Effect of Latanoprost in Glaucoma Patients. J Glaucoma. 2010 Jun 23.

Stein JD, Newman-Casey PA, Niziol LM, et al. Association between the use of glaucoma medications and **mortality**. Arch Ophthalmol. 2010 Feb;128(2):235-40.

Stein JD, Talwar N, Laverne AM, Nan B, Lichter PR. Trends in Use of **Ancillary Glaucoma Tests** for Patients with Open-Angle Glaucoma from 2001 to 2009. Ophthalmology. 2012 Jan 3.

Tanna AP, Rademaker AW, Stewart WC, Feldman RM. Meta-analysis of the Efficacy and Safety of {alpha}2-**Adrenergic Agonists**, **{beta}-Adrenergic** Antagonists, & **Topical Carbonic Anhydrase Inhibitors With Prostaglandin Analogs**. Arch Ophthalmol. 2010 Jul;128(7):825-33. All 3 classes are similarly effective in lowering mean diurnal IOP when used in combination with PGAs. The AA class is statistically significantly less effective in reducing IOP at trough compared with BBs and TCAIs. The types of adverse events that were identified varied among the different classes of adjunctive therapies.

Trocme S, Hwang LJ, Bean GW, et al. The role of **benzalkonium chloride** in the occurrence of punctate keratitis: a meta-analysis of randomized, controlled clinical trials. Ann Pharmacother. 2010 Dec;44(12):1914-21.

Treatment Guidelines: The Medical Letter. Drugs for Some Common **Eye Disorders**. January 2007;5(53):1-3 ⇒ **January 2010**.

U.S. Preventive Services Task Force (**USPSTF**). Screening for glaucoma: recommendation statement. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2005 Mar. 9. http://www.ahrq.gov/clinic/3rduspstf/glaucoma/glaucrs.pdf

U.S. Preventive Services Task Force (**USPSTF**). Screening for glaucoma: recommendation statement. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2005 Mar. 9 http://www.ahrq.gov/clinic/uspstf/uspsglau.htm

van Issum C, Mavrakanas N, Schutz JS, Shaarawy T. **Topiramate-induced** acute bilateral angle closure and myopia: pathophysiology and treatment controversies. Eur J Ophthalmol. 2010 Nov 4. pii: 6E44A60D-B624-4EDA-9C14-7205923AE923.

Wiggs JL, Yaspan BL, Hauser MA, et al. Common variants at **9p21 and 8q22** are associated with increased susceptibility to optic

TOP

nerve degeneration in glaucoma. PLoS Genet. 2012 Apr;8(4):e1002654.

Wright TM, Freedman SF. Exposure to topical apraclonidine in children with glaucoma. J Glaucoma. 2009 Jun-Jul;18(5):395-8. In contrast to brimonidine, topical apraclonidine 0.5% can safely be administered for short-term treatment of most infants and children undergoing angle surgery for glaucoma, rarely producing systemic side effects.

Yildirim N, Sahin A, Gultekin S. The effect of **latanoprost, bimatoprost, and travoprost** on circadian variation of intraocular pressure in patients with open-angle glaucoma. J Glaucoma. 2008 Jan-Feb;17(1):36-9. Latanoprost, bimatoprost, and travoprost were comparable in their ability to reduce IOP in open-angle glaucoma patients. On the basis of our data, the IOP reduction of these drugs is indistinguishable within statistical parameters.

Zelefsky JR, Fine HF, Rubinstein VJ, Hsu IS, Finger PT. Escitalopram-induced uveal effusions and bilateral angle closure **glaucoma**. Am J Ophthalmol. 2006 Jun;141(6):1144-7.

Other drugs for Glaucoma:

- Osmotic Agents (used for acute rises in IOP)
    - Glycerol – onset 10 min; max effect in 1-2 hours
    - Mannitol – Onset 10-30min; max effect in 1 hour

TOP

[1] Bagchus WM, Hust R, Maris F, Schnabel PG, Houwing NS. Important effect of food on the bioavailability of oral testosterone undecanoate. Pharmacotherapy. 2003 Mar;23(3):319-25.
[2] Bagchus WM, Hust R, Maris F, Schnabel P, Houwing N. Important Effect of Food on the Bioavailablility of Oral Testosterone Undecanoate. Pharmacotherapy 2003;23 (3):319-325.
[3] Gooren LJ. A ten-year safety study of the oral androgen testosterone undecanoate. J Androl. 1994 May-Jun;15(3):212-5.
[4] Padero MC, Bhasin S, Friedman TC. Androgen supplementation in older women: too much hype, not enough data. J Am Geriatr Soc. 2002 Jun;50(6):1131-40.
(Barton DL, Wender DB, Sloan JA, et al. Randomized controlled trial to evaluate transdermal testosterone in female cancer survivors with decreased libido; North Central Cancer Treatment Group protocol N02C3.J Natl Cancer Inst. 2007 May 2;99(9):672-9. Increased testosterone level did not translate into improved libido, possibly because women on this study were estrogen depleted.) (El-Hage G, Eden JA, Manga RZ. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder. Climacteric. 2007 Aug;10(4):335-43.Testosterone cream significantly improved sexual scores in menopausal women with low sexual desire. It was effective, easy to use and had no side-effects over the 3-month period of active treatment. It offers a novel and acceptable method of administering testosterone to menopausal women.) Davis SR, Nijland EA. Pharmacological Therapy for Female Sexual Dysfunction : Has Progress Been Made? Drugs. 2008;68(3):259-264.
[5] Gruenewald DA, Matsumoto AM. Testosterone Supplementation Therapy for Older Men: Potential Benefits and Risks. J Am Geriatr Soc. 2003 Jan;51(1):101-115.
[6] Tenover L. Male Hormone Replacement Therapy Including "Andropause". Endocrin and Metab Clinics of N America 1998;27(4):969-87.
[7] Vermeulen A. Decreased androgen levels and obesity in men. Ann Med. 1996 Feb;28(1):13-5.
[8] Wang C, Eyre DR, et al. Sublingual testosterone replacement improves muscle mass and strength, decreases bone resorption, and increases bone formation markers in hypogonadal men--a clinical research center study. J Clin Endocrinol Metab. 1996 Oct;81(10):3654-62.
[9] Morales A, Lunenfeld B. Investigation, treatment & monitoring of late-onset hypogonadism in males. Official ISSAM. International Society for the Study of the Aging Male.Aging Male.2002 Jun;5(2):74-86.
[10] Report of National Institute on Aging Advisory Panel on Testosterone Replacement in Men. J Clin Endocrinol Metab. 2001 Oct;86(10):4611-4.
[11] Heaton JP. POINT: Urologists should take an active role in the diagnosis and treatment of hypogonadism in the aging male. Can J Urol. 2002 Dec;9(6):1677-80.
[12] Wespes E, Schulman CC. Male andropause: myth, reality, and treatment. Int J Impot Res. 2002 Feb;14 Suppl 1:S93-8.
[13] Report of National Institute on Aging Advisory Panel on Testosterone Replacement in Men. J Clin Endocrinol Metab. 2001 Oct;86(10):4611-4.
[14] Morales A, Tenover JL. Androgen deficiency in the aging male: when, who, and how to investigate and treat. Urol Clin North Am. 2002 Nov;29(4):975-82.
[15] Tenover L. Male Hormone Replacement Therapy Including "Andropause". Endocrin and Metab Clinics of N America 1998;27(4):969-87.
[16] Stas SN, Anastasiadis AG, Fisch H, Benson MC, Shabsigh R. Urologic aspects of andropause. Urology. 2003 Feb;61(2):261-6.
[17] Bhasin S, Bagatell CJ, Bremner WJ, Plymate SR, et al. Issues in testosterone replacement in older men. J Clin Endocrinol Metab. 1998 Oct;83(10):3435-48.
[18] Pope HG Jr, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry 2003 Jan;160:105-11.
[19] Benkert O, Witt W, Adam W, Leitz A. Effects of testosterone undecanoate on sexual potency and the hypothalamic-pituitary-gonadal axis of impotent males. Arch Sex Behav. 1979 Nov;8(6):471-9.
[20] Fairfield WP, Treat M, Rosenthal DI, et al. Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. J Appl Physiol. 2001 Jun;90(6):2166-71.
[21] Bhasin S, Storer TW, et al. Effects of testosterone replacement with a nongenital, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. J Clin Endocrinol Metab. 1998 Sep;83(9):3155-62.
[22] Rhoden E, Morgentaler A. Risks of **Testosterone-Replacement Therapy** and Recommendations for Monitoring. N Engl J Med 2004;350:482-492. (also Editorial pg 440-442)
[23] Pechersky AV, Mazurov VI, et al. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestosterone, oestradiol and prostate volume. Int J Androl. 2002 Apr;25(2):119-25.
[24] Weiss EL, Bowers MB Jr, Mazure CM. Testosterone-patch-induced psychotic mania. Am J Psychiatry. 1999 Jun;156(6):969.

Additional references:

American College of Obstetricians and Gynecologists (**ACOG**). **Female sexual dysfunction**. Washington: American College of Obstetricians and Gynecologists (ACOG); 2011 Apr. 12 p. (ACOG practice bulletin; no. 119).
Anawalt BD, Hotaling JM, Walsh TJ, Matsumoto AM. **Performance of total testosterone measurement** to predict free testosterone for the biochemical evaluation of male hypogonadism. J Urol. 2012 Apr;187(4):1369-73.
Araujo AB, Esche GR, Kupelian V, O'donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB. Prevalence of Symptomatic Androgen Deficiency in Men. J Clin Endocrinol Metab. 2007 Aug 14; [Epub ahead of print] Prevalence of symptomatic androgen deficiency in **men 30 and 79 y of age is 5.6%,** and increases substantially with age.
Arunakumari PS, Walker S. Reduced **sexual desire in women**. BMJ. 2009 Aug 10;339:b2371. doi: 10.1136/bmj.b2371.
Baggish AL, Weiner RB, Kanayama G, et al. Long term **anabolic-androgenic steroid use** is associated with **left ventricular dysfunction**. Circ Heart Fail 2010.
Basaria, Shehzad, Coviello, Andrea D., Travison, Thomas G., et al. **Adverse Events** Associated with Testosterone Administration. (**TOM**) N Engl J Med 2010 0: NEJMoa1000485. In this population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events. The small size of the trial and the unique population prevent broader inferences from being made about the safety of testosterone therapy.
Basson R, Brotto LA, Petkau AJ, Labrie F. Role of **androgens in women's sexual dysfunction**. Menopause. 2010 Sep-Oct;17(5):962-71.
Barton DL, Wender DB, Sloan JA, Dalton RJ, et al. RCT to evaluate transdermal testosterone in female cancer survivors with decreased libido; North Central Cancer Treatment. J Natl Cancer Inst. 2007 May 2;99(9):672-9. {InfoPOEMs: In female cancer survivors, transdermal testosterone does not improve sexual desire even though it increases hormone levels. (LOE = 1b)}
Basson R. Clinical practice. Sexual desire and arousal disorders in **women**. N Engl J Med. 2006 Apr 6;354(14):1497-506.
Bhasin S, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an **endocrine society clinical practice guideline**. J Clin Endocrinol Metab. **2006** Jun;91(6):1995-2010. Epub 2006 May 23. Erratum in: J Clin Endocrinol Metab. 2006 Jul;91(7):2688. We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. We recommend confirmation of the diagnosis by repeating the measurement of morning total testosterone and in some patients by measurement of free or bioavailable testosterone level, using accurate assays. We recommend testosterone therapy for symptomatic men with androgen deficiency, who have low testosterone levels, to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. We recommend against starting testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or induration or prostate-specific antigen greater than 3 ng/ml without further urological evaluation, erythrocytosis (hematocrit > 50%), hyperviscosity, untreated obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score (IPSS) greater than 19, or class III or IV heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan.
Bhasin S, Cunningham GR, Hayes FJ, et al. **Testosterone therapy in men with androgen deficiency syndromes**: an **Endocrine Society clinical practice** guideline. J Clin Endocrinol Metab **2010**;95:2536-59. We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. We recommend confirmation of the diagnosis by repeating the measurement of morning total testosterone and, in some men in whom total testosterone is near the lower limit of normal or in whom SHBG abnormality is suspected by measurement of free or bioavailable testosterone level, using validated assays. We recommend testosterone therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. We recommend agai

TOP

testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or induration or prostate-specific antigen greater than 4 ng/ml or greater than 3 ng/ml in men at high risk for prostate cancer such as African-Americans or men with first-degree relatives with prostate cancer without further urological evaluation, hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score above 19, or uncontrolled or poorly controlled heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan.

Bhasin S, Travison TG, Storer TW, et al. Effect of **testosterone supplementation** with and without a dual **5 alpha-reductase inhibitor** (dutasteride) on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA*. 2012; 307(9):931-939. n=139

Bodybuilding.com and FDA Nov/09 notified healthcare professionals and patients of a nationwide and international recall of all lots and expiration dates of 65 dietary supplement products that were sold through the Company's website, www.bodybuilding.com. FDA believes that the recalled products contain the following ingredients that are currently classified, or the FDA believes should be classified, as steroids: **"Superdrol," "Madol," "Tren," "Androstenedione," and/or "Turinabol."** Acute liver injury is known to be a possible harmful effect of using steroid-containing products. In addition, steroids may cause other serious long-term adverse health consequences in men, women, and children. These include shrinkage of the testes and male infertility, masculinization of women, breast enlargement in males, short stature in children, a higher predilection to misuse other drugs and alcohol, adverse effects on blood lipid levels, and increased risk of heart attack, stroke, and death.

Braunstein GD, et al. Safety & efficacy of a testosterone patch for the treatment of hypoactive sexual desire in surgically menopausal **women**: a randomized, placebo-controlled trial. Arch Intern Med. 2005 Jul 25;165(14):1582-9.

Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal **women**: a randomized trial. Obstet Gynecol. 2005 May;105(5):944-52.

Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in **women**. JAMA. 2005 Jul 6;294(1):91-6. CONCLUSIONS: No single androgen level is predictive of low female sexual function, and the majority of women with low dehydroepiandrosterone sulfate levels did not have low sexual function. (InfoPOEMs: Low total testosterone and free testosterone levels are not associated with low sexual desire and function in women. A serum dehydroepiandrosterone sulfate (DHEA) level below the aged-adjusted 10th percentile is a better marker for low sexual desire and function, but the majority of women with a low DHEA level do not have sexual dysfunction. There is no evidence to support measurement of serum testosterone in women with low sexual desire or function. The practice of prescribing exogenous testosterone for women with low sexual desire or function requires further study and should not be routine. (LOE = 2c))

Davis SR, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Menopause. 2006 May 25

Davis S, Papalia MA, Norman RJ, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in **premenopausal women**: a randomized trial. Ann Intern Med. 2008 Apr 15;148(8):569-77. A daily 90-microL dose of transdermal testosterone improves self-reported sexual satisfaction for premenopausal women with reduced libido and low serum-free testosterone levels by a mean of 0.8 SSE per month. The rate of SSEs with higher and lower testosterone doses did not differ from that with placebo.

Davis SR, Moreau M, Kroll R, et al. **APHRODITE** Study Team. Testosterone for **low libido in postmenopausal women** not taking estrogen. N Engl J Med. 2008 Nov 6;359(19):2005-17. In postmenopausal women not receiving estrogen therapy, treatment with a patch delivering 300 microg of testosterone per day resulted in a modest but meaningful improvement in sexual function. The long-term effects of testosterone, including effects on the breast, remain uncertain.

de Ronde W, Vogel S, Bui HN, Heijboer AC. Reduction in 24-hour plasma testosterone levels in subjects who **showered 15 or 30 minutes after application** of testosterone gel. Pharmacotherapy. 2011 Mar;31(3):248-52.

Elsharkawy A, McPherson S, Masson S. Cholestasis secondary to anabolic steroid (**methandrostenolone**) use in young men. BMJ 2012; 344 doi: 10.1136/bmj.e468 (Published 2 February 2012)

Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, Aleman A, Lock TM, Bosch JL, Grobbee DE, van der Schouw YT. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA. 2008 Jan 2;299(1):39-52. Testosterone supplementation during 6 months to older men with a low normal testosterone concentration did not affect functional status or cognition but increased lean body mass and had mixed metabolic effects.

Endogenous Hormones, Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. **Endogenous sex hormones and prostate cancer**: a collaborative analysis of 18 prospective studies J Natl Cancer Inst. 2008 Feb 6;100(3):170-83. Epub 2008 Jan 29. In this collaborative analysis of the worldwide data on endogenous hormones and prostate cancer risk, serum concentrations of sex hormones were not associated with the risk of prostate cancer.

FDA May/09 notified healthcare professionals that it will require two prescription topical testosterone gel products, AndroGel 1% and Testim 1%, to include a boxed warning on the products' labels after receiving reports of adverse effects in **children** who were **inadvertently exposed** to testosterone through contact with another person being treated with these products. Of the fully reviewed cases, adverse events reported in these **children** included inappropriate enlargement of the genitalia (penis or clitoris), premature development of pubic hair, advanced bone age, increased libido and aggressive behavior.

FDA Aug/09 not to use body-building products marketed as containing **steroids or steroid-like substances** such as TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, and TT-40-Xtreme..

FDA Nov/09 & IDS Sports notified consumers that five of the IDS's dietary supplement products (**Bromodrol, Dual Action Grow Tabs, Grow Tabs, Mass Tabs, and Ripped Tabs TR**) contain the following undeclared substances, which FDA considers to be steroids: "Madol," "Turinabol," "Superdrol," &/or "Androstenedione."

FDA Dec/09 for **S-DROL**: a voluntary recall by the manufacturer of one lot (lot# 810481, expiry date 01/2012) of S-DROL after FDA testing found it to contain undeclared desoxymethyltestosterone.

FDA Dec/09 warned consumers to stop using bodybuilding products manufactured by American Cellular Labs after they were found to contain unauthorized synthetic steroids in **TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, TT-40-Xtreme.**

FDA Jan/10 & **MuscleMaster(dot)com**, Inc. notified consumers and healthcare professionals of the voluntary nationwide recall of all lots and expiration dates of the seventeen dietary supplements listed in the firm press release, sold between June 1, 2009 and November 17, 2009. FDA informed MuscleMaster(dot)com that it believes that the recalled products contain ingredients that are **steroids**.

FDA Oct/11 notified the manufacturer that lab analyses found that the product; **Uprizing 2.0** , sold as a testosterone booster, contains **superdrol**, a synthetic steroid, making it an unapproved new drug.

Feldman HA, Longcope C, Derby CA, et al. **Age trends in the level of serum testosterone** and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2002;87:589-98.

Gaylis FD, Lin DW, Ignatoff JM, Amling CL, Tutrone RF, Cosgrove DJ. **Prostate cancer** in men using testosterone supplementation. J Urol. 2005 Aug;174(2):534-8; discussion 538.

Gault Emma Jane, Perry Rebecca J, Cole Tim J, et al. , on behalf of the British Society for Paediatric Endocrinology and Diabetes. Effect of **oxandrolone** and timing of pubertal induction on final height in Turner's syndrome: randomised, double blind, placebo controlled trial. *BMJ 2011;342:doi:10.1136/bmj.d1980 (Published 14 April 2011)*

Gettler LT, McDade TW, Feranil AB, Kuzawa CW. Longitudinal evidence that **fatherhood decreases testosterone** in human males. Proc Natl Acad Sci U S A. 2011 Sep 12.

Health Canada Feb /06 is warning consumers not to use the product M1T(methyl-1-testosterone) Andro Technologies, or any other supplements containing the synthetic steroid methyl-1-testosterone, due to such potentially serious health risks as liver disorders and hardening of the arteries. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_06_e.html

Health Canada July/07 is warning Canadians not to use the dietary supplement **MdMt**, or any other supplements containing the synthetic steroids methyl-1-testosterone or methyldienolone that are obtained without a prescription, due to potentially serious health risks including reduced fertility and liver disorders.

Hembree WC, Cohen-Kettenis P, et al. Endocrine Society. Endocrine treatment of **transsexual persons**: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009 Sep;94(9):3132-54. [

Idan Amanda, Griffiths Kaye A., Harwood D. Tim, et al. Long-Term Effects of **Dihydrotestosterone** Treatment on Prostate Growth in Healthy, Middle-Aged Men Without Prostate Disease: A Randomized, Placebo-Controlled Trial. Ann Intern Med November 16, 2010 153:621-632. (24 months has no beneficial or adverse effect on prostate growth, but decreases spinal BMD)

Jones TH, Arver S, Behre HM, et al. **TIMES2** Investigators. Testosterone Replacement in Hypogonadal Men With Type 2 **Diabetes and/or Metabolic Syndrome** (the TIMES2 Study). Diabetes Care. 2011 Apr;34(4):828-37.

Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men. European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) prospective population study. Circulation 2007; DOI: 10.1161/CIRCULATIONAHA.107.719005. In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.

Köhler TS, Kim J, Feia K, et al. Prevalence of androgen deficiency in men with **erectile dysfunction**. Urology. 2008 Apr;71(4):693-7. Epub 2008 Mar 3. Androgen deficiency was quite common in men presenting with ED and correlated significantly with age, uncontrolled diabetes, hypercholesteremia, and anemia. Although additional prospective studies evaluating the effect of testosterone supplementation in this population are needed, clinicians, including urologists, should be keenly aware of the large overlap of patients with ED who might also have the entity

TOP

deficiency in the aging male.
Leproult Rachel, Cauter Eve Van. Effect of 1 Week of **Sleep Restriction on Testosterone Levels** in Young Healthy Men. JAMA. 2011;305(21):2173-2174.doi:10.1001/jama.2011.710.
Lu PH, Masterman DA, Mulnard R, et al. Effects of Testosterone on Cognition and Mood in Male Patients With Mild **Alzheimer Disease** and Healthy Elderly Men. Arch Neurol. 2005 Dec 12; [Epub ahead of print] (InfoPOEMs: In this very small study, testosterone supplementation had negligible effects in men with Alzheimer's disease . (LOE = 2b))
Malkin CJ, Pugh PJ, West JN, et al. Testosterone therapy in men with moderate severity **heart failure**: a double-blind randomized placebo controlled trial. Eur Heart J. 2005 Aug 10; [Epub ahead of print]
Marks LS, et al. Effect of Testosterone Replacement Therapy on Prostate Tissue in Men With Late-Onset Hypogonadism: A Randomized Controlled Trial. JAMA. 2006 Nov 15;296(19):2351-2361. (N=44 over 6 months) These preliminary data suggest that in aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions. Establishment of prostate safety for large populations of older men undergoing longer duration of TRT requires further study.
Medical Letter: **Drugs for Female Sexual Dysfunction**. April 23, 2007.
Miller KK, Biller BM, Beauregard C, et al. Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2006 May;91(5):1683-90. Epub 2006 Feb 14. This is the first randomized, double-blind, placebo-controlled study to show a positive effect of testosterone on bone density, body composition, and neurobehavioral function in women with severe androgen deficiency due to hypopituitarism.
Mylonakis E, Koutkia P, Grinspoon S. Diagnosis and treatment of androgen deficiency in **human immunodeficiency virus**-infected men and women. Clin Infect Dis. 2001 Sep 15;33(6):857-64.
Nair KS, et al. **DHEA** (50mg) in elderly **women** and DHEA (75mg) or testosterone in **elderly men**. N Engl J Med. 2006 Oct 19;355(16):1647-59. (n= 2yr 87 males, 57 women) Men who received testosterone had a slight increase in fat-free mass, and men in both treatment groups had an increase in BMD at the femoral neck. Women who received DHEA had an increase in BMD at the ultradistal radius. Neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life. {InfoPOEMS: There is no evidence that supplementation with dehydroepiandrosterone (DHEA) or testosterone has any meaningful clinical benefit for older patients with low serum levels of those hormones.}
North American Menopause Society. NAMS Board of Trustees. The role of testosterone therapy in postmenopausal **women**: position statement of The North American Menopause Society. Menopause. 2005 Sep 1;12(5):497-511 [Epub ahead of print] CONCLUSIONS:
Postmenopausal women with decreased sexual desire associated with personal distress and with no other identifiable cause may be candidates for testosterone therapy. Testosterone treatment without concomitant estrogen therapy cannot be recommended because of a lack of evidence. When evaluating awoman for testosterone therapy, recommendations are to rule out causes not related to testosterone levels (eg, physical and psychosocial factors, medications) and to ensure that there is a physiologic cause for reduced testosterone levels (eg, bilateral oophorectomy). Laboratory testing of testosterone levels should be used only to monitor for supraphysiologic levels before and during therapy, not to diagnose testosterone insufficiency. Monitoring should also include subjective assessments of sexual response, desire, and satisfaction as well as evaluation for potential adverse effects. Transdermal patches and topical gels or creams are preferred over oral products because of first-pass hepatic effects documented with oral formulations. Custom-compounded products should be used with caution because the dosing may be more inconsistent than it is with government-approved products. Testosterone products formulated specifically for men have a risk of excessive dosing, although some clinicians use lower doses of these products in women. Testosterone therapy is contraindicated in women with breast or uterine cancer or in those with cardiovascular or liver disease. It should be administered at the lowest dose for the shortest time that meets treatment goals. Counseling regarding the potential risks and benefits should be provided before initiating therapy.
Ohlsson C, Barrett-Connor E, Bhasin S, et al. **High serum testosterone is associated with reduced risk of cardiovascular events** in elderly men. **The MrOS** (osteoporotic fractures in men) Study in Sweden. J Am Coll Cardiol 2011; 58:1674-1681.
Ohlsson C, Wallaschofski H, Lunetta KL, et al. **Genetic** determinants of serum **testosterone** concentrations in men. PLoS Genet. 2011 Oct;7(10):e1002313.
Okun MS, et al. Testosterone therapy in men with **Parkinson** disease: results of the TEST-PD Study. Arch Neurol. 2006 May;63(5):729-35.
Orme C, Imaeda S. Images in clinical medicine. **Eschar formation from testosterone patch.** N Engl J Med. 2012 May 3;366(18):e28.
Orwoll E, et al. **Osteoporotic Fractures** in Men Study Group. Endogenous testosterone levels, physical performance, and fall risk in older men. Arch Intern Med. 2006 Oct 23;166(19):2124-31. Falls were common among older men. Fall risk was higher in men with lower bioavailable testosterone levels. The effect of testosterone level was independent of poorer physical performance, suggesting that the effect of testosterone on fall risk may be mediated by other androgen actions.
Ottenbacher KJ, et al. Androgen treatment and **muscle strength** in elderly men: a meta-analysis. J Am Geriatr Soc. 2006 Nov;54(11):1666-73.
Page ST, Amory JK, Bowman ED, et al. Exogenous **testosterone** (T) alone or with finasteride increases **physical performance**, grip, strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005;90:1502-10.
Palmert Mark R, Dunkel Leo. **Delayed Puberty**. N Engl J Med 2012; 366:443-453.
Pearson J, Blackman MR. Longitudinal effects of **aging on serum total and free testosterone levels** in healthy men. J Clin Endocrinol Metab 2001;86:724-31.
Pharmacists Letter. **Testim** (Testosterone 1% gel). June 2007.
Qaseem A, Snow V, Denberg TD, Casey DE Jr, Forciea MA, Owens DK, Shekelle P, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. **Hormonal testing** and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2009 Nov 3;151(9):639-49.
Raynor MC, Carson CC, Pearson MD, Nix JW. **Androgen deficiency in the aging male**: a guide to diagnosis and testosterone replacement therapy. **Can J Urol. 2007** Dec;14 Suppl 1:63-8.
Rosenthal BD, et al. Adjunctive use of AndroGel(testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone.Urology.2006Mar;67(3):571-4.
Shifren JL, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal **women**: results from the INTIMATE NM1 Study. Menopause. 2006 Aug 22; [Epub ahead of print]
Shimon I, Eshed V, Doolman R, Sela BA, Karasik A, Vered I. **Alendronate for osteoporosis** in men with androgen-repleted hypogonadism. Osteoporos Int. 2005 Dec;16(12):1591-6. Epub 2005 Mar 15.
Somboonporn W, Davis S, Seif M, Bell R, Davis S. Testosterone for peri- and postmenopausal **women**. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004509.
Srinivas-Shankar U et al. Effects of **testosterone** on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: A randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2010 Feb; 95:639.
Stanworth RD, Kapoor D, Channer KS, Jones TH. Statin therapy is associated with lower total but not bioavailable or free testosterone in men with type 2 diabetes. Diabetes Care. 2008 Dec 29. [Epub ahead of print] Assessing androgen status using TT in men with type 2 diabetes treated with statins, particularly **atorvastatin**, may potentially lead to diagnostic error. BT or FT are recommended for the assessment of hypogonadism in this group if TT levels are borderline.
Tanrikut C, Goldstein M, Rosoff JS, Lee RK, Nelson CJ, Mulhall JP. **Varicocele** as a risk factor for androgen deficiency and effect of repair. BJU Int. 2011 Mar 24. doi: 10.1111/j.1464-410X.2010.10030.x.
Toma M, McAlister FA, Coglianese EE, et al. **Testosterone Supplementation in Heart Failure**: A Meta-Analysis. Circ Heart Fail. 2012 Apr 17.
Walter LC, Bertenthal D, Lindquist K, Konety BR. **PSA screening** among elderly men with limited life expectancies. JAMA. 2006 Nov 15;296(19):2336-42.
Wang C, Nieschlag E, Swerdloff R, et al. **Investigation, treatment, and monitoring** of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. J Androl 2009;30:1-9.
Wierman ME, Basson R, Davis SR, Khosla S, et al. **Androgen therapy in women**: an Endocrine Society Clinical Practice guideline. J Clin Endocrinol Metab. 2006 Oct;91(10):3697-710. Epub 2006 Oct 3.
Wu, Frederick C.W., Tajar, Abdelouahid, Beynon, Jennifer M. et al; the EMAS Group, **Identification of Late-Onset Hypogonadism** in Middle-Aged and Elderly Men. N Engl J Med 2010 0: NEJMoa0911101. Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per liter (3.2 ng per milliliter) and a free testosterone level of less than 220 pmol per liter (64 pg per milliliter).
Wunder DM, et al.; Swiss HIV Cohort Study. Androgen and gonadotropin patterns differ in **HIV-1**-infected men who develop lipoatrophy during antiretroviral therapy: a case-control study. HIV Med. 2008 Jul;9(6):427-32.
Wylie K, Rees M, Hackett G, et al. **Androgens, health and sexuality in women and men**. Hum Fertil (Camb). 2010 Dec;13(4):277-97.
Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. **Testosterone and depression**: systematic review and meta-analysis. J Psychiatr Pract. 2009 Jul;15(4):289-305.

TOP

References – 1. Intranasal Nasal Corticosteroids Comparative Chart (INCS) - **www.RxFiles.ca**

[1] Bousquet J. Van Cauwenberge P. Allergic Rhinitis and its Impact on Asthma (**ARIA**) In collaboration with the World Health Organization. Allergy 2002 Sept;57:841-855. http://www.whiar.com (access verified Dec 9/03)
[2] Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. **Drug Saf. 2003**;26(12):863-93.
[3] Micromedex 2010
[4] Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with **meta-analysis**. Ann Allergy Asthma Immunol. 2002 Nov;89(5):479-84.
[5] Trangsrud AJ, Whitaker AL, Small RE. Intranasal corticosteroids for allergic rhinitis. Pharmacotherapy. 2002 Nov;22(11):1458-67.
[6] Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis: superior relief? Drugs. 2001;61(11):1563-79.
[7] Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ. 1998 Dec 12;317(7173):1624-9.
[8] Kaszuba SM, Baroody FM, deTineo M, et al.. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the **as-needed** treatment of seasonal allergic rhinitis. Arch Intern Med. 2001 Nov 26;161(21):2581-7.
[9] Bachert C, El-Akkad T. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol. 2002 Sep;89(3):292-7.
[10] Shah SR, Miller C, et al. Two multicenter, randomized, single-blind, single-dose, crossover studies of specific sensory attributes of budesonide aqueous & fluticasone nasal spray. Clin Ther. 2003 Aug;25(8):2198-214.
[11] Lumry W, Hampel F, et al. A comparison of od triamcinolone acet. aqueous & bid beclomethasone diprop. aqueous nasal sprays in the treatment of seasonal allergic rhinitis. Allergy Asthma Proc. 2003 May-Jun;24(3):203-10.
[12] Sheth KK. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol. 2003 May;90(5):576; author reply 577.
[13] Waddell A.N.; Patel S.K.; Toma A.G.; Maw A.R. Intranasal steroid sprays in the treatment of rhinitis: is one better than another? Journal of Laryngology & Otology, 1 November 2003, vol. 117, no. 11, pp. 843-845(3)
[14] Therapeutic Choices 4rd edition, Canadian Pharmaceutical Association 2003
[15] **Treatment Guidelines**: **Drugs for Allergic Disorders**. The Medical Letter: **Feb 2010.**
Wallace DV, Dykewicz MS, Bernstein DI, et al. Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. **The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008** Aug;122(2 Suppl):S1-84.
[16] Compendium of Pharmaceuticals & Specialties –The Canadian Drug Reference for Health Professionals CPS 2003
[17] Benninger MS, Ahmad N, Marple BF. The safety of intranasal steroids. Otolaryngol Head Neck Surg. **2003 Dec**;129(6):739-750.
[18] Lieberman P. Best Practice Report: Rhinitis. May 2001 (Update March 2002). Available at: http://merck.praxis.md/index.asp?page=bpm_brief&article_id=BPM01AL07 (access verified Dec 9/02).
[19] Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD.2011.
[20] Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of **growth** suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics. 2000 Feb;105(2):E23.
[21] Wilson AM, Sims EJ, McFarlane LC, Lipworth BJ. Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. J Allergy Clin Immunol. 1998 Oct;102(4 Pt 1):598-604.
[22] Pipkorn U, Pukander J, Suonpaa J, Makinen J, Lindqvist N. Long-term safety of budesonide nasal aerosol: a 5.5-year follow-up study. Clin Allergy. 1988 May;18(3):253-9.
[23] Lindqvist N, Balle VH, Karma P, Karja J, Lindstrom D, Makinen J, Pukander J, et al.Long-term safety and efficacy of budesonide nasal aerosol in perennial rhinitis. A 12-month multicentre study. Allergy. 1986 Apr;41(3):179-86.
[24] Bacharier LB, Raissy HH, Wilson L, et al. Long-term (3 yr) effect of **budesonide** on hypothalamic-pituitary-adrenal axis function in children with mild to moderate asthma. Pediatrics. 2004 Jun;113(6):1693-9.
[25] Wihl JA, Andersson KE, Johansson SA. Systemic effects of two nasally administered glucocorticosteroids. Allergy. 1997 Jun;52(6):620-6.
[26] Moller C, Ahlstrom H, Henricson KA, et al. Safety of nasal budesonide in the long-term (1-2 year -**growth**) treatment of children with perennial rhinitis. Clin Exp Allergy. 2003 Jun;33(6):816-22.(Murphy K, et al. Growth velocity in children with perennial allergic rhinitis treated with budesonide aqueous nasal spray. Ann Allergy Asthma Immunol. 2006 May;96(5):723-30. n=229 age 4-8yrs 1yr trial)
[27] Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med. 2000 Oct 12;343(15):1054-63.
[28] Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med. 2000 Oct 12;343(15):1064-9.
[29] Thorsson L, Borga O, et al. Systemic availability of budesonide after nasal administration of three different formulations: pressurized aerosol, aqueous pump spray, and powder. Br J Clin Pharmacol. 1999 Jun;47(6):619-24.
[30] Bolland MJ, Bagg W, Thomas MG, Lucas JA, Ticehurst R, Black PN. Cushing's syndrome due to interaction between inhaled corticosteroids and itraconazole. Ann Pharmacother. 2004 Jan;38(1):46-9.
[31] Gillman SA, Anolik R, Schenkel E, Newman K. One-year trial on safety and normal linear growth with flunisolide HFA in children with asthma. Clin Pediatr (Phila). 2002 Jun;41(5):333-40.
[32] Wilson AM, et al.. Effects of repeated once daily dosing of three intranasal corticosteroids on basal & dynamic measures of hypothalamic-pituitary-adrenal-axis activity. J Allergy Clin Immunol. 1998 Apr;101(4 Pt 1):470-4.
[33] Allen DB, Meltzer EO, et al. No growth suppression in children treated with the maximum recommended dose of fluticasone propionate aqueous nasal spray for one year. Allergy Asthma Proc. 2002 Nov-Dec;23(6):407-13.
[34] Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. Fluticasone Propionate Asthma Study Group. J Pediatr. 1998 Mar;132(3 Pt 1):472-7.
[35] Health Canada Endorsed Important Safety Information on FLUTICASONE PROPIONATE (FLONASE/ FLOVENT/ ADVAIR) and RITONAVIR (NORVIR/KALETRA) Jan 22, 2004
[36] Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of **growth** retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics. 2000 Feb;105(2):E22.
[37] Skoner DP, Gentile DA, Doyle WJ. Effect on growth of long-term treatment with intranasal triamcinolone acetonide aqueous in children with allergic rhinitis. Ann Allergy Asthma Immunol. 2008 Oct;101(4):431-6. Triamcinolone acetonide aqueous titered to control AR symptoms and given for 1 or 2 years had no significant effect on statural growth in children with AR.
[38] Nsouli Talal M. Nasal Steroids: Contralateral Hand-Nostril Technique Curbs Epistaxis American College of Allergy, Asthma, and Immunology meeting Nov 2003. http://www.medscape.com/viewarticle/464241
[39] Saengpanich S, deTineo M, Naclerio RM, Baroody FM. Fluticasone nasal spray and the combination of loratadine and montelukast in seasonal allergic rhinitis. Arch Otolaryngol Head Neck Surg. 2003 May;129(5):557-62.
[40] Howarth PH. A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis. Allergy. 2000;55 Suppl 62:6-11.
[41] Vaidyanathan S, Barnes M, Williamson P, et al. Treatment of chronic rhinosinusitis with nasal polyposis with **oral steroids (prednisolone 25mg po od x 2wks) followed by topical steroids**: a randomized trial. Ann Intern Med. 2011 Mar 1;154(5):293-302.

Additional information:

Al Sayyad JJ, Fedorowicz Z, Alhashimi D, Jamal A. Topical **nasal steroids** for intermittent and persistent allergic rhinitis in **children**. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD003163. The three included trials provided some weak and unreliable evidence for the effectiveness of Beconase(R) and flunisolide used topically intranasally for the treatment of intermittent and persistent allergic rhinitis in children
Baroody FM, Brown D, Gavanescu L, et al. **Oxymetazoline adds to the effectiveness of fluticasone** furoate in the treatment of perennial allergic rhinitis. J Allergy Clin Immunol. 2011 Apr;127(4):927-34.
Baysoy G, Arslan S, Karabay O, Uyan AP. **Nasal carriage of Staphylococcus aureus** in children with allergic rhinitis and the effect of intranasal fluticasone propionate treatment on carriage status. Int J Pediatr Otorhinolaryngol. 2006 Nov 8; [Epub ahead of print]
Benninger M. **Diagnosis and management of nasal congestion**: the role of intranasal corticosteroids. Postgrad Med. 2009 Jan;121(1):122-31.
Blaiss MS; Food and Drug Administration (U.S.); ACAAI-ACOG(American College of Allergy, Asthma, and Immunology and American College of Obstetricians and Gynecologists.). Management of rhinitis and asthma in **pregnancy**. Ann Allergy Asthma Immunol. 2003 Jun;90(6 Suppl 3):16-22.
Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. **Allergic Rhinitis and its Impact on Asthma** (**ARIA**) **guidelines**: **2010** revision. J Allergy Clin Immunol. 2010 Sep;126(3):466-76.
Chadha NK, Chadha R. 10-minute consultation: sinusitis. BMJ. 2007 Jun 2;334(7604):1165.
Croft AM, Bager P, Kumar S. **Helminth therapy (worms) for allergic rhinitis**. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD009238. There is currently insufficient evidence on the efficacy, tolerability and likely costs of helminth therapy to support its use in the routine management of allergic rhinitis.
Creticos PS, et al. Immune Tolerance Network Group. Immunotherapy with a ragweed-toll-like receptor 9 agonist **vaccine** for allergic rhinitis. N Engl J Med. 2006 Oct 5;355(14):1445-55.
Demoly P, Piette V, Daures JP. Treatment of allergic rhinitis during **pregnancy**. Drugs. 2003;63(17):1813-20.
de Groot H, Brand PL, Fokkens WF, Berger MY. **Allergic rhinoconjunctivitis in children**. BMJ. 2007 Nov 10;335(7627):985-8.

TOP

de Vries et al. Reported **adverse drug reactions during the use of inhaled steroids** in children with asthma in the Netherlands. Eur J Clin Pharmacol. 2006 May;62(5):343-6. Epub 2006 Apr 1. Alteration of behaviour was the most frequently reported sADR. There are more indications that alterations of behaviour could be a real sADR of ICS. Non-fatal adrenal insufficiency was the only reported possible life threatening sADR. The association of hypertrichosis and teeth abnormalities after ICS in children has not been reported in the literature before.

Desrosiers M, Evans GE, Keith PK, et al. **Canadian clinical practice guidelines for acute and chronic rhinosinusitis**. Allergy Asthma Clin Immunol 2011;7:2. www.aacijournal.com/content/pdf/1710-1492-7-2.pdf

Frew AJ. **Sublingual immunotherapy**. N Engl J Med. 2008 May 22;358(21):2259-64. (Grass pollen sl tabs -Grazax is available in Europe)

Gilbert C, Mazzotta P, Loebstein R, Koren G. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug Saf. 2005;28(8):707-19.

Gluth MB, McDonald DR, Weaver AL, et al. Management of **eustachian tube dysfunction** with nasal steroid spray: a prospective, randomized, placebo-controlled trial. Arch Otolaryngol Head Neck Surg. 2011 May;137(5):449-55. (not support steroid spray use)

Greiner AN, Hellings PW, Rotiroti G, Scadding GK. **Allergic rhinitis**. Lancet. 2011 Jul 21.

Hayward G, Heneghan C, Perera, R, Thompson M. Intranasal corticosteroids in management of **acute sinusitis**: a systematic review and meta-analysis. Ann Fam Med. 2012;10(3):241-249. (small therapeutic benefit in acute sinusitis, which may be greater with high doses and with courses of 21 days' duration

Hissaria P, et al. Short course of systemic corticosteroids in **sinonasal polyposis**: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. J Allergy Clin Immunol. 2006 Jul;118(1):128-33. Epub 2006 May 19. (InfoPOEMs: Fourteen days of oral prednisolone (50 mg daily) significantly improves nasal function scores and reduces polyp size. The duration of this benefit, however, is not clear. (LOE = 1b))

Jankowski R, Klossek JM, Attali V, Coste A, Serrano E. Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of **nasal polyposis**. Allergy. 2009 Jun;64(6):944-50. Epub 2009 Mar 3. The study demonstrated the efficacy of FPANS 200 microg bd in acute treatment and FPANS 200 microg od as a sufficient dose to maintain a long-term efficacy in the treatment for NP.

Jorissen M, Bachert C. Effect of **corticosteroids** on wound healing after endoscopic sinus surgery. Rhinology. 2009 Sep;47(3):280-6. These results suggest that treatment with MFNS following sinus surgery may improve wound healing, particularly in subjects with **nasal polyps**.

Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive **sleep apnea syndrome**. Pediatrics. 2008 Jul;122(1):e149-55. A 6-week treatment with intranasal budesonide effectively reduced the severity of mild obstructive sleep apnea syndrome and the magnitude of the underlying adenoidal hypertrophy, and this effect persisted for at least 8 weeks after cessation of therapy. These findings justify the use of topical steroids as the initial therapeutic option in otherwise healthy children with mild obstructive sleep apnea.

Lange B, Lukat KF, Rettig K, et al. Efficacy, cost-effectiveness, and tolerability of **mometasone** furoate, levocabastine, and disodium cromoglycate nasal sprays in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2005 Sep;95(3):272-82.

Leger D, Annesi-Maesano I, Carat F, Rugina M, Chanal I, Pribil C, El Hasnaoui A, Bousquet J. Allergic rhinitis and its consequences on **quality of sleep**: An unexplored area. Arch Intern Med. 2006 Sep 18;166(16):1744-8.

Marogna M, Bruno M, Massolo A, Falagiani P. Long-Lasting Effects of **Sublingual Immunotherapy** for House Dust Mites in Allergic Rhinitis with Bronchial Hyperreactivity: A Long-Term (13-Year) Retrospective Study in Real Life. Int Arch Allergy Immunol. 2006 Oct 2;142(1):70-78 [Epub ahead of print]

Martin BG, et al. Comparison of **fluticasone** propionate aqueous nasal spray and oral montelukast for the treatment of seasonal allergic rhinitis symptoms. Ann Allergy Asthma Immunol. 2006 Jun;96(6):851-7.

McCormack PL, Scott LJ. **Fluticasone furoate**: intranasal use in allergic rhinitis. Drugs. 2007;67(13):1905-15.

Medical Letter. Treatment Guidelines. Drugs for **Allergic Disorders**. Feb 2010.

Medical Letter. Fluticasone furoate (Veramyst) for Allergic Rhinitis. Nov 5, 2007.

Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of **mometasone** furoate nasal spray, amoxicillin, and placebo. J Allergy Clin Immunol. 2005 Dec;116(6):1289-95. Epub 2005 Oct 24. (InfoPOEMs: The vast majority of patients with acute uncomplicated rhinosinusitis improve in 2 to 4 weeks without any specific treatment. Treatment with mometasone furoate nasal spray (Nasonex) 200 ug twice daily significantly reduces the time to resolution compared with amoxicillin alone or placebo. Patients who "must do something" may still find it easier and cheaper to try other modalities such as nasal saline. (LOE = 1b))

Meltzer EO, Andrews C, Journeay GE, Lim J, Prillaman BA, Garris C, et al. Comparison of patient preference for sensory attributes of **fluticasone furoate or fluticasone propionate** in adults with seasonal allergic rhinitis: a randomized, placebo-controlled, double-blind study. Ann Allergy Asthma Immunol. 2010 Apr;104(4):331-8.

Meltzer EO, Gates D, Bachert C. **Mometasone** furoate nasal spray increases the number of minimal-symptom days in patients with **acute rhinosinusitis**. Ann Allergy Asthma Immunol. 2012 Apr;108(4):275-9.

Nasser M, Fedorowicz Z, Aljufairi H, McKerrow W. **Antihistamines used in addition to topical nasal steroids** for intermittent and persistent allergic rhinitis in children. Cochrane Database Syst Rev. 2010 Jul 7;7:CD006989. In view of the lack of evidence for the benefit or lack of benefit of antihistamine add-on therapy with topical nasal steroids for children with intermittent or persistent allergic rhinitis, it is important that clinicians are mindful of the adverse effects of antihistamines and the additional costs that may be incurred.

Okubo K, Nakashima M, Miyake N, Komatsubara M, Okuda M. Comparison of **fluticasone furoate and fluticasone propionate** for the treatment of Japanese cedar pollinosis. Allergy Asthma Proc. 2009 Jan;30(1):84-94.

Ozturk F, Bakirtas A, Ileri F, et al. Efficacy and tolerability of systemic **methylprednisolone** (oral) in children and adolescents with chronic rhinosinusitis: a double-blind, placebo-controlled randomized trial. J Allergy Clin Immunol. 2011 Aug;128(2):348-52.

Paton J, et al. **Adrenal responses** to low dose synthetic ACTH (Synacthen) in children receiving high dose **inhaled fluticasone**. Arch Dis Child. 2006 Oct;91(10):808-13. Epub 2006 Mar 23.

Penagos M, et al. Efficacy of **sublingual immunotherapy** in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol. 2006 Aug;97(2):141-8.

Pharmacist's Letter. Fluticasone furoate (Avamyst) for Allergic Rhinitis. Dec, 2007.

Plaut M, Alleric Rhinitis. N Engl J Med 2005;353:193-44.

Pokladnikova J, Meyboom RH, Vlcek J, Edwards RI. Can intranasal corticosteroids cause **migraine-like headache**? Cephalalgia. 2009 Mar;29(3):360-4. Epub 2008 Oct 22.

Radulovic S, Calderon MA, Wilson D, Durham S. **Sublingual immunotherapy** for allergic rhinitis. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.pub2. This updated review reinforces the conclusion of the original 2003 Cochrane Review that sublingual immunotherapy is effective for allergic rhinitis and has been proven to be a safe route of administration.

Ratner PH, Melchior A, Dunbar SA, et al. Pharmacokinetic Profile of **Beclomethasone** Dipropionate Hydrofluoroalkane After **Intranasal** Administration Versus **Oral Inhalation** in Healthy Subjects: Results of a Single-Dose, Randomized, Open-Label, 3-Period Crossover Study. Clin Ther. 2012 May 21.

Saleh HA, Durham SR. **Perennial rhinitis**. BMJ. 2007 Sep 8;335(7618):502-7.

Schroer B, Pien LC. **Nonallergic rhinitis**: Common problem, chronic symptoms. Cleve Clin J Med. 2012 Apr;79(4):285-93.

Simpson SA, Lewis R, van der Voort J, et al. Oral **or topical nasal steroids for hearing loss associated with otitis media** with effusion in children. Cochrane Database Syst Rev. 2011 May 11;5:CD001935. While oral steroids, especially when used in combination with an oral antibiotic, lead to a quicker resolution of OME in the short term, there is no evidence of longer-term benefit and no evidence that they relieve symptoms of hearing loss. We found no evidence of benefit from treatment of OME with topical intranasal steroids, alone or in combination with an antibiotic, either at short or longer-term follow up.

Skoner DP, Maspero J, Banerji D; and the Ciclesonide Pediatric Growth Study Group. Assessment of the Long-term Safety of Inhaled **Ciclesonide** on **Growth** in Children With Asthma. Pediatrics. 2007 Dec 10; [Epub ahead of print]n=661 1yr. Ciclesonide demonstrated no detectable effect on childhood growth velocity, even at the highest dosage, which may ease concerns about systemic adverse events.

Slapak I, Skoupá J, Strnad P, Horník P. Efficacy of **isotonic nasal wash (seawater)** in the treatment and prevention of rhinitis in children. Arch Otolaryngol Head Neck Surg. 2008 Jan;134(1):67-74.

Small CB, Hernandez J, Reyes A, et al. Efficacy and safety of mometasone furoate nasal spray in **nasal polyposis**. J Allergy Clin Immunol. 2005 Dec;116(6):1275-1281. Epub 2005 Sep 26.

Snidvongs K, Kalish L, Sacks R, et al. **Topical steroid for chronic rhinosinusitis without polyps**. Cochrane Database Syst Rev. 2011 Aug 10;(8):CD009274. Topical steroid is a beneficial treatment for CRS without polyps and the adverse effects are minor. It may be included in a comprehensive treatment of CRS without polyps. Direct delivery of steroid to the sinuses may bring more beneficial effect.

Stelmach R, et al. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent **asthma**. Chest. 2005 Nov;128(5):3140-7.

Stjärne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg. 2009 Mar;135(3):296-302. Postoperative use of mometasone furoate, 200 microg once daily, provided a statistically significant longer time to relapse of nasal polyps than did placebo in subjects with bilateral nasal polyposis who had undergone FESS. The ability of mometasone to prevent or prolong the time to relapse among subjects undergoing FESS is important because this may prolong the time to subsequent surgery.

Stjarne P, Mosges R, Jorissen M, Passali D, Bellussi L, Staudinger H, Danzig M. A randomized controlled trial of mometasone furoate nasal spray for the treatment of **nasal polyposis**. Arch Otolaryngol Head Neck Surg. 2006 Feb;132(2):179-85.

Sussman G, Sussman D, Sussman A. Intermittent **allergic rhinitis**. CMAJ. 2010 Jun 15;182(9):935-7.

Sur DK, Scandale S. Treatment of **allergic rhinitis**. Am Fam Physician. 2010 Jun 15;81(12):1440-6.

Van Hoecke H, Vandenbulcke L, Van Cauwenberge P. **Histamine and leukotriene receptor antagonism** in the treatment of allergic rhinitis : an update. Drugs. 2007;67(18):2717-26.

Venekamp RP, Thompson MJ, Hayward G, et al. **Systemic corticosteroids for acute sinusitis**. Cochrane Database Syst Rev. 2011 Dec 7;12:CD008115. Current evidence suggests that oral corticosteroids as an adjunctive therapy to oral antibiotics are effective for short-term relief of symptoms in acute sinusitis. However, data are limited and there is a significant risk of bias.

Williamson IG, Rumsby K, Benge S, Moore M, Smith PW, Cross M, Little P. **Antibiotics and topical nasal steroid for treatment of acute** maxillary sinusitis: a randomized controlled trial. JAMA. 2007 Dec 5;298(21):2487-96. Neither an antibiotic nor a topical steroid alone or in combination was effective as a treatment for acute sinusitis in the primary care setting.

Williamson I, Benge S, Barton S, et al. A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with **persistent bilateral otitis media** with effusion in primary care. Health Technol Asses

TOP

1-144. Use of topical intranasal corticosteroids is very unlikely to be a clinically effective treatment for OME (glue ear) in the primary care setting.
Williamson Ian, Benge Sarah, Barton Sheila, et al. Topical intranasal corticosteroids in 4-11 year old children with **persistent bilateral otitis media** with effusion in primary care: double blind randomised placebo controlled trial. BMJ 2009;339:b4984, doi: 10.1136/bmj.b4984 (Published 16 December 2009) Topical steroids are unlikely to be an effective treatment for otitis media with effusion in general practice. High rates of natural resolution occurred by 1-3 months.
Zalmanovici A, Yaphe J. Steroids for acute sinusitis. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005149.For **acute sinusitis** confirmed by radiology or nasal endoscopy, current evidence is limited, but supports the use of INCS as a monotherapy or as an adjuvant therapy to antibiotics. Clinicians should weigh the modest but clinically important benefits against possible minor adverse events when prescribing therapy.
Vaidyanathan S, Barnes M, Williamson P, et al. Treatment of chronic rhinosinusitis with nasal polyposis with **oral steroids followed by topical steroids**: a randomized trial. Ann Intern Med. 2011 Mar 1;154(5):293-302.

TOP

Extras – RxFiles.ca – Oral Hypoglycemics

Hypoglycemics & Sulfa Allergy

Articles: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1783707/?tool=pubmed
Pharmacist's Letter document (Canadian Pharmacist's Letter 2010; 26(6):260601).

Summary & Overview:

⇨Warnings don't always correspond with available evidence; there is little information to suggest cross-sensitivity among the different sulfa chemical classes, however, those who have experienced a previous allergic reaction (to any drug) are more likely to experience a subsequent allergic reaction (to a related or unrelated drug)

⇨ Specific drugs

- *Chlorpropamide (Diabinese) (Apo-Chlorpropamide - Canada) - no warning*
- *Gliclazide (Diamicron) – Warning- (Contraindicated-Health Canada)*
- *Glimepiride (Amaryl)- Warning- (Contraindicated-Health Canada)*
- *Glipizide (Glucotrol)- no warning*
- *Glyburide (DiaBeta, others) - Warning (Contraindicated-Health Canada)*
- *Tolbutamide (Orinase) (Apo-Tolbutamide - Canada) - Warning*

⇨One case report of contact dermatitis with tolbutamide in a patient with sensitivity to sulfanilamide vaginal cream. After discontinuation of tolbutamide, therapy was changed to chlorpropamide, which was tolerated without difficulty.
⇨Another case report describes an allergic reaction to glyburide in a patient with a known allergy to sulfamethoxazole.

REFERENCES

Antihyperglycemic agents- Oral Anti-Hyperglycemic Agents -OAHA {(HYPOGLYCEMIC AGENTS (OHA)} - Comparison Chart

[1] Tuomilehto J, Lindstrom J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001 May 3;344(18):1343-50. (Sigal RJ, Kenny GP, Boule NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med. 2007 Sep 18;147(6):357-69. Summary for patients in: Ann Intern Med. 2007 Sep 18;147(6):I16. Either aerobic or resistance training alone improves glycemic control in type 2 diabetes, but the improvements are greatest with **combined aerobic and resistance training**.)
Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a **20-year follow-up** study. Lancet. 2008 May 24;371(9626):1783-9. Group-based lifestyle interventions over 6 years can prevent or delay diabetes for up to 14 years after the active intervention. However, whether lifestyle intervention also leads to reduced CVD and mortality remains unclear.
Martínez-González MA, Fuente-Arrillaga CD, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. BMJ. 2008 May 29. [Epub ahead of print] Adherence to a Mediterranean diet is associated with a reduced risk of diabetes.
Coppell Kirsten J, Kataoka Minako, Williams Sheila M, et al. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (**LOADD**) study: randomised controlled trial.BMJ 2010
Look AHEAD Group. Long-term Effects of a **Lifestyle** Intervention on Weight and Cardiovascular Risk Factors in Individuals With Type 2 Diabetes Mellitus: Four-Year Results of the Look AHEAD Trial. Arch Intern Med. 2010;170(17):1566-1575.
Church TS.; Blair SN.; Cocreham S; et al. Effects of **Aerobic and Resistance Training** on Hemoglobin A1c Levels in Patients With Type 2 Diabetes: A Randomized Controlled Trial(**HART-D**). JAMA. 2010;304(20):2253-2262.
Balducci Stefano; Zanuso Silvano; Nicolucci Antonio; et al. for the Italian Diabetes Exercise Study (**IDES**) Investigators. Effect of an Intensive Exercise Intervention Strategy on Modifiable Cardiovascular Risk Factors in Subjects With Type 2 Diabetes Mellitus: A Randomized Controlled Trial: The Italian Diabetes and Exercise Study (IDES). Arch Intern Med. 2010;170(20):1794-1803.
Tobias DK, Zhang C, van Dam RM, Bowers K, Hu FB. **Physical activity before and during pregnancy** and risk of gestational diabetes mellitus: a meta-analysis. Diabetes Care. 2011 Jan;34(1):223-9.
Chudyk Anna, Petrella Robert J.. Effects of **Exercise** on Cardiovascular Risk Factors in Type 2 Diabetes: A meta-analysis Diabetes Care May 2011 34:1228-1237; doi:10.2337/dc10-1881
Salas-Salvadó J, Bulló M, Babio N, et al.; **PREDIMED** Study Investigators. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care 2011;34:14–19.
Mayo Clinic [website]. *Mediterranean diet: choose this heart-healthy diet option.* Rochester, MN: Mayo Clinic; 2010. Available from: www.mayoclinic.com/health/mediterranean-diet/CL00011 . Accessed 2011 May 24.

[2] Canada's food guide to healthy eating. Website: **http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index_e.html**

[3] Health Canada's Fitness and Healthy Living. Website: **http://www.hc-sc.gc.ca/hppb/fitness** ; CADTH Diabetes Self Management Action Plan: http://www.cadth.ca/media/compus/pdf/C1109-Self-Management-Action-Plan-e.pdf

[4] Impact of Intensive Lifestyle and Metformin Therapy on Cardiovascular Disease Risk Factors in the Diabetes Prevention Program. Diabetes Care. 2005 Apr;28(4):888-894.

[5] Charpentier G, Riveline JP, Varroud-Vial M. Management of drugs affecting blood glucose in diabetic patients with renal failure. Diabetes Metab 2000;26 Suppl 4:73-85

[6] Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care 1999;22:925-7.

[7] Lalau JD and JM Race. Lactic acidosis in metformin therapy. Drugs 1999;58 Suppl 1:55-60.

[8] Salpeter SR, Greyber E, Pasternak GA, et al. Risk of Fatal and Nonfatal Lactic Acidosis With Metformin Use in Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis. Arch Intern Med. 2003 Nov 24;163(21):2594-602. &
(DePalo VA, Mailer K, Yoburn D, Crausman RS. Lactic acidosis. Lactic acidosis associated with metformin use in treatment of type 2 diabetes mellitus. Geriatrics. 2005 Nov;60(11):36, 39-41.)(Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. **2006** Jan 25;(1):CD002967.)
Tahrani AA, Varughese GI, Scarpello JH, Hanna FW. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ. 2007 Sep 8;335(7618):508-12.
Kamber N, Davis WA, Bruce DG, Davis TM. Metformin and **lactic acidosis** in an Australian community setting: the Fremantle Diabetes Study. Med J Aust. 2008 Apr 21;188(8):446-9. The incidence of lactic acidosis in patients with type 2 diabetes is low but increases with age & duration of diabetes, as cardiovascular and renal causes become more prevalent. Metformin does not increase the risk of lactic acidosis, even when other recognised precipitants are present.
Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: A prognostic and therapeutic study*. Crit Care Med. 2009 May 29. [Epub ahead of print] in overdose.
Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD002967.

[9] Lalau JD and Race JM. Metformin and lactic acidosis in diabetic humans. Diabetes, Obesity and Metabolism 2000;2:131-137.

[10] Micromedex 2011; Drugs in Pregnancy & Lactation, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD.2011.

TOP

.; Hansten & Horn-Drug Interactions 2008.
[11] Rosenstock J. Management of type 2 diabetes mellitus in the elderly. Drugs & Aging 2001;18(1)31-44.
[12] Fisman EZ, Tenenbaum A, et al. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clin Cardiol. 2001 Feb;24(2):151-8.
[13] Gale, EAM. Lessons from the glitazones: a story of drug development. Lancet 2001;357:1870-75.
[14] Moses R, Slobodniuk R, Boyages S, Colagiuri S et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 1999 Jan;22(1):119-124
[15] Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. JAMA 2000;283(13):1695-1702.
[16] Einhorn D, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The pioglitazone 027 study group. Clin Ther 2000 2000;1395-1409.
[17] Rosenstock J; Rood J; Cobitz A; Biswas N; Chou H; Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2006; 8(6):650-60.
[18] Rosenstock J, Brown A, Fisher J, Jain A et al. Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. Diabetes Care 1998;21(12):2050-2055.
[19] Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized controlled trial. Ann Intern Med 1999;130:389-96.
Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009 Mar 23;169(6):616-25.
[20] Raskin P, Rendell M, Riddle MC et al. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. Diabetes Care 2001 Jul;24(7):1226-32
[21] Krentz AJ, Bailey CJ, Melander A. Thiazolidinediones for type 2 diabetes: new agents reduce insulin resistance but need long term clinical trials. BMJ 2000;321:252-3.
[22] Chehade AM, Mooradian AD. A rational approach to drug therapy of type 2 diabetes mellitus. Drugs 2000;60(1):95-113.
[23] Drug Information Handbook 17th Edition. Lacy CF et al (editors). American Pharmaceutical Association. Lexi-Comp Inc, Hudson Ohio, 2008-2009 edition.
[24] Boctor, MA. Diabetes Mellitus in Therapeutic Choices (3rd edition). Gray, Jean (editor). Canadian Pharmacists Association. Web-com Ltd, Ottawa, ON, 2000.
[25] Management of Type II Diabetes. Clinical Trends in Pharmacy Practice, 3rd issue, 1997 (p46-52).
[26] Campbell IW. Antidiabetic drugs present and future. Drugs 2000; 60 (5): 1017-28.
[27] Rendell MS and Kirchain WR. Pharmacotherapy of Type 2 Diabetes Mellitus. Ann Pharmacother 2000; 34:878-95.
[28] Yki-Jarvinen, H. Management of Type 2 Diabetes Mellitus and cardiovascular risk- lessons from intervention trials. Drugs 2000; 60(5): 975-83.
[29] Meltzer S, Leiter L, Daneman D. et al 1998 Clinical practice guidelines for the management of diabetes in **Canada**. CMAJ **1998**;159 (8 Suppl).
[30] American Diabetes Association: Clinical Practice Recommendations 2003, Diabetes Care 2003 26:Supplement 1.
(**Standards of Medical Care in Diabetes-2006**-American-Diabetes-Association http://care.diabetesjournals.org/cgi/content/full/29/suppl_1/s4)(Nathan DM, et al. Management of hyperglycemia in type 2 diabetes: a **consensus algorithm** for the initiation and adjustment of therapy: a consensus statement from the **American Diabetes Association** and the **European Association** for the Study of Diabetes. Diabetes Care. 2006 Aug;29(8):1963-72.)
American Diabetes Association (ADA). Standards of medical care in diabetes. IV. **Prevention/delay of type 2 diabetes**. Diabetes Care 2007 Jan;30(Suppl 1):S7-8.
American Diabetes Association (ADA). Standards of medical care in diabetes. VI. **Prevention and management of diabetes complications. Diabetes Care 2007** Jan;30(Suppl 1):S15-24. http://care.diabetesjournals.org/cgi/content/full/30/suppl_1/S4#SEC14
American Diabetes Association (ADA). Standards of medical care in diabetes--2008. Diabetes Care. 2008 Jan;31 Suppl 1:S12-54. http://care.diabetesjournals.org/cgi/content/full/31/Supplement_1/S12
American Diabetes Association. Standards of medical care in diabetes--2009. Diabetes Care. **2009** Jan;32 Suppl 1:S1-97. http://care.diabetesjournals.org/content/vol32/Supplement_1/
Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. Medical management of **hyperglycemia** in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the ADA and the European Association for the Study of Diabetes. Diabetes Care. **2009** Jan;32(1):193-203.
Epub 2008 Oct 22. http://care.diabetesjournals.org/cgi/reprint/32/1/193?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=nathan&fulltext=hyperglycemia&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT .
Hobbs C, Pogach L, Aron D, et al. **VA/DoD (Veterans Affaris/ Dept of Defense) clinical practice guideline for the management of diabetes mellitus**. Version 4.0. http://www.healthquality.va.gov/diabetes/DM2010_FUL-v4e.pdf . Aug **2010**.
ADA Diabetes Guidelines- Standards of Medical Care in Diabetes—**2010** http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html
ADA American Diabetes Association. **Diagnosis and Classification** of Diabetes Mellitus Diabetes Care January 2010 33:S62-S69; doi:10.2337/dc10-S062.
ADA- American Diabetes Association. Standards of Medical Care in Diabetes—**2011** Diabetes Care January 2011 34:S11-S61; doi:10.2337/dc11-S011. http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html
ADA 2012: American Diabetes Association Position Statement: **Executive Summary**: Standards of Medical Care in Diabetes—2012Diabetes Care January 2012 35:S4-S10; doi:10.2337/dc12-s004
http://care.diabetesjournals.org/content/35/Supplement_1/S4.full.pdf
ADA 2012: American Diabetes Association Position Statement: **Diagnosis and Classification** of Diabetes MellitusDiabetes Care January 2012 35:S64-S71; doi:10.2337/dc12-s064 http://care.diabetesjournals.org/content/35/Supplement_1/S64.full.pdf
ADA 2012: American Diabetes Association Position Statement: **Standards of Medical Care** in Diabetes—2012Diabetes Care January 2012 35:S11-S63; doi:10.2337/dc12-s011. http://care.diabetesjournals.org/content/35/Supplement_1/S11.full.pdf
Inzucchi SE, Bergenstal RM, Buse JB, et al. **Management of Hyperglycemia in Type 2 Diabetes**: A Patient-Centered Approach: Position Statement of the American Diabetes Association (**ADA**) and the European Association for the Study of Diabetes(**EASD**). Diabetes Care. 2012 Apr 19.
[31] **Treatment Guidelines**: Drugs for Diabetes. **The Medical Letter**: September, **2002**; (1) pp. 1-6. **Updated Aug 2011.**
[32] Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/**American Geriatrics Society** Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc. **2003** May;51(5 Suppl Guidelines):S265-80.
Greenfield Sheldon, Billimek John, Pellegrini Fabio, Comorbidity Affects the Relationship Between Glycemic Control and Cardiovascular Outcomes in Diabetes: A Cohort Study . Ann Intern Med December 15, 2009 151:854-860; doi:10.1059/0003-4819-151-12-200912150-00005.
Lee SJ, Boscardin WJ, Stijacic Cenzer I, Huang ES, Rice-Trumble K, Eng C. The risks and benefits of implementing glycemic control guidelines in **frail older adults** with diabetes mellitus. J Am Geriatr Soc. 2011 Apr;59(4):666-72.
[33] **Canadian 2003 Diabetes Guidelines** http://www.diabetes.ca/cpg2003/download.aspx
Canadian 2008 Guidelines (Sept 2008): http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
(Bhattacharyya OK, Estey EA, Cheng AY; Canadian Diabetes Association 2008. Update on the Canadian Diabetes Association 2008 clinical practice guidelines. Can Fam Physician. 2009 Jan;55(1):39-43.)
[34] Cheng AY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. **CMAJ**. **2005** Jan 18;172(2):213-26.
[35] Krentz AJ, Bailey CJ. Oral antidiabetic agents : current role in type 2 diabetes mellitus. **Drugs**. **2005**;65(3):385-411.
[36] Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med. 2002 Jul 2;137(1):25-33.
Roussel Ronan; Travert Florence; Pasquet Blandine; et al.; for the Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Metformin Use and Mortality Among Patients With Diabetes and Atherothrombosis. Arch Intern Med. 2010;170(21):1892-1899.
Bennett Wendy L., Maruthur Nisa M., Singh Sonal, et al. Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations. Ann Intern Med E-336published ahead of print March 14, 2011, doi:10.1059/0003-4819-154-9-201105030-00336
[37] Polycystic Ovary Syndrome (PCOS)Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. Endocr Pract 2005 Mar-Apr;11(2):125-34. http://www.aace.com/clin/guidelines/PCOSpositionstatement.pdf (Moll E, et al. Effect of clomifene citrate plus metformin and **clomifene citrate plus placebo** on induction of ovulation in women with newly

TOP

diagnosed polycystic ovary syndrome: randomised double blind clinical trial. BMJ. 2006 Jun 13; Epub ahead of print. **Metformin is not an effective** addition to clomifene citrate as the primary method of inducing ovulation in women with polycystic ovary syndrome.)(De Leo V, Musacchio MC, Morgante G, Piomboni P, Petraglia F. Metformin treatment is effective in obese teenage girls with PCOS. Hum Reprod. 2006 Jun 19; [Epub ahead of print]) (Legro RS, Barnhart HX, Schlaff WD, et al. Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007 Feb 8;356(6):551-66. Clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication. InfoPOEMs: Clomiphene is more effective than metformin for enhancing fertility in women with polycystic ovary syndrome (PCOS). This study did not find that the combination of clomiphene and metformin was more effective than clomiphene alone. (LOE = 1b))
Legro RS, Zaino RJ, Demers LM, Kunselman AR, Gnatuk CL, Williams NI, Dodson WC. The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am J Obstet Gynecol. 2007 Apr;196(4):402.e1-10; discussion 402.e10-1.
Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med. 2008 Jan 3;358(1):47-54.
Tang T, Lord JM, Norman RJ, et al. Insulin-sensitising drugs (**metformin**, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003053.
Vause TD, Cheung AP, Sierra S, Claman P, Graham J, Guillemin JA, Lapensée L, Steward S, Wong BC. Ovulation induction in polycystic ovary syndrome. J Obstet Gynaecol Can. 2010 May;32(5):495-502. Ovulation Induction in Polycystic Ovary Syndrome **SOGC**-2010 http://sogc.org/guidelines/documents/gui242CPG1005E.pdf
Vanky E, Stridsklev S, Heimstad R, et al. **Metformin Versus Placebo** from First Trimester to Delivery in Polycystic Ovary Syndrome: A Randomized, Controlled Multicenter Study. J Clin Endocrinol Metab. 2010 Oct 6.
Wilson Jennifer F.. In the Clinic: The **Polycystic Ovary Syndrome**. Ann Intern Med February 1, 2011 154:ITC2-1.
Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with **polycystic ovary syndrome**: population based cohort study. BMJ 2011;343:d6309.
[38] Lalau JD and Race JM. Metformin and lactic acidosis in diabetic humans. Diabetes, Obesity and Metabolism 2000;2:131-137.
[39] Knowler WC, Barrett-Connor E, Fowler SE, et al.; **Diabetes Prevention Program** Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403 (Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. Diabetes Care. 2003 Apr;26(4):977-80. The primary analysis of the DPP demonstrated that metformin decreased the risk of diabetes by 31%. The washout study shows that 26% of this effect can be accounted for by a pharmacological effect of metformin that did not persist when the drug was stopped. After the washout the incidence of diabetes was still reduced by 25%.) (Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med. 2005 Aug 16;143(4):251-64. Summary for patients in: Ann Intern Med. 2005 Aug 16;143(4):I22.) (Lindstrom J, et al. Finnish Diabetes Prevention Study Group. (**FDPS**) Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006 Nov 11;368(9548):1673-9. (InfoPOEMs: Diet and exercise are effective in delaying the diagnosis of diabetes in patients at increased risk. (LOE = 2b)))
Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009 Nov 14;374(9702):1677-86.
[40] Dills DG, Schneider J. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. Glimepiride/Glyburide Research Group. Horm Metab Res. 1996 Sep;28(9):426-9.
[41] Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev. 2001 Nov-Dec;17(6):467-73.
[42] Graal MB, Wolffenbuttel HR. The use of sulphonylureas in the elderly. Drugs and Aging 1999;15(6):471-81.
[43] Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2003 Nov;26(11):2983-9.
[44] Nesto RW, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2004 Jan;27(1):256-63. (Pharmacist's Letter Sept 2006. The use of Glitazones in persons with congestive heart failure) (see also DREAM & PROACTIVE trial results) (Singh S, Loke YK, Furberg CD. Thiazolidinediones and Heart Failure: A Teleo-Analysis. Diabetes Care. 2007 May 29; [Epub ahead of print] Our teleo-analysis confirms the increased magnitude of the risk of heart failure with thiazolidinediones. We estimate the Number-Needed-to-Harm with thiazolidinediones to be around 50 over 2.2 years.) (Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. Lancet. 2007 Sep 29;370(9593):1129-36. Congestive heart failure in patients given TZDs might not carry the risk that is usually associated with congestive heart failure which is caused by progressive systolic or diastolic dysfunction of the left ventricle. Longer follow-up and better characterisation of such patients is needed to determine the effect of TZDs on overall cardiovascular outcome.)
Winkelmayer WC, Setoguchi S, Levin R, Solomon DH. Comparison of Cardiovascular Outcomes in Elderly Patients With Diabetes Who Initiated Rosiglitazone vs Pioglitazone Therapy. Arch Intern Med. 2008 Nov 24;168(21):2368-75. Our findings from a large population-based cohort of US seniors are compatible with an increased risk of all-cause mortality and congestive heart failure in patients initiating therapy with rosiglitazone compared with similar patients initiating therapy with pioglitazone.
[45] Gegick C, Altheimer M. Comparison of effect of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. Endocr Pract 2001;7:162-169.
[46] Blickle J. Thiazolidinediones: donnees cliniques et perspectives (French language). Diabetes Metab 2001;27:279-285.
[47] Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone monothreapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab 2001;86:280-8.
[48] Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med. 2004 Oct 25;164(19):2097-104.
[49] Yki-Jarvinen Hannele, Drug Therapy: Thiazolidinediones. N Engl J Med 2004;351:1106-18.
[50] Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of **lipid** and glycemic effects of **pioglitazone and rosiglitazone** in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005 Jul;28(7):1547-54.
[51] Phillips LS, Grunberger G, Miller E, Patwardhan R, et al.. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. Diabetes Care. 2001 Feb;24(2):308-15.
[52] Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; **STOP-NIDDM** Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003 Jul 23;290(4):486-94.

Additional articles:

Abuissa H, Jones PG, Marso SP, et al. **ACE or ARB** for prevention of type 2 diabetes a meta-analysis of randomized clinical trials. J Am Coll Cardiol. 2005 Sep 6;46(5):821-6.
AACE Diabetes Mellitus Practice Guidelines Task Force. **American** Assoc. of Clinical **Endocrinologists** medical **guidelines** for clinical practice for the management of diabetes mellitus. Endocr Pract. **2007** May-Jun;13 Suppl 1:1-68.
Abdelghaffar S, Attia AM. **Metformin added to insulin therapy for type 1 diabetes** mellitus in adolescents. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006691. There is some evidence suggesting improvement of metabolic control in poorly controlled adolescents with type 1 diabetes, on addition of metformin to insulin therapy. Stronger evidence is required from larger studies, carried out over longer time periods to document the long-term effects on metabolic control, health-related quality of life as well as morbidity and mortality in those patients.
ACCORD Study Group, Effects of Intensive **Blood-Pressure** Control in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001286
ACCORD Study Group, Effects of Combination **Lipid** Therapy (simvastatin with fenofibrate) in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001282.
ACCORD Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive **Glucose** Lowering in Type 2 Diabetes. N Engl J Med. 2008 Jun 6. [Epub ahead of print]
ACCORD Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between **A1C and all-cause mortality** during a median 3.4 year follow up of glycemic treatment in the ACCORD. Diabetes Care 2010; 33:983-990.
ACCORD Study Group and ACCORD Eye Study Group, Effects of Medical Therapies on **Retinopathy** Progression in Type 2 Diabetes. N Engl J Med 2010 0: NEJMoa1001288.
ACCORD Ismail-Beigi F, Craven T, Banerji MA. Effect of intensive treatment of hyperglycaemia on **microvascular** outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial.The Lancet, Early Online Publication, 29 June 2010 doi:10.1016/S0140-6736(10)60576-4.
ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011 Mar 3; 364:818.
ACCORD Anderson RT, Narayan KM, Feeney P, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Investigators. Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial. Diabetes Care. 2011 Apr;34(4):807-12.
Adler AI, Shaw EJ, Stokes T, Ruiz F; Guideline Development Group. **Newer agents** for blood glucose control in type 2 diabetes: summary of **NICE guidance**. BMJ. 2009 May 22;338:b1668. doi: 10.1136/bmj.b1668.

TOP

http://www.nice.org.uk/nicemedia/pdf/CG87ShortGuideline.pdf

ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2008 Jun 6. [Epub ahead of print] (Poulter NR. Blood pressure and glucose control in subjects with diabetes: new analyses from ADVANCE. J Hypertens. 2009 May;27 Suppl 1:S3-8. Additional blood pressure lowering and intensive glucose control, as achieved in ADVANCE, produce independent benefits and, when combined, substantially reduced cardiovascular mortality and all-cause mortality and improved renal outcomes.) Zoungas S, de Galan BE, Ninomiya T, et al. on behalf of the ADVANCE Collaborative Group. The combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes; new results from ADVANCE. Diabetes Care. 2009 Aug 3. [Epub ahead of print] The effects of routine blood pressure lowering and intensive glucose control were independent of one another and when combined produced additional reductions in clinically relevant outcomes.

AFSSAPS June/11 The antidiabetes drug **pioglitazone** (marketed in the U.S. as **Actos) is to be taken off the market in France because of concerns over a "slightly increased risk" for bladder cancer**, Bloomberg reports.

Agarwal MM, Dhatt GS, et al. **Gestational** diabetes mellitus: simplifying the **international association** of diabetes and pregnancy diagnostic algorithm using fasting plasma glucose. (IADPSG) Diabetes Care. 2010 Sep;33(9):2018-20.

Amed S, Dean H, Sellers EA, et al. **Risk factors for medication-induced** diabetes and type 2 diabetes. J Pediatr. 2011 Aug;159(2):291-6.

Ajay Varanasi, Natalie Bellini, Deepti Rawal, et al. **Liraglutide** as Additional Treatment in Type 1 Diabetes *Eur J Endocrinol* 2011 EJE-11-0330

Akilen R, Tsiami A, Devendra D, et al. Glycated Haemoglobin and Blood Pressure-Lowering Effect of **Cinnamon** in Multi-Ethnic Type 2 Diabetic Patients in the UK: A Randomized, Placebo-Controlled, Double-Blind Clinical Trial. Diab Med. 2010;27:1159-1167.

Al-Arouj M, Bouguerra R, Buse J, et al. Recommendations for management of diabetes during **Ramadan**. Diabetes Care. 2005 Sep;28(9):2305-11.

Albers JW, Herman WH, Pop-Busui R, et al. for the **DCCT/EDIC** Research Group. Effect Of Prior Intensive Insulin Treatment During The Diabetes Control And Complications Trial (DCCT) On **Peripheral Neuropathy** In Type 1 Diabetes During The Epidemiology Of Diabetes Interventions, And Complications (EDIC) Study. Diabetes Care. 2010 Feb 11.

Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The **metabolic syndrome**--a new worldwide definition. Lancet. 2005 Sep 24-30;366(9491):1059-62.

Ali K, Harnden A, Edge JA. **Type 1 diabetes in children**. BMJ. 2011 Feb 16;342:d294. doi: 10.1136/bmj.d294.

Alvarez-Blasco F, et al. Prevalence and characteristics of the **polycystic ovary syndrome** in overweight and obese women. Arch Intern Med. 2006 Oct 23;166(19):2081-6.

American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, et al. **Diet and lifestyle recommendations revision 2006**: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006 Jul 4;114(1):82-96.

American College of Obstetricians and Gynecologists (**ACOG**). **Polycystic ovary syndrome**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2009 Oct. 14 p. (ACOG practice bulletin; no. 108).

American College of Sports Medicine, American Diabetes Association. **Exercise and type 2 diabetes**: American College of Sports Medicine and the American Diabetes Association: joint position statement. Med Sci Sports Exerc 2010 Dec;42(12):2282-303.

Amin R, Turner C, van Aken S, Bahu TK, et al. The relationship between **microalbuminuria and glomerular filtration** rate in young type 1 diabetic subjects: The Oxford Regional Prospective Study. Kidney Int. 2005 Oct;68(4):1740-9.

Amori RE, et al. Efficacy and safety of **incretin therapy** in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007 Jul 11;298(2):194-206. Incretin therapy offers an alternative option to currently available hypoglycemic agents for nonpregnant adults with type 2 diabetes, with modest efficacy & a favorable weight-change profile. Careful postmarketing surveillance for adverse effects, especially among the DPP4 inhibitors, & continued evaluation in longer-term studies and in clinical practice are required to determine the role of this new class among current pharmacotherapies for type 2 diabetes.

Anderson RJ, Bahn GD, Moritz TE, et al.; for the **VADT** Study Group. Blood Pressure and Cardiovascular Disease risk in the Veterans Affairs Diabetes Trial (VADT) Diabetes Care. 2010 Nov 8. DBP <70 mmHg elevated CVD risk.

Andrews RC, Cooper AR, Montgomery AA, et al. **Diet or diet plus physical activity versus usual care** in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet 2011; June 25.

Andrade Susan E, Lo Joan C, Roblin Douglas, et al. **Antipsychotic Medication Use Among Children** and Risk of Diabetes Mellitus. Pediatrics 2011; peds.2011-0855; ahead of print November 21, 2011.

Anthonisen NR, Skeans MA, Wise RA, et al.; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005 Feb 15;142(4):233-9.

Arad Y, Fonseca V, Peters A, et al. Beyond the **Monofilament for the Insensate Diabetic Foot**: A systematic review of randomized trials to prevent the occurrence of plantar foot ulcers in patients with diabetes. Diabetes Care. 2011 Apr;34(4):1041-6.

Araneta MR, Grandinetti A, Chang HK. **A1C and diabetes diagnosis among Filipino Americans, Japanese Americans, and Native Hawaiians**. Diabetes Care. 2010 Dec;33(12):2626-8.

Armstrong DG, Lavery LA; Diabetic Foot Study Consortium. **Negative pressure wound** therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005 Nov 12;366(9498):1704-10.

Aroda VR, Henry RR, Han J, et al. Efficacy of **GLP-1 Receptor Agonists and DPP-4 Inhibitors**: Meta-Analysis and Systematic Review. Clin Ther. 2012 May 17.

Aschner PJ, Chan J, Owens DR, et al, **EASIE** investigators. **Insulin glargine versus sitagliptin** in insulin-naive patients with type 2 diabetes mellitus uncontrolled **on metformin** (EASIE): a multicentre, randomised, open-label trial. Lancet 2012; online June 9.

Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin **glargine** in people with Type 1 diabetes using meal-time **insulin aspart**. Diabet Med. 2006 Aug;23(8):879-86.

Atkin S. Commentary: controversies in NICE guidance on management of type 2 diabetes. BMJ 2008;336:1308-1309.

Avandaryl (Rosiglitazone/Glimepiride) Medical Letter Mar 13,2006.

Azhary H, Farooq MU, Bhanushali M, Majid A, Kassab MY. **Peripheral neuropathy**: differential diagnosis and management. Am Fam Physician. 2010 Apr 1;81(7):887-92.

Azoulay L, Yin H, Filion KB, et al. The use of **pioglitazone and the risk of bladder cancer** in people with type 2 diabetes: nested case-control study. BMJ 2012; DOI:10.1136/bmj.e3645

Babenko AP, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med. 2006 Aug 3;355(5):456-66.

Baker WL, Gutierrez-Williams G, White CM, Kluger J, Coleman CI. Effect of **cinnamon on glucose control** and lipid parameters. Diabetes Care. 2008 Jan;31(1):41-3. Epub 2007 Oct 1. Cinnamon does not appear to improve A1C, FBG, or lipid parameters in patients with type 1 or type 2 diabetes.

Bakris G, et al. Differences in glucose tolerance between fixed-dose **antihypertensive drug combinations** in people with **metabolic syndrome**. Diabetes Care. 2006 Dec;29(12):2592-7.

Bailey Clifford J, Gross Jorge L, Pieters Anne, et al., Effect of **dapagliflozin** in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial, The Lancet, Volume 375, Issue 9733, 26 June 2010-2 July 2010, Pages 2223-2233

Bailey Clifford J. The challenge of **managing coexistent type 2 diabetes and obesity**. BMJ 2011;342:doi:10.1136/bmj.d1996 (Published 13 April 2011)

Bang Heejung, Edwards Alison M., Bomback Andrew S., Development and Validation of a **Patient Self-assessment Score for Diabetes Risk**. Ann Intern Med December 1, 2009 151:775-783.

Bangalore S, Kumar S, Lobach I, et al. **Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose**: Observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011. DOI: 10.1161/CIRCULATIONAHA.110.016337.

Bao Y, Ma X, Li H, et al. Glycated haemoglobin **A1c for diagnosing** diabetes in **Chinese** population: cross sectional epidemiological survey. BMJ. 2010 May 17

Barnard ND, et al. A **low-fat vegan diet** improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care. 2006 Aug;29(8):1777-83.

Barnett AH, et al. An open, randomized, parallel-group study to compare the efficacy and safety profile of **inhaled human insulin (Exubera) with metformin** as adjunctive therapy in patients with type 2 diabetes poorly controlled on a sulfonylurea. Diabetes Care. 2006 Jun;29(6):1282-7.

Barone BB, Yeh HC, Snyder CF, et al. Long-term All-Cause **Mortality in Cancer Patients** With Preexisting Diabetes Mellitus: A Systematic Review and Meta-analysis. JAMA. 2008 Dec 17;300(23):2754-64. Patients diagnosed with cancer who have preexisting diabetes are at increased risk for long-term, all-cause mortality compared with those without diabetes.

BARI 2D study group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med.* 2009; 360:2503-2515.

Battelino T, Phillip M, Bratina N, et al. Effect of **continuous glucose monitoring** on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800.

Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after **gestational diabetes**: a systematic review and meta-analysis. Lancet. 2009 May 23;373(9677):1773-1779.

Belfort R, et al. A placebo-controlled trial of **pioglitazone** in subjects with **nonalcoholic steatohepatitis**. N Engl J Med. 2006 Nov 30;355(22):2297-307. (n=55 6months) In this proof-of-concept study, the administration of pioglitazone 45mg/d led to metabolic and histologic improvement in subjects with nonalcoholic steatohepatitis. Larger controlled trials of longer duration are warranted to assess the long-term clinical benefit of pioglitazone.

Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of **pancreatic cancer**: A meta-analysis of cohort studies. Eur J Cancer. 2011 Sep;47(13):1928-37.

Bennett Wendy L., Maruthur Nisa M., Singh Sonal, et al. **Comparative Effectiveness and Safety of Medications for Type 2 Diabetes**: An Update Including New Drugs and 2-Drug Combinations. Ann Intern Med E-336published ahead

TOP

of print March 14, 2011. Evidence supports metformin as a first-line agent to treat type 2 diabetes. Most 2-drug combinations similarly reduce hemoglobin A1c levels, but some increased risk for hypoglycemia and other adverse events.
Bennett WL, Odelola OA, Wilson LM,et al. **Evaluation of guideline recommendations** on oral medications for type 2 diabetes mellitus: a systematic review. Ann Intern Med. 2012 Jan 3;156(1 Pt 1):27-36
Bergenstal RM, Wysham C, Macconell L, et al. for the **DURATION-2** Study Group. Efficacy and safety of **exenatide once weekly versus sitagliptin or pioglitazone** as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010 Jun 25.
Berria R, et al. **Reduction in hematocrit** level after **pioglitazone** treatment is correlated with decreased plasma free testosterone level, not hemodilution, in women with polycystic ovary syndrome.Clin Pharmacol Ther. 2006 Aug;80(2):105-14. Epub 2006 Jun 30.
Biggio JR Jr et al. **Fetal anomalies in obese women**: The contribution of diabetes. Obstet Gynecol 2010 Feb; 115:290.
Bihan H, Fysekidis M, Harbuz V, Reach G, Cohen R. **False-positive blood glucose and ketone** values with **lightening cream**. Ann Intern Med. 2011 Nov 1;155(9):649.
Bilik D, McEwen LN, Brown MB, et al. **Thiazolidinediones and Fractures**: Evidence from Translating Research into Action for Diabetes. J Clin Endocrinol Metab. 2010 Jul 14.
Black C, et al. **Meglitinide** analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD004654. Meglitinides may offer an alternative oral hypoglycaemic agent of similar potency to metformin, and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated. However, there is no evidence available to indicate what effect meglitinides will have on important long-term outcomes, particularly mortality.
Blind E, Dunder K, de Graeff PA, and Abadie E. **Rosiglitazone: a European regulatory perspective**. Diabetologia 2010; DOI:10.1007/s00125-010-1992-5.
Blomgren KB, Sundström A, Steineck G, Wiholm BE. Obesity and treatment of diabetes with **glyburide** may both be risk factors for **acute pancreatitis**. Diabetes Care. 2002 Feb;25(2):298-302.
Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care. 2008 Nov;31(11):2086-91. Epub 2008 Sep 9. **Lactic acidosis** during current use of oral antidiabetes drugs was very rare and was associated with concurrent comorbidity. Hypoglycemic episodes were substantially more common among sulfonylurea users than among users of metformin.
Bodmer M, Becker C, Meier C et al. Use of Antidiabetic Agents and the Risk of **Pancreatic Cancer**: A Case-Control Analysis. Am J Gastroenterol. 2012 Jan 31. (Metformin reduced risk in women)
Bolen S, Feldman L, Vassy J, et al. Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. Ann Intern Med. 2007 Jul 16; [Epub ahead of print] Compared with newer, more expensive agents (thiazolidinediones, alpha-glucosidase inhibitors, and meglitinides), older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control, lipids, and other intermediate end points.
Bonds Denise E, Miller Michael E, Bergenstal Richard M, et al. The association between symptomatic, severe **hypoglycaemia** and mortality in type 2 diabetes: retrospective epidemiological analysis of the **ACCORD** study. BMJ 2010;340:b4909, doi: 10.1136/bmj.b4909 (Published 8 January 2010)
Bonfig W, Kapellen T, Dost A, Fritsch M, Rohrer T, Wolf J, et al. **Growth in children and adolescents** with type 1 diabetes. J Pediatr 2012;160:900-3.
Booth GL, Kapral MK, Fung K, & Tu JV. Relation between age and cardiovascular disease in men and women with **diabetes compared with nondiabetic** people: a population-based retrospective cohort study. Lancet 2006; 368: 29-36.
Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of **intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes**: meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.
Boussageon R, Supper I, Bejan-Angoulvant T, et al. **Reappraisal of metformin** efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med. 2012 Apr;9(4):e1001204.
Bowker SL, et al. Increased **cancer-related mortality** for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care. 2006 Feb;29(2):254-8. (InfoPOEMs: Death due to cancer seems to be more prevalent in patients with type 2 diabetes treated with either insulin or a sulfonylurea than in patients treated with metformin (Glucophage). It may be that hyperinsulinemia increases cancer risk, or that metformin is protective. Another explanation could be that, although cancer is related to certain medication use, it is not caused by their use. We need a controlled study to answer these questions. (LOE = 2b))
Bressler NM, Beck RW, Ferris FL 3rd. **Panretinal photocoagulation** for proliferative diabetic retinopathy. N Engl J Med. 2011 Oct 20;365(16):1520-6.
Bril V., England J., Franklin G.M., et al. Evidence-based guideline: Treatment of **painful diabetic neuropathy**: Report of the American Academy of Neurology (**AAN**), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology May 17, 2011 76:1758-1765; published ahead of print April 11, 2011. http://www.neurology.org/content/early/2011/04/08/WNL.0b013e3182166ebe.full.pdf+html
Brown JB, Conner C, Nichols GA. **Secondary failure of metformin** monotherapy in clinical practice. Diabetes Care. 2010 Mar;33(3):501-6. Epub 2009 Dec 29.
Brownstein JS, Murphy SN, Goldfine AB, et al. Rapid identification of **myocardial infarction risk** associated with diabetes medications using electronic medical records. Diabetes Care. 2010 Mar;33(3):526-31. Epub 2009 Dec 15.
Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a **coronary risk equivalent**? Systematic review and meta-analysis. Diabet Med. 2009 Feb;26(2):142-8. This meta-analysis found no evidence to support the contention that diabetes alone is a coronary heart disease (CHD) risk equivalent to a history of prior myocardial infarction (MI). The blanket use of aspirin and statins for patients with type 2 diabetes, regardless of their lipid levels, is not supported by the evidence. (LOE = 2a)
Burant CF, Viswanathan P, Marcinak J, et al. **TAK-875** (FFAR1) versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2012; online Feb 27.
Burr JF, Shephard RJ, Riddell MC. **Physical activity** in type 1 diabetes mellitus: Assessing risks for physical activity clearance and prescription. Can Fam Physician. 2012 May;58(5):533-5.
Buse JB, Ginsberg HN, Bakris GL, et al. American Heart Association; American Diabetes Association. **Primary prevention of cardiovascular diseases in people with diabetes mellitus**: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2007 Jan 2;115(1):114-26. Epub 2006 Dec 27.
Buse JB et al. **Liraglutide** once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (**LEAD-6**). Lancet 2009 Jul 4; 374:39.
Buse JB, Drucker DJ, Taylor KL, et al. for the DURATION-1 Study Group. DURATION-1: **Exenatide Once Weekly** Produces Sustained Glycemic Control and Weight Loss Over 52 Weeks. Diabetes Care. 2010 Mar 9.
Buse JB, Sesti G, Schmidt WE, et al. for the Liraglutide Effect and Action in Diabetes (LEAD)-6 Study Group. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care. 2010 Mar 23.
Buse JB, Bergenstal RM, Glass LC, et al. Use of **Twice-Daily Exenatide** in Basal Insulin-Treated Patients With Type 2 Diabetes: A Randomized, Controlled Trial. Ann Intern Med. 2010 Dec 6.
Callahan Alfred; Amarenco Pierre; Goldstein Larry B.; et al. for the **SPARCL** Investigators. Risk of Stroke and Cardiovascular Events After Ischemic Stroke or Transient Ischemic Attack in Patients With Type 2 Diabetes or Metabolic Syndrome: Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL-**atorvastatin**) Trial Arch Neurol. 2011;0(2011):archneurol.2011.146.
Callaghan BCC, Cheng HT, Stables CL et al. **Diabetic neuropathy**: clinical manifestations and current treatments. Lancet Neurol 2012; 11: 521–34.
Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced **glucose control for preventing and treating diabetic neuropathy**. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD007543. According to high-quality evidence, enhanced glucose control significantly prevents the development of clinical neuropathy and reduces nerve conduction and vibration threshold abnormalities in type 1 diabetes mellitus. In type 2 diabetes mellitus, enhanced glucose control reduces the incidence of clinical neuropathy, although this was not formally statistically significant (P = 0.06). However, enhanced glucose control does significantly reduce nerve conduction and vibration threshold abnormalities. Importantly, enhanced glucose control significantly increases the risk of severe hypoglycemic episodes, which needs to be taken into account when evaluating its risk/benefit ratio.
Canadian Hypertension Education Program **2011 Recommendations** www.hypertension.ca **Canadian Hypertension Education Program. 2011 CHEP recommendations for the management of hypertension**. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf
Carson AP, Reynolds K, Fonseca VA, et al. Comparison of **A1C** and fasting glucose criteria to **diagnose diabetes** among U.S. adults. Diabetes Care. 2010 Jan;33(1):95-7. Epub 2009 Oct 6.
Carter P., Gray L. J., Troughton J., Khunti K., Davies M. J. **Fruit and vegetable intake** and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. BMJ 2010;341:c4229, doi: 10.1136/bmj.c4229
Casas JP, et al. Effect of inhibitors of the **renin-angiotensin system** and other antihypertensive drugs on **renal outcomes**: systematic review and meta-analysis. Lancet. 2005 Dec 10;366(9502):2026-2033. INTERPRETATION: The benefits of ACE inhibitors or ARBs on renal outcomes in placebo-controlled trials probably result from a blood-pressure-lowering effect. In patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain unproven, and there is uncertainty about the greater renoprotection seen in non-diabetic renal disease.
Catalano PM, McIntyre HD, Cruickshank JK, et al. **HAPO** Study Cooperative Research Group. The **hyperglycemia and adverse pregnancy outcome study**: associations of GDM and obesity with pregnancy outcomes. Diabetes Care. 2012 Apr;35(4):780-6.
Cebul RD, Love TE, Jain AK, Hebert CJ. **Electronic health records** and quality of diabetes care. N Engl J Med. 2011 Sep 1;365(9):825-33.
Chanoine JP, Hampl S, Jensen C, et al. Effect of **orlistat** on weight and body composition in obese adolescents. A randomized controlled trial. JAMA 2005;293:2873-83. (InfoPOEMs: Orlistat (Xenical), in combination with diet, exercise, & behavioral modification, improves weight management in obese adolescents. No major safety issues were identified after 1 year, but further follow-up for sustained weight management and safety is important. (LOE = 1b))

TOP

Charbonnel B, et al. Efficacy & safety of the dipeptidyl peptidase-4 inhibitor **sitagliptin** added to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care. 2006 Dec;29(12):2638-43.
Charpentier G, et al. Should **postprandial hyperglycaemia** in prediabetic and type 2 diabetic patients be treated? Drugs. 2006;66(3):273-86.
Chatterjee Ranee; Yeh Hsin-Chieh; Shafi Tariq; et al. **Serum and Dietary Potassium** and Risk of Incident Type 2 Diabetes Mellitus: The Atherosclerosis Risk in Communities (ARIC) Study. Arch Intern Med. 2010;170(19):1745-1751.
Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. Diabetes Care. 2008 Oct;31(10):1927-32. Epub 2008 Jun 12. n=50. A 6-month course of insulin therapy, compared with OAD treatment, could more effectively achieve adequate glycemic control and significant improvement of beta-cell function in new-onset type 2 diabetic patients with severe hyperglycemia.
Chlebowski RT, McTiernan A, Wactawski-Wende J, et al. Diabetes, **Metformin, and Breast Cancer** in Postmenopausal Women. J Clin Oncol. 2012 Jun 11.
Chudyk Anna, Petrella Robert J.. Effects of **Exercise** on Cardiovascular Risk Factors in Type 2 Diabetes: A meta-analysis Diabetes Care May 2011 34:1228-1237; doi:10.2337/dc10-1881
Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of **renal end points** in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med. 2012;172 (10):761-769.
COIITSS Study Investigators, Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for **septic shock** in adults: a randomized controlled trial. JAMA. 2010 Jan 27;303(4):341-8.
Collins GS, Altman DG. External validation of **QDSCORE**((R)) for predicting the 10-year risk of developing Type 2 diabetes. Diabet Med. 2011 May;28(5):599-607. doi: 10.1111/j.1464-5491.2011.03237.x
Cone CJ, Bachyrycz AM, Murata GH. **Hepatotoxicity Associated with Metformin** Therapy in Treatment of Type 2 Diabetes Mellitus with Nonalcoholic Fatty Liver Disease**.** Ahead of Print 1Oct2010. Ann Pharmacother ;44:1655-1659.
Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of **continuous glucose monitoring** on HbA1c in insulin-treated diabetes (MITRE Study). . Diabet. Med. 2009 May;26:540–7.
Coppell Kirsten J, Kataoka Minako, Williams Sheila M, et al. **Nutritional intervention** in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial. BMJ 2010;341:c3337.
Coustan DR. Pharmacological management of **gestational diabetes**: an overview. Diabetes Care. 2007 Jul;30 Suppl 2:S206-8. Review. Erratum in: Diabetes Care. 2007 Dec;30(12):3154.
Cowie CC, et al. **Prevalence** of **diabetes and impaired fasting glucose** in adults in the **U.S.** population: National Health And Nutrition Examination Survey 1999-2002. Diabetes Care. 2006 Jun;29(6):1263-8.
Craig J. Currie, Chris D. Poole, Sara Jenkins-Jones, et al. Mortality After Incident **Cancer** in People With and Without Type 2 Diabetes: Impact of **metformin on survival**. Diabetes Care February 2012 35:299-304; published ahead of print Jan 20, 2012.
Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of metformin in **polycystic ovary syndrome.** Obstet Gynecol 2008;111:959-968. {Info POEMs: Metformin induces ovulation in women with polycystic ovarian syndrome (PCOS). Metformin plus clomiphene induces ovulation and results in early pregnancy for clomiphene-resistant women. Data are insufficient to determine whether metformin increases live births in women with PCOS. Future studies should compare metformin head-to-head with clomiphene as the primary treatment. (LOE = 1a-)}
Creatore, Maria Isabella, Moineddin, Rahim, Booth, Gillian, et al. Age- and sex-related prevalence of diabetes mellitus among **immigrants to Ontario**, Canada. CMAJ 2010 0: cmaj.091551.
Crume TL, Ogden L, Maligie M, et al. Long-Term Impact of Neonatal **Breastfeeding** on Childhood Adiposity and Fat Distribution Among Children Exposed to Diabetes In Utero. Diabetes Care Mar 2011 34:641-645.
Cryer PE, Axelrod L, Grossman AB, et al.; Endocrine Society. Evaluation and management of adult **hypoglycemic disorders**: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.
Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD. **Survival as a function of HbA(1c)** in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010 Jan 26. [Epub ahead of print]
Danaei G, Lawes CMM, et al. Global and regional mortality from ischaemic heart disease and stroke attributable to **higher-than-optimum blood glucose** concentration: comparative risk assessment. Lancet 2006; 368: 1651-1659.
Dagenais GR, Lu J, Faxon DP, et al. Effects of Optimal Medical Treatment With or Without Coronary Revascularization on Angina and Subsequent Revascularizations in Patients With Type 2 Diabetes Mellitus and Stable Ischemic Heart Disease. Circulation. 2011 Mar 28. (**BARI 2D**)
Dailey George. **Early and Intensive Therapy** for Management of Hyperglycemia and Cardiovascular Risk Factors in Patients With Type 2 Diabetes. Clinical Therapeutics, Volume 33, Issue 6, June 2011
Danaei G, Finucane MM, Lu Y, et al, on behalf of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose). **National, regional, and global trends in fasting plasma glucose and diabetes** prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011
Davies MJ, Heller S, Skinner TC, et al; Diabetes Education and Self Management for Ongoing and Newly Diagnosed Collaborative. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ. 2008 Mar 1;336(7642):491-5. Epub 2008 Feb 14. Erratum in: BMJ. 2008 Apr 9;336(7649):doi:10.1136/bmj.39553.528299.AD. A 6-hour well-constructed educational intervention given to patients with newly diagnosed diabetes was no better than usual care in improving their overall glucose control over 1 year of evaluation. However, the intervention resulted in a greater average weight loss and prompted more patients to quit smoking, though these results were not the primary goal of the intervention. (LOE = 1b-)
Davies MJ, Chubb BD, Smith IC, et al. Cost-utility analysis of **liraglutide compared with sulphonylurea or sitagliptin**, all as add-on to metformin monotherapy in Type 2 diabetes mellitus. Diabet Med. 2012 Mar;29(3):313-20.
DCCT/EDIC Research Group. Intensive Diabetes Therapy and **Glomerular Filtration** Rate in Type 1 Diabetes. N Engl J Med. 2011 Nov 12.
De Berardis G, Sacco M, Strippoli GF, et al. **Aspirin for primary prevention** of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009 Nov 6;339:b4531. doi: 10.1136/bmj.b4531.
de Boer H, et al. Glycaemic control without weight gain in insulin requiring type 2 diabetes: 1-year results of the **GAME** regimen. Diabetes Obes Metab. 2006 Sep;8(5):517-23. All patients were treated with the GAME regimen, a combination of **glimepiride** administered at 20:00 hours for nocturnal glycaemic control, **insulin aspart** three times daily for meal-related glucose control and metformin.
de Boer IH, Kestenbaum B, Rue TC, et al. Diabetes Control and Complications Trial (**DCCT**)/Epidemiology of Diabetes Interventions and Complications (**EDIC**) Study Research Group. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med. 2008 Sep 22;168(17):1867-73. Hyperglycemia is a risk factor for incident hypertension in type 1 diabetes, and intensive insulin therapy reduces the long-term risk of developing hypertension.
de Boer IH.; Rue Tessa C.; Cleary Patricia A.; et al.; for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. **Long-term Renal Outcomes** of Patients With Type 1 Diabetes Mellitus and Microalbuminuria: An Analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort **DCCT/EDIC**. Arch Intern Med. 2011;171(5):412-420.
de Boer IH., Rue Tessa C., Hall Yoshio N., et al. Temporal **Trends in the Prevalence of Diabetic Kidney Disease** in the United States. JAMA. 2011;305(24):2532-2539.doi:10.1001/jama.2011.861.
DeFronzo RA, Tripathy D, Schwenke DC, et al. for **ACT NOW**. **Pioglitazone for Diabetes Prevention** in Impaired Glucose Tolerance. N Engl J Med 2011; 364:1104-1115. {↓progression to T2DM (incidence of 2.1 vs 7.6%/yr; NNT=19/yr) but ↑weight (3.9 vs 0.77kg) & edema (12.9 vs 6.4%)}.
de Jager Jolien, Kooy Adriaan, Lehert Philippe et al. Long term treatment with **metformin** in patients with type 2 diabetes and risk of **vitamin B-12 deficiency**: randomised placebo controlled trial. BMJ 2010;340
Desai Shrey; Brinker Allen; Swann Joslyn; et al. **Sitagliptin-Associated Drug Allergy**: Review of Spontaneous Adverse Event Reports Arch Intern Med. 2010;170(13):1169-1171.
Despres, JP, Golay A, Sjostrom L. Effects of **rimonabant** on metabolic risk factors in overweight patients with dyslipidemia (**Rio-Lipids**). N Engl J Med 2005;353:2121-34. (Weight loss: **6.7kg** at 1yr by repeated-measures method)
Dhulkotia JS, Ola B, Fraser R, et al. **Oral hypoglycemic agents vs insulin in management of gestational diabetes**: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010 Nov;203(5):457.e1-9.
Diamant M et al. Safety and efficacy of **once-weekly exenatide compared with insulin glargine** titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care [Epub ahead of print] 22 February 2012; doi:10.2337/dc11-1233.
Digman C, Klein AK, Pittas AG. Leukopenia and thrombocytopenia caused by **thiazolidinediones**. Ann Intern Med. 2005 Sep 20;143(6):465-6.
Dixon JB, le Roux CW, Rubino F, Zimmet P. **Bariatric surgery** for type 2 diabetes. Lancet. 2012 Jun 8.
Diamant Michaela, Van Gaal Luc, Stranks Stephen, et al., Once **weekly exenatide** compared with insulin glargine titrated to target in patients with type 2 diabetes (**DURATION-3**): an open-label randomised trial, The Lancet, Volume 375, Issue 9733, 26 June 2010-2 July 2010
DiPersio JF. **Diabetic stem-cell "mobilopathy"**. N Engl J Med. 2011 Dec 29;365(26):2536-8.
Dixon JB, O'Brien PE, Playfair J, et al. Adjustable **gastric banding** and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008 Jan 23;299(3):316-23. Participants randomized to surgical therapy were more likely to achieve remission of type 2 diabetes through greater weight loss.
Donnelly LA, Doney AS, Hattersley AT, Morris AD, Pearson ER. The effect of **obesity on glycaemic response** to metformin or sulphonylureas in Type 2 diabetes. Diabet Med. 2006 Feb;23(2):128-33.
Donner T, Muñoz M. **Update on insulin** therapy for type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1405-13.
Dormandy JA, Charbonnel B, Eckland DJ, et al. PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. (**PROACIVE**) Lancet. 2005 Oct 8;366(9493):1279-89. (Jarvinen H. The PROactive study: some answers, many questions. -**more heart failures, weight gain & more edema**. Lancet. 2005 Oct 8;366(9493):1241-2.) INTERPRETATION: Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events. (**n=5328 34.5months** follow-up, Pioglitazone vs placebo, primary endpoint not significant, secondary endpoint of composite of all-cause mortality, non-fatal MI & stroke was 11.6 vs 13.6%, more to hospital with heart failure 6 vs 4%, 22% vs 13% edema, weight gain ↑ 3.6kg vs 0.4kg decrease) (InfoPOEMs: In patients

TOP

with type 2 diabetes and comorbid macrovascular disease, 3 years of intensive diabetes care using pioglitazone did not significantly prevent further complications or mortality compared with placebo. (LOE = 1b))
Wilcox R, Kupfer S, and Erdmann E. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: Results from Prospective Pioglitazone Clinical Trial in Macrovascular Events (**PROactive 10**). Am Heart J 2008; DOI:10.1016/j.ahj.2007.11.029 In patients with advanced type 2 diabetes at high risk for cardiovascular events, pioglitazone treatment resulted in significant risk reductions in MACE composite end points to 3 years.

Dormuth CR, Carney G, Carleton B, et al. Thiazolidinediones and **fractures in men and women**. *Arch Intern Med.* 2009; 169:1395-1402.

Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of **fractures associated with thiazolidinediones**: a self-controlled case-series study. PLoS Med. 2009 Sep;6(9):e1000154. Epub 2009 Sep 29.

DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, et al. Effect of **rosiglitazone** on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105. Cardiovascular event rates were much the same in both groups, although 14 (0.5%) participants in the rosiglitazone group and two (0.1%) in the placebo group developed heart failure (p=0.01). (InfoPOEMs: Patients at increased risk of developing diabetes were less likely to develop diabetes if taking rosiglitazone (Avandia) than if given a placebo. We don't know how well rosiglitazone compares with other interventions also known to delay diabetes: diet and exercise, metformin, or acarbose. We also don't know if clinically relevant outcomes are improved. (LOE = 1b));
(Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. BMJ. 2007 Apr 28;334(7599):882-4.)
(Nathan DM, Berkwits M. Trials that matter: rosiglitazone, ramipril, and the prevention of type 2 diabetes. Ann Intern Med. 2007 Mar 20;146(6):461-3.)

Drucker DJ, et al. The incretin system: **glucagon-like peptide-1 receptor agonists** and **dipeptidyl peptidase-4 inhibitors** in type 2 diabetes. Lancet. 2006 Nov 11;368(9548):1696-705. (eg. exenatide, liraglutide, sitagliptin, vildagliptin)

Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med. 2008 Dec 17. (**VADT** study) Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications.

Dumville JC, Deshpande S, O`Meara S, et al. **Foam dressings for healing diabetic foot ulcers**. Cochrane Database Syst Rev. 2011 Sep 7;9:CD009111. Currently there is no research evidence to suggest that foam wound dressings are more effective in healing foot ulcers in people with diabetes than other types of dressing however all trials in this field are very small.

Dumville JC, Deshpande S, O`Meara S, et al. **Hydrocolloid dressings** for healing **diabetic foot ulcers**. Cochrane Database Syst Rev. 2012 Feb 15;2:CD009099. Currently there is no research evidence to suggest that any type of hydrocolloid wound dressing is more effective in healing diabetic foot ulcers than other types of dressing.

Duncan GE. Prevalence of diabetes and impaired fasting glucose levels among **US adolescents**: National Health and Nutrition Examination Survey, 1999-2002. Arch Pediatr Adolesc Med. 2006 May;160(5):523-8.

Durso SC. Using clinical guidelines designed for **older adults** with diabetes mellitus and complex health status. JAMA. 2006 Apr 26;295(16):1935-40.

Eckel RH, et al. Preventing **cardiovascular risk and diabetes**. A call to action from the American Diabetes Association and the American Heart Association. Circulation 2006; DOI: 10.1161/CIRCULATIONAHA.106.176583. http://www.circulationaha.org

Edelman S, et al. A double-blind, placebo-controlled trial assessing **pramlintide** treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care. 2006 Oct;29(10):2189-95.

Edwards J, Stapley S. **Debridement of diabetic foot ulcers**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003556. There is evidence to suggest that hydrogel increases the healing rate of diabetic foot ulcers compared with gauze dressings or standard care and larval therapy resulted in significantly greater reduction in wound area than hydrogel.

Egi M, Finfer S, Bellomo R. **Glycemic control in the ICU**. Chest. 2011 Jul;140(1):212-20.

Ehrmann DA. **Polycystic ovary** syndrome. N Engl J Med. 2005 Mar 24;352(12):1223-36.

Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. **Pancreatitis, pancreatic, and thyroid cancer** with glucagon-like peptide-1-based therapies (**sitagliptin, exenatide**). Gastroenterology. 2011 Jul;141(1):150-6.

Elder DA, Herbers PM, Weis T et al. **β-cell Dysfunction in Adolescents** and **Adults** with Newly Diagnosed Type 2 Diabetes Mellitus. J Pediatr. 2012 Jan 10.

EMA July/11 The European Medicines Agency (EMA) has reached a decision:pioglitazone (Actos, Takeda), opting to recommend new contraindications & warnings be added to the drug label, noting that there is a small increased risk of bladder cancer.

Emerging Risk Factors Collaboration, Diabetes mellitus, **fasting blood glucose** concentration, & risk of vascular disease: a collaborative meta-analysis of 102 prospective studies, Lancet, Volume 375, Issue 9733, 26 June 2010-2 July 2010, Pages 2215-2222.

Emerging Risk Factors Collaboration. Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death. N Engl J Med 2011; 364:829-841.

Esposito K., Maiorino M. I., Ciotola M., et al. Effects of a **Mediterranean-Style Diet** on the Need for Antihyperglycemic Drug Therapy in Patients With Newly Diagnosed Type 2 Diabetes: A Randomized Trial. Ann Intern Med 2009; 306-314.

Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with **metformin** in patients with diabetes and **heart failure**. Diabetes Care. 2005 Oct;28(10):2345-51.

Eurich DT, McAlister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, Varney J, Johnson JA. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ. 2007 Aug 30; [Epub ahead of print] **Metformin was the only** antidiabetic agent not associated with harm in patients with heart failure and diabetes. It was associated with reduced all cause mortality in two of the three studies.

Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of **epidural steroid injections** on blood glucose levels in patients with diabetes mellitus. Spine (Phila Pa 1976). 2012 Jan 1;37(1):E46-50.

Farmer A, Wade A, Goyder E, et al. Impact of **self-monitoring of blood glucose** in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 2007; DOI: 10.1136/bmj.39247.447431. Evidence is not convincing of an effect of self monitoring blood glucose, with or without instruction in incorporating findings into self care, in improving glycaemic control compared with usual care in reasonably well controlled non-insulin treated patients with type 2 diabetes. (see also Pharmacist's Letter Sept 2007) (Peel E, Douglas M, Lawton J. Self monitoring of blood glucose in type 2 diabetes: longitudinal qualitative study of patients' perspectives. BMJ. 2007 Sep 8;335(7618):493. Epub 2007 Aug 30.)
O'Kane MJ, Bunting B, Copeland M, Coates VE; on behalf of the **ESMON** study group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. BMJ. 2008 Apr 17; [Epub ahead of print] In patients with newly diagnosed type 2 diabetes self monitoring of blood glucose concentration has no effect on glycaemic control but is associated with higher scores on a depression subscale. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A; on behalf of the Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the **DiGEM** trial. BMJ. 2008 Apr 17; [Epub ahead of print] Self monitoring of blood glucose with or without additional training in incorporating the results into self care was associated with higher costs and lower quality of life in patients with non-insulin treated type 2 diabetes. In light of this, and no clinically significant differences in other outcomes, self monitoring of blood glucose is unlikely to be cost effective in addition to standardised usual care.
Gomes, Tara, Juurlink, David N, Shah, Baiju R, et al. Blood glucose test strips: options to reduce usage. CMAJ 2009 0: cmaj.091017.
Cameron, Chris, Coyle, Doug, Ur, Ehud, Klarenbach, Scott. Cost-effectiveness of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin. CMAJ 2009 0: cmaj.090765.

Farmer AJ, Perera R, Ward A, et al. Meta-analysis of individual patient data in randomised trials of self monitoring of blood glucose (**SMBG**) in people with non-insulin treated type 2 diabetes. BMJ. 2012 Feb 27;344:e486.

FDA Aug/09 Patients with diabetes who take therapeutic products containing nonglucose sugars (e.g., **peritoneal dialysis solution and some immunoglobulins**) can have falsely elevated readings from blood glucose test strips that use glucose dehydrogenase pyrroloquinoline quinone (**GDH-PQQ**) technology, according to an FDA public health notification. The strips are in wide use, and we have provided a link to a listing of the affected products. The FDA cites 13 deaths associated with hypoglycemia not detected by the test strips, which cannot distinguish between lucose and other sugars such as maltose and xylose. Ten patients were receiving icodextrin peritoneal dialysis solution. The FDA advises physicians to avoid using GDH-PQQ test strips in health care facilities and to rely, instead, on laboratory assays of glucose — especially in patients taking the therapeutic products listed in the alert. Interfering products containing nonglucose sugars include icodextrin peritoneal dialysis solution, certain immunoglobulins, abatacept (Orencia, Bristol-Myers Squibb), tositumomab (Bexxar, GlaxoSmithKline), and any product containing or metabolized into maltose, galactose, or xylose. Several test strips and associated monitors use GDH-PQQ methodology: ACCU-CHEK (Roche), FreeStyle (Abbott Diabetes Care), TRUEtest (Home Diagnostics), CoZmonitor blood glucose module (for use with the Deltec Cozmo insulin pump, Smiths Medical MD), and OmniPod insulin management system (Insulet).

FDA Sep/10 & Takeda, conducted a planned analysis of the study data at the five-year mark, and submitted their results to FDA. Overall, there was no statistically significant association between **Actos exposure and bladder cancer risk**. However, further analyses were also performed looking at how long patients were on Actos and the total amount of the drug they received during that time. An increased risk of bladder cancer was observed among patients with the longest exposure to Actos, as well as in those exposed to the highest cumulative dose of Actos. FDA notified healthcare professionals and patients that the Agency is reviewing data from an ongoing, ten-year epidemiological study designed to evaluate whether Actos (pioglitazone) is associated with an increased risk of bladder cancer.

FDA May/11 Updated risk evaluation and mitigation strategy **(REMS) to restrict access to rosiglitazone**-containing medicines including Avandia, Avandamet, and Avandaryl. May 18, 2011. http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm

FDA June/11 **Victoza** (liraglutide [rDNA origin]) Injection: REMS - Risk of **Thyroid C-cell Tumors, Acute Pancreatitis**. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm

FDA June/11 drug safety communication: Update to ongoing safety review of **Actos (pioglitazone) and increased risk of bladder cancer**- use for more than 12 months linked to an increased risk of bladder cancer. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm

Ferrannini E, Ramos SJ, Salsali A, et al. **Dapagliflozin** monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010 Oct;33(10):2217-24.

Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage **renal disease** in patients with type 1 diabetes. JAMA. 2005 Oct 12;294(14):1782-7. CONCLUSIONS: With regard to ESRD, the prognosis of type 1 diabetes has improved during the past 4 decades. Children diagnosed as having diabetes before age 5 years have the most favorable prognosis. Overall, incidence of ESRD appears to be lower than previously estimated.

Finucane MM, Stevens GA, Cowan MJ. **National, regional, and global trends in body-mass index since 1980**: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011; DOI: 10.1016/S0140-6736(10)62035-5.

Fitzgerald E, Mathieu S, Ball A. Metformin associated **lactic acidosis**. BMJ. 2009 Sep 16;339:b3660. doi: 10.1136/bmj.b3660.

TOP

Franco OH, de Laet C, Peeters A, Jonker J, Mackenbach J, Nusselder W. Effects of **physical activity** on life expectancy with cardiovascular disease. Arch Intern Med. 2005 Nov 14;165(20):2355-60.
Franciosi M, Lucisano G, Pellegrini F, et al. ROSES Study Group. Role of **self-monitoring of blood glucose** and intensive education in patients with Type 2 diabetes not receiving insulin. A pilot randomized clinical trial. Diabet Med. 2011 Jul;28(7):789-96.
Franks, Paul W., Hanson, Robert L., Knowler, William C., et al. **Childhood Obesity**, Other Cardiovascular Risk Factors, and **Premature Death**. N Engl J Med 2010 362: 485-493.
Frid A, Hirsch L, Gaspar R, et al. Scientific Advisory Board for the Third Injection Technique Workshop. **New injection recommendations for patients with diabetes**. Diabetes Metab. 2010 Sep;36 Suppl 1:S3-18.
Fox CS, et al. Trends in the Incidence of **Type 2 Diabetes Mellitus From the 1970s to the 1990s.** The Framingham Heart Study. Circulation. 2006 Jun 19; [Epub ahead of print]
Frosch DL, Uy V, Ochoa S, Mangione CM. Evaluation of a **behavior support intervention** for patients with poorly controlled diabetes [published online October 10, 2011]. Arch Intern Med. doi:10.1001/archinternmed.2011.497.
Gallwitz B, Guzman J, Dotta F, et al. **Exenatide twice daily versus glimepiride** for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (**EUREXA**): an open-label, randomised controlled trial. Lancet 2012; online June 9.
Garber A et al. **Liraglutide** versus glimepiride monotherapy for type 2 diabetes (**LEAD-3 Mono**): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009 Feb 7; 373:473.
Garg R, Chen W, Pendergrass M. Acute **pancreatitis** in type 2 diabetes treated with **exenatide or sitagliptin**: a retrospective observational pharmacy claims analysis. Diabetes Care. 2010 Nov;33(11):2349-54. Epub 2010 Aug 3.
Genest J, McPherson R, Frohlich J, et al. **2009 Canadian** Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol. 2009 Oct;25(10):567-79.
Gerich J, Raskin P, Jean-Louis L, Purkayastha D, Baron MA. PRESERVE-beta: two-year efficacy and safety of initial combination therapy with **nateglinide** or glyburide **plus metformin**. Diabetes Care. 2005 Sep;28(9):2093-9.
Gerstein HC, Ratner RE, Cannon CP, et al. the **APPROACH** Study Group. Effect of Rosiglitazone on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease. The Assessment on the Prevention of Progression by **Rosiglitazone** on Atherosclerosis in Diabetes Patients With Cardiovascular History Trial. Circulation. 2010 Mar 1
Gillies CL, Abrams KR, et al. **Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes** in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007 Jan 19; [Epub ahead of print] Lifestyle and pharmacological interventions reduce the rate of progression to type 2 diabetes in people with impaired glucose tolerance. Lifestyle interventions seem to be at least as effective as drug treatment. (InfoPOEMs: Diet, exercise, or diet and exercise changes, at least those in study situations, will slow the progression of diabetes by approximately 50% in patients with impaired glucose tolerance. Drug therapy with either oral diabetes drugs or the weight loss drug orlistat (Xenical) will also slow progression. The preventive effect of the drugs is not maintained when they are stopped, and research has not been conducted for long enough to determine whether diabetes onset is prevented or just delayed. (LOE = 1a))
Gilbert C, Valois M, Koren G. **Pregnancy** outcome after first-trimester exposure to **metformin**: a meta-analysis. Fertil Steril. 2006 Sep;86(3):658-63. Epub 2006 Jul 31. On the basis of the limited data available today, there is no evidence of an increased risk for major malformations when metformin is taken during the first trimester of pregnancy. Large studies are needed to corroborate these preliminary results.
Giovannucci, Edward, Harlan, David M., Archer, Michael C., et al. **Diabetes and Cancer**: A Consensus Report. CA Cancer J Clin 2010 0: caac.20078.
Glatstein MM, Djokanovic N, Garcia-Bournissen F, Finkelstein Y, Koren G. Use of **hypoglycemic drugs during lactation**. Can Fam Physician. 2009 Apr;55(4):371-3.
Glueck CJ, Salehi M, Sieve L, Wang P. Growth, motor, and social development in **breast- and formula-fed infants of metformin**-treated women with polycystic ovary syndrome. J Pediatr. 2006 May;148(5):628-632.
Goldberg RB, Holman R, Drucker DJ. Clinical decisions. **Management of type 2 diabetes**. N Engl J Med. 2008 Jan 17;358(3):293-7.
Goldenberg RM, Cheng AYY, Punthakee Z, Clement M. **CDA** Position statement: use of glycated hemoglobin (**A1C**) in the diagnosis of type 2 diabetes mellitus in adults. Can J Diabetes 2011;35:247-9.
Goldfine AB, et al. **Family history** of diabetes is a major determinant of endothelial function. J Am Coll Cardiol. 2006 Jun 20;47(12):2456-61. Epub 2006 May 30.
Goldfine Allison B., Fonseca Vivian, Jablonski Kathleen A., Et al. and for the TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The Effects of **Salsalate** on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Trial. *Ann Intern Med* March 16, 2010
Gonzalez-Perez A, Schlienger RG, Rodríguez LA. **Acute pancreatitis** in association with type 2 diabetes and **antidiabetic drugs**: a population-based cohort study. Diabetes Care. 2010 Dec;33(12):2580-5.
Gregg EW, Cheng YJ, Saydah S, et al. Trends in **death rates among US adults with and without diabetes between 1997 and 2006**.Diabetes Care 2012; 35:1252-1257.
Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Eff ect of early **intensive multifactorial therapy on 5-year cardiovascular outcomes** in individuals with type 2 diabetes detected by screening (**ADDITION-Europe**):a cluster-randomised trial. Lancet 2011; published online June 25
Gross Jorge L., Kramer Caroline K., Leitão Cristiane B., et al. , for the Diabetes and Endocrinology Meta-analysis Group (DEMA). Effect of Antihyperglycemic **Agents Added to Metformin** and a Sulfonylurea on Glycemic Control and Weight Gain in Type 2 Diabetes: A Network Meta-analysis. Ann Intern Med May 17, 2011 154:672-679.
Grundy SM. **Metabolic syndrome**: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol. 2006 Mar 21;47(6):1093-100. Epub 2006 Feb 23.
Grundy SM, et al. American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the **metabolic syndrome**: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005 Oct 25;112(17):2735-52. Epub 2005 Sep 12. Erratum in: Circulation. 2005 Oct 25;112(17):e297. Circulation. 2005 Oct 25;112(17):e298.
Grøntved A, Hu FB. **Television viewing** and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. JAMA. 2011 Jun 15;305(23):2448-55.
Gulliford MC, Charlton J, Latinovic R. Risk of Diabetes Associated With Prescribed **Glucocorticoids** in a Large Population. Diabetes Care. 2006 Dec;29(12):2728-2729. The researchers found that the adjusted odds ratio for diabetes associated with 3 or more prescriptions for oral glucorticoids was 1.36. Such patients appeared to account for about 2% of incident cases of diabetes.
Gupta AK, Dahlof B, et al. Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. (**ASCOT**) Diabetes Care. 2008 May;31(5):982-8. Epub 2008 Jan 30. Baseline FPG >5 mmol/l, BMI, and use of an atenolol +/- diuretic regimen were among the major determinants of NOD in hypertensive patients. The model developed from these data allows accurate prediction of NOD among hypertensive subjects.
Handelsman Y, Mechanick JI, Blonde L, et al. **AACE** Task Force for Developing Diabetes **Comprehensive Care Plan**. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011 Mar-Apr;17(Suppl 2):1-53.
Harder T, Roepke K, Diller N, et al. **Birth weight, early weight gain**, and subsequent risk of type 1 **diabetes**: systematic review and meta-analysis. Am J Epidemiol. 2009 Jun 15;169(12):1428-36. Epub 2009 Apr 10. This meta-analysis indicates that high birth weight and increased early weight gain are risk factors for type 1 diabetes.
Harjutsalo V, Forsblom C, Groop PH. **Time trends in mortality** in patients with type 1 diabetes: nationwide population based cohort study. BMJ. 2011 Sep 8;343:d5364. doi: 10.1136/bmj.d5364.
Health Canada Dec/05 Association of **AVANDIA** & **AVANDAMET** with new onset and/or worsening of **macular edema** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/avandia_avandamet_hpc-cps_e.html
Health Canada Jan/06 & July/07 Association of **AVANDIA** & 6 reports of parotid gland enlargement http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n1_e.html#2
Health Canada Apr/07 is warning consumers from The Hong Kong Department of Health found **Lanmei Keili Ji to be adulterated with gliclazide**, a hypoglycaemic agent (lowers blood sugar).
Health Canada May/07 is advising consumers not to use **Xiaokeshuping Jiangtangning Jiaonang** capsules in Hong Kong to contain the undeclared pharmaceutical drugs phenformin, rosiglitazone, and glibenclamide, which may be used in diabetes to lower blood sugar.
Health Canada May& June/07 is advising consumers & health professionals about heart risks with **Avandia** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2007/avandia_pc-cp_3_e.html
Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang, J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.
Health Canada Nov/07 Rosiglitazone (**AVANDIA**®) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated. Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated. Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV).
Health Canada April/08 warns that Singapore's Health Sciences Authority (HSA) advised the public not to use the product **Power 1 Walnut**, because it was found to contain the prescription drugs sildenafil and glibenclamide.
Health Canada April/08 is advising consumers not to use The Hong Kong Department of Health advised the public not to use the product **Tian Sheng Yi Bao** because it was found to contain two pharmaceutical products, glibenclamide and phenformin.
Health Canada June/08 **Nangen Zengzhangsu** (may also be known as Nangen or Nangeng), Sanbianwan, Jiu Bian Wang, Tian Huang Gu Shen Dan, Zui Xian Dan Gong Shi Zi, and Power Up. The Hong Kong Department of Health has warned consumers not to use these herbal/proprietary Chinese medicine products promoted for erectile dysfunction because they have been found to contain sildenafil and/or glibenclamide.

TOP

Health Canada June/08 **Zhong Hua Niu Bian**. Zhong Hua Niu Bian is an herbal/proprietary Chinese medicine product promoted for erectile dysfunction. Singapore's Health Sciences Authority has warned against the use of this product because it has been found to contain sildenafil, glibenclamide, tadalafil and sibutramine

Health Canada Nov/08 is advising consumers not to use foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lu Quan** because it contains undeclared glibenclamide and sildenafil.

Health Canada Nov/10 AVANDIA®/AVANDAMET®/AVANDARYL® is now indicated only in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance. Prior to starting or renewing a prescription for **AVANDIA®/AVANDAMET®/ AVANDARYL®,** physicians should consider whether a rosiglitazone-containing product is an appropriate therapeutic choice, and if so: Document the eligibility of patients to meet the above criteria; Counsel each patient on the risks and benefits of AVANDIA®/AVANDAMET®/ AVANDARYL®, including the cardiovascular risks; and Obtain the patient's written informed consent to take the drug.

Health Canada Nov/11 **Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a prescription drug (glyburide). **Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al, and Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine).

Health Canada Apr/12 has recently completed a safety assessment of the available data for **rosiglitazone-ACTOS**, an oral anti-diabetic drug, and the label was updated to reflect the potential risk of **bladder cancer** in treated patients.

Health Canada May/12 1. **Jin Yu Tang Tai Han Kang Pai Pu Ling Jiao Nang; TangBaoKouFuYiDaoSuJiaoNang; Tangren 365 Kangxunpai sangge huoyisu jiaonang; Tong Ren Xiu Fu Kou Fu Yi Dao Su.** The Hong Kong Department of Health warned that these products contain a combination of prescription drugs (metformin, glibenclamide [also known as glyburide], rosiglitazone, glimepiride, hydrochlorothiazide) and unauthorized drugs (phenolphthalein, phenformin).

HEALTHY Study Group, A **School-Based Intervention** for Diabetes Risk Reduction. N Engl J Med 2010 0: NEJMoa1001933.

Heianza Y, Hara S, Arase Y, et al. **HbA(1c)** 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (**TOPICS 3**): a longitudinal cohort study. Lancet. 2011 Jun 24.

Heikes KE, et al. **Diabetes Risk Calculator**: a simple tool for detecting undiagnosed diabetes and pre-diabetes. Diabetes Care. 2008 May;31(5):1040-5. Epub 2007 Dec 10. The Diabetes Risk Calculator is the only currently available noninvasive screening tool designed and validated to detect both pre-diabetes and undiagnosed diabetes in the U.S. population.

Heine RJ, Van Gaal LF, Johns D, et al.; GWAA Study Group. **Exenatide** versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005 Oct 18;143(8):559-69.

Heisler Michele, Vijan Sandeep, Makki Fatima, et al. Diabetes Control With Reciprocal Peer Support Versus Nurse Care Management: A Randomized Trial. *Ann Intern Med* October 19, 2010 153:507-515.

Hemmingsen B, Lund SS, Gluud C, et al. Targeting **intensive glycaemic control versus targeting conventional glycaemic control** for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD008143. DOI: 10.1002/14651858.CD008143.pub2. The included trials did not show significant differences for all-cause mortality and cardiovascular mortality when targeting intensive glycaemic control compared with conventional glycaemic control. Targeting intensive glycaemic control reduced the risk of microvascular complications while increasing the risk of hypoglycaemia. Furthermore, intensive glycaemic control might reduce the risk of non-fatal myocardial infarction in trials exclusively dealing with glycaemic control in usual care settings.

Hemmingsen B, Lund SS, Gluud C, et al. **Intensive glycaemic control for patients with type 2 diabetes**: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ. 2011 Nov 24;343:d6898.

Hemmingsen B, Christensen LL, Wetterslev J, et al. Comparison of **metformin and insulin versus insulin alone** for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. BMJ. 2012 Apr 19;344:e1771.

Henry RR, Mudaliar S, Kanitra L, Woloschak M, Balena R; for the T-Emerge 3 Study Group. Efficacy and Safety of **Taspoglutide** in Patients with Type 2 Diabetes Inadequately Controlled with Metformin Plus Pioglitazone over 24 Weeks: T-Emerge 3 Trial. J Clin Endocrinol Metab. 2012 Apr 26.

Hillier TA, et al. **Screening for gestational diabetes** mellitus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2008 May 20;148(10):766-75. Limited evidence suggests that gestational diabetes treatment after 24 weeks improves some maternal and neonatal outcomes. Evidence is even more sparse for screening before 24 weeks` gestation.

Hippisley-Cox J, Coupland C, Robson J, Sheikh A, Brindle P. **Predicting risk of type 2 diabetes** in England and Wales: prospective derivation and validation of **QDScore**. BMJ. 2009 Mar 17;338:b880. doi: 10.1136/bmj.b880.

Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of **medication nonadherence** on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med 2006; 166: 1836-1841.

Ho JM, Juurlink DN. Considerations when prescribing **trimethoprim-sulfamethoxazole**. CMAJ. 2011 Oct 11.

Hober D, Sane F. **Enteroviruses** and type 1 diabetes. BMJ. 2011 Feb 3;342:c7072. doi: 10.1136/bmj.c7072.Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC; the **4-T Study** Group. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. N Engl J Med. 2007 Sep 21; [Epub ahead of print]

A single analogue-insulin formulation added to **metformin & sulfonylurea** resulted in a glycated hemoglobin level of 6.5% or less in a minority of patients at 1 year. The addition of biphasic or prandial insulin aspart reduced levels more than the addition of basal insulin detemir but were associated with greater risks of hypoglycemia and weight gain.

Holman, Rury R., Farmer, Andrew J., Davies, Melanie J., et al. the **4-T** Study Group, Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes.N Engl J Med 2009 0: NEJMoa0905479.

Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes. N Engl J Med. 2008 Sep 10. [Epub ahead of print] (**UKPDS 81**) The benefits of previously improved blood-pressure control were not sustained when between-group differences in blood pressure were lost. Early improvement in blood-pressure control in patients with both type 2 diabetes and hypertension was associated with a reduced risk of complications, but it appears that good blood-pressure control must be continued if the benefits are to be maintained.

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. **10-Year Follow-up** of Intensive Glucose Control in Type 2 Diabetes. (**UKPDS-80**) N Engl J Med. 2008 Sep 10. [Epub ahead of print] Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up. A continued benefit after metformin therapy was evident among overweight patients.

Holzinger Ulrike, Warszawska Joanna, Kitzberger Reinhard. **Real-Time Continuous Glucose Monitoring** in Critically Ill Patients: A prospective randomized trial. Diabetes Care March 2010 33:467-472.;

Home P, Mant J, Diaz J, Turner C; Guideline Development Group. Management of type 2 diabetes: summary of updated **NICE guidance**. BMJ. **2008** Jun 7;336(7656):1306-8. http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11983

Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (**RECORD**): A multicentre, randomised, open-label trial. *Lancet* 2009; DOI:10.1016/S0140-6736(09)60953-3 Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes is confirmed to increase the risk of heart failure and of some fractures, mainly in women. Although the data are inconclusive about any possible effect on myocardial infarction, rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs

Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with **gestational diabetes** mellitus: systematic review and meta-analysis. BMJ. 2010 Apr 1.

House Andrew A.; Eliasziw Misha; Cattran Daniel C.; et al. Effect of **B-Vitamin Therapy** on Progression of Diabetic Nephropathy: A Randomized Controlled Trial. *JAMA*. 2010;303(16):1603-1609.

Hovorka R, Kumareswaran K, Harris J, Allen JM, Elleri D, Xing D, et al. **Overnight closed loop insulin delivery (artificial pancreas)** in adults with type 1 diabetes: crossover randomised controlled studies. BMJ 2011;342:1855.

Howard BV, et al. Coronary heart disease risk equivalence in diabetes depends on **concomitant risk factors**. Diabetes Care. 2006 Feb;29(2):391-7.

Howard BV, Manson JE, Stefanick ML, Beresford SA, et al. **Low-fat dietary pattern** and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. JAMA. 2006 Jan 4;295(1):39-49. (InfoPOEMs: Following the long-term recommendations to reduce dietary fat and increase consumption of fruits, vegetables, and whole grains does not cause weight gain among postmenopausal women. (LOE = 2b))

Howard BV, et al. **Low-fat dietary** pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006 Feb 8;295(6):655-66.

Howard BV, Roman MJ, Devereux RB, et al. Effect of **lower targets for blood pressure and LDL** cholesterol on atherosclerosis in diabetes: The **SANDS** randomized trial. JAMA. 2008;299:1678-1689. Reducing LDL-C and SBP to lower targets resulted in regression of carotid IMT and greater decrease in left ventricular mass in individuals with type 2 diabetes. Clinical events were lower than expected and did not differ significantly between groups. Further follow-up is needed to determine whether these improvements will result in lower long-term CVD event rates and costs and favorable risk-benefit outcomes.

Hsiao FY, et al. **Thiazolidinediones** and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study of over 473 000 Patients Using the National Health Insurance Database in Taiwan. Drug Saf. 2009;32(8):675-90.

Hu E, Pan A, Malik V, Sun Q. **White rice consumption** and risk of type 2 diabetes: meta-analysis and systematic review. BMJ 2012;344:e1454.

Hughes RC, Rowan JA. **Pregnancy** in women with Type 2 diabetes: who takes **metformin** and what is the outcome? Diabet Med. 2006 Mar;23(3):318-22.

Hughes R. Investigation of **peripheral neuropathy**. BMJ. 2010 Nov 5;341:c6100. doi: 10.1136/bmj.c6100.

Hui E, Bravis V, Hassanein M, et al. Management of people with diabetes wanting to fast during **Ramadan**. BMJ 2010;340:c3053.

TOP

Huxley R, Barzi F, Woodward M. Excess risk of **fatal coronary heart disease** associated with **diabetes** in men and **women**: meta-analysis of 37 prospective cohort studies. BMJ. 2005 Dec 21; [Epub ahead of print]

Ibanez L, et al. Metformin therapy during puberty delays menarche, prolongs pubertal growth, and augments adult height: a randomized study in **low-birth-weight girls** with early-normal onset of puberty. J Clin Endocrinol Metab. 2006 Jun;91(6):2068-73. Epub 2006 Feb 21. (InfoPOEMs: Three years of metformin treatment resulted in a mean increase of at least an additional 3.5 cm of adult height in girls with history of low birth weight (LBW) and onset of puberty at 8 to 9 years of age. Larger studies are needed to assess safety, and to address girls with early-normal onset of puberty associated with insulin resistance but without history of LBW. (LOE = 1b-))

IDF: International Diabetes Federation. **Bariatric surgical** and procedural interventions in the treatment of obese patients with type 2 diabetes 2011 http://www.idf.org/webdata/docs/IDF-Position-Statement-Bariatric-Surgery.pdf

Idris I, Warren G, Donnelly R. Association between **thiazolidinedione treatment and risk of macular edema** among patients with type 2 diabetes [published online June 11, 2012]. Arch Intern Med. doi:10.1001/archinternmed

Ijas H, Vaarasmaki M, Morin-Papunen L, et al. **Metformin should be considered in the treatment of gestational diabetes**: a prospective randomised study. BJOG. 2011 Jun;118(7):880-5.

Imfeld P, Bodmer M, Jick SS, Meier CR. **Metformin**, Other Antidiabetic Drugs, and **Risk of Alzheimer's** Disease: A Population-Based Case-Control Study. J Am Geriatr Soc. 2012 Mar 28. **International** Expert Comittee. International Expert Committee Report on the Role of the **A1C Assay in the Diagnosis of Diabetes**. Diabetes Care. 2009 Jun 5. [Epub ahead of print]

International Association of Diabetes and **Pregnancy** Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care March 2010 33:676-682

Inzucchi SE, Bergenstal RM, Buse JB, et al. **Management of Hyperglycemia in Type 2 Diabetes**: A Patient-Centered Approach: Position Statement of the American Diabetes Association (**ADA**) and the European Association for the Study of Diabetes(**EASD**). Diabetes Care. 2012 Apr 19.

Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for **obesity**. Drugs. 2005;65(10):1391-418.

Ismail-Beigi Faramarz, Moghissi Etie, Tiktin Margaret, et al. **Individualizing Glycemic Targets** in Type 2 Diabetes Mellitus: Implications of Recent Clinical Trials. *Ann Intern Med* April 19, 2011 154:554-559.

Ismail-Beigi F. Clinical practice. **Glycemic management of type 2 diabetes mellitus**. N Engl J Med. 2012 Apr 5;366(14):1319-27.

Iványi T, Fövényi J, Faludi P, et al. Long-Term Effects (up to 132 weeks) of Adding **Exenatide** to a Regimen of Metformin and/or Sulfonylurea in Type 2 Diabetes: An Uncontrolled, Open-Label Trial in Hungary. Clin Ther. 2012 May 16.

Jenkins DJ, Kendall CW, McKeown-Eyssen G, et al. Effect of a **low-glycemic index or a high-cereal fiber** diet on type 2 diabetes: a randomized trial. JAMA. 2008 Dec 17;300(23):2742-53. In the low-glycaemic diet, beans, peas, lentils, nuts, pasta, and briefly boiled rice were emphasised. Breads (including pumpernickel, rye pita, and quinoa and flaxseed) and breakfast cereals (including large-flake oatmeal and oat bran) were emphasised in the low-glycaemic diet. In patients with type 2 diabetes, 6-month treatment with a low-glycemic index diet resulted in moderately lower HbA(1c) levels compared with a high-cereal fiber diet.

Johnsen SP, et al. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. Am J Ther. 2006 Mar-Apr;13(2):134-40.

Johnston Stephen S., Conner Christopher, Aagren Mark, et al. Evidence Linking **Hypoglycemic Events to an Increased Risk of Acute Cardiovascular Events** in Patients With Type 2 Diabetes. Diabetes Care May 2011 34:1164-1170; published ahead of print March 18, 2011, doi:10.2337/dc10-1915

Jokela M, et al. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet. 2009 Jun 8. [Epub ahead of print] In this study, we show changes in glucose concentrations, insulin sensitivity, and insulin secretion as much as 3-6 years before diagnosis of diabetes. The description of biomarker trajectories leading to diabetes diagnosis could contribute to more-accurate risk prediction models that use repeated measures available for patients through regular check-ups.

Juurlink David N, Gomes Tara, Lipscombe Lorraine L, et al. Adverse cardiovascular events during treatment with pioglitazone and **rosiglitazone**: population based cohort study. BMJ 2009;339:b2942, doi: 10.1136/bmj.b2942 (Published 18 August 2009)

Juvenile Diabetes Research Foundation **Continuous Glucose Monitoring** Study JDRF Group, Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76. Epub 2008 Sep 8.

Justesen TI, et al. **Albumin-to-creatinine ratio** in random urine samples might replace 24-h urine collections in screening for micro- and macroalbuminuria in pregnant woman with type 1 diabetes. Diabetes Care. 2006 Apr;29(4):924-5.

Kahn R, Buse J, Ferrannini E, Stern M; American Diabetes Association; European Association for the Study of Diabetes. The **metabolic syndrome**: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2005 Sep;28(9):2289-304.

Kahn SE, Haffner SM, Heise MA, et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. (**ADOPT** trial) N Engl J Med. 2006 Dec 4; [Epub ahead of print] Calculated monotherapy failure at 5 years was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. Kaplan-Meier analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. This represents a risk reduction of 32% for rosiglitazone, as compared with metformin, and 63%, as compared with glyburide (P<0.001 for both comparisons). The difference in the durability of the treatment effect was greater between rosiglitazone and glyburide than between rosiglitazone and metformin. Glyburide was associated with a lower risk of cardiovascular events (including congestive heart failure) than was rosiglitazone (P<0.05), and the risk associated with metformin was similar to that with rosiglitazone. Rosiglitazone was associated with more weight gain, edema and fractures than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide (P<0.001 for all comparisons). An editorialist criticizes the study's use of fasting glucose rather than glycated hemoglobin to ascertain failure. When looked at from the latter standpoint, he writes, rosiglitazone shows "a clinically less impressive effect. "Given the modest glycemic benefit of rosiglitazone (with the risk of fluid retention & weight gain) & higher cost (including the need for more statins and diuretics), metformin remains the logical choice when initiating pharmacotherapy for type 2 diabetes. (**n=4360 median 4yrs**) .Feb/07 Health Canada Avandia fracture warning: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_3_e.html & May/07 for Actos http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/actos_hpc-cps_2_e.html

Kao SL, Chan CL, Tan B, Lim CC, Dalan R, Gardner D, Pratt E, Lee M, Lee KO. An unusual outbreak of hypoglycemia. N Engl J Med. 2009 Feb 12;360(7):734-6. No abstract available. Hypoglycaemia outbreak linked to contamination of illegal **sexual-enhancement drugs with glyburide**.

Kahn SE, et al. **Rosiglitazone-associated fractures** in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008 May;31(5):845-51. Epub 2008 Jan 25. Further investigation into the risk factors and underlying pathophysiology for the increased fracture rate in women taking rosiglitazone is required to relate them to preclinical data and better understand the clinical implications of and possible interventions for these findings.

Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of **screening** to detect type 2 diabetes: a cost-effectiveness analysis. Lancet 2010; DOI:10.1016/s0140-6736(09)62162-0.

Kanaya AM, Herrington D, Vittinghoff E, et al. Impaired fasting glucose and cardiovascular outcomes in **postmenopausal women** with coronary artery disease. Ann Intern Med. 2005 May 17;142(10):813-20. (Among postmenopausal women with coronary artery disease, the 2003 definition for impaired fasting glucose was **not** associated with increased risk for new CHD, stroke or TIA, or CHF).

Kanji Jamil N.; Anglin Rebecca E. S.; Hunt Dereck L.; et al. Does This Patient With Diabetes Have Large-Fiber **Peripheral Neuropathy**? *JAMA*. 2010;303(15):1526-1532.

Kao SL, Chan CL, et al. An unusual outbreak of hypoglycemia. N Engl J Med. 2009 Feb 12;360(7):734-6. No abstract available. Hypoglycaemia outbreak linked to contamination of **illegal sexual-enhancement drugs** with glyburide.

Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. **Dipeptidyl peptidase-4 inhibitors** (DPP-4) for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369.

Kaul Sanjay, Bolger Ann F., Herrington David, et al. **Thiazolidinedione Drugs and Cardiovascular Risks**. A Science Advisory From the American Heart Association and American College of Cardiology Foundation. Circulation published February 23, 2010, doi:10.1161/CIR.0b013e3181d34114.

Kawamori R et al. **Voglibose** for prevention of type 2 diabetes mellitus: A randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet 2009 May 9; 373:1607.

Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. **Glucose Control and Cardiovascular Disease** in Type 2 Diabetes. Ann Intern Med. 2009 Jul 20.

Kendall DM, et al. Improvement of glycemic control, triglycerides, and HDL cholesterol levels with **muraglitazar**, a dual (alpha/gamma) peroxisome proliferator-activated receptor activator, in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A double-blind, randomized, pioglitazone-comparative study. Diabetes Care. 2006 May;29(5):1016-23.

KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for **Diabetes and Chronic Kidney Disease**. Am J Kidney Dis. 2007 Feb;49(2 Suppl 2):S12-154.

Khoza S, Barner JC, Bohman TM, Rascati K, Lawson K, Wilson JP. Use of **antidepressant agents** and the risk of type 2 diabetes. Eur J Clin Pharmacol. 2011 Nov 26.

Khunti K, et al. Randomised controlled trial of **near-patient testing for glycated haemoglobin** in people with type 2 diabetes mellitus. Br J Gen Pract. 2006 Jul;56(528):511-7. (InfoPOEMs: Rapid testing of glycated hemoglobin in office settings does not save money or improve glycemic control compared with usual care. (LOE = 2b))

Khunti K, Gray LJ, Skinner T, et al. Effectiveness of a **diabetes education** and self management programme (**DESMOND**) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. BMJ 2012;344:e2333.

TOP

Kirkman MS, et al. Treating **postprandial hyperglycemia** (**acarbose** 100mg tid vs placebo) does not appear to delay progression of early type 2 diabetes: the early diabetes intervention program. Diabetes Care. 2006 Sep;29(9):2095-101. Ameliorating postprandial hyperglycemia did not appear to delay progression of early type 2 diabetes. Factors other than postprandial hyperglycemia may be greater determinants of progression of diabetes. Alternatively, once FPG exceeds 126 mg/dl, beta-cell failure may no longer be remediable.

Kirsh SR, Aron DC. Choosing targets for **glycaemia, blood pressure and low-density lipoprotein cholesterol in elderly** individuals with diabetes mellitus. Drugs Aging. 2011 Dec 1;28(12):945-60.

Kitzmiller JL, Block JM, Brown FM, et al. **Managing preexisting diabetes for pregnancy**: summary of evidence and consensus recommendations for care. Diabetes Care. 2008 May;31(5):1060-79.

Klarenbach S, Cameron C, Singh S, Ur E. Cost-effectiveness of **second-line antihyperglycemic therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin**. CMAJ. 2011 Oct 3. For most patients with type 2 diabetes that is inadequately controlled with metformin monotherapy, the addition of a sulphonylurea represents the most cost-effective second-line therapy.

Kleefstra N, et al. Chromium tx has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. Diabetes Care. 2006 Mar;29(3):521-5.

Klein S, Sheard NF, Pi-Sunyer X, et al.Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. Diabetes Care 2004 Aug;27(8):2067-73.

Knip Mikael, Virtanen Suvi M, Seppä Karri, et al.. for the Finnish TRIGR Study Group. **Dietary Intervention** in Infancy and Later Signs of Beta-Cell Autoimmunity. N Engl J Med 2010; 363:1900-1908.

Kooy A, et al. Long-term effects of **metformin** on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009 Mar 23;169(6):616-25.

Korownyk C, Ivers N, Allan GM. Strategies for **initiating insulin** in type 2 diabetes. Can Fam Physician. 2011 May;57(5):562.

Kuenen JC, Borg R, Kuik DJ, et al. ADAG Study Group. Does **glucose variability influence** the relationship between mean plasma glucose and **HbA1c levels in type 1** and type 2 diabetic patients? Diabetes Care. 2011 Aug;34(8):1843-7.

Kumaraguru J, Flanagan SE, Greeley SA, et al. **Tooth discoloration** in patients with neonatal diabetes after transfer onto glibenclamide: a previously unreported side effect. Diabetes Care. 2009 Aug;32(8):1428-30. Epub 2009 May 12.

Lai SW, Muo CH, Liao KF, et al. Risk of **acute pancreatitis in type 2 diabetes** and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. Am J Gastroenterol. 2011 Sep;106(9):1697-704.

Lamanna C, Monami M, Marchionni N, et al. Effect of **metformin on cardiovascular events and mortality**: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2011 Mar;13(3):221-8.

Lambert BL, et al. Diabetes risk associated with use of **olanzapine, quetiapine, and risperidone** in veterans health administration patients with schizophrenia. Am J Epidemiol. 2006 Oct 1;164(7):672-81. Epub 2006 Aug 30.

Langan RC, Zawistoski KJ. Update on **Vitamin B12 Deficiency**. Am Fam Physician. 2011 Jun 15;83(12):1425-1430.

Landon MB, Thom E, Spong CY, et al. A planned randomized clinical trial of treatment for mild gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2002 Apr;11(4):226-31.

Landon MB et al. A multicenter, randomized trial of treatment for mild **gestational diabetes**. N Engl J Med 2009 Oct 1; 361:1339.

Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with **gestational diabetes mellitus**. N Engl J Med. 2000 Oct 19;343(16):1134-8. In women with gestational diabetes, glyburide is a clinically effective alternative to insulin therapy.

Lalau JD. **Lactic acidosis** induced by metformin: incidence, management and prevention. Drug Saf. 2010 Sep 1;33(9):727-40. doi: 10.2165/11536790-000000000-00000.

Lansang MC, Hustak LK. **Glucocorticoid-induced diabetes and adrenal suppression**: How to detect and manage them. Cleve Clin J Med. 2011 Nov;78(11):748-56.

Lasserson D, Fox R, Farmer A. **Late onset type 1 diabetes**. BMJ. 2012 Apr 30;344:e2827.

Launer LJ, Miller ME, Williamson JD, et al; **ACCORD MIND** investigators. Effects of **intensive glucose lowering** on **brain** structure and function in people with type 2 diabetes: a randomised open-label substudy. Lancet Neurol. 2011 Nov;10(11):969-77.

Lavine Joel E., Schwimmer Jeffrey B., Van Natta Mark L., et al., for the **Nonalcoholic Steatohepatitis** Clinical Research Network. Effect of **Vitamin E or Metformin** for Treatment of Nonalcoholic Fatty Liver Disease in Children and Adolescents: The TONIC Randomized Controlled Trial. JAMA. 2011;305(16):1659-1668.

Lazar HL, McDonnell MM, Chipkin S, et al. Effects of **aggressive versus moderate glycemic** control on clinical outcomes in diabetic **coronary artery bypass graft patients**. Ann Surg. 2011 Sep;254(3):458-63; discussion 463-4.

Lee Phillip H, Stockton M David, Franks Andrea S. **Acute Pancreatitis Associated with Liraglutide.** Articles Ahead of Print published on 1 April 2011, DOI 10.1345/aph.1P714. Ann Pharmacother ;45:e22.

Lee SJ, Boscardin WJ, Stijacic Cenzer I, Huang ES, Rice-Trumble K, Eng C. The **risks and benefits of implementing glycemic control guidelines in frail older adults** with diabetes mellitus. J Am Geriatr Soc. 2011 Apr;59(4):666-72.

Lee JM, Wu EL, Tarini B, et al. Diagnosis of diabetes using **hemoglobin A1c: should recommendations in adults be extrapolated to adolescents**?. J Pediatr. 2011 Jun;158(6):947-952.e1-3.

Lee JM, Wu EL, Tarini B, et al. **Diagnosis of diabetes using hemoglobin A1c**: should recommendations in adults be extrapolated to **adolescents**?. J Pediatr. 2011 Jun;158(6):947-952.e1-3.

Leiter LA, et al.; International Prandial Glucose Regulation Study Group. **Postprandial glucose** regulation: new data and new implications. Clin Ther. 2005;27 Suppl B:S42-56.

Leonetti F, Capoccia D, Coccia F, et al. Obesity, type 2 diabetes mellitus, and other comorbidities: a prospective cohort study of **laparoscopic sleeve gastrectomy vs medical treatment** [online ahead of print April 16, 2012]. Arch Surg. 2012.

Lewis JD, Ferrara A, Peng T, et al. Risk of **Bladder Cancer Among Diabetic Patients Treated With Pioglitazone**: Interim report of a longitudinal cohort study. Diabetes Care. 2011 Apr;34(4):916-22. In this cohort of patients with diabetes, short-term use of pioglitazone was not associated with an increased incidence of bladder cancer, but use for more than 2 years was weakly associated with increased risk.

Li R, Zhang P, Barker LE, et al. **Cost-effectiveness of interventions to prevent** and control diabetes mellitus: a systematic review. Diabetes Care. 2010 Aug;33(8):1872-94.

Li Yanfeng, Burrows Nilka Ríos, Gregg Edward W., et al. **Declining** Rates of Hospitalization for Nontraumatic **Lower-Extremity Amputation** in the Diabetic Population Aged 40 Years or Older: U.S., 1988–2008. Diabetes Care February 2012 35:273-277.

Lind M, Bounias I, Olsson M, Gudbjörnsdottir S, et al. **Glycaemic control and incidence of heart failure** in 20 985 patients with type 1 diabetes: an observational study. Lancet 2011; published online June 25.

Lindstrom J, et al. **Finnish Diabetes** Prevention Study Group. (FDPS) Sustained reduction in the incidence of type 2 diabetes by **lifestyle** intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006 Nov 11;368(9548):1673-9.

Lipscombe LL, Levesque L, Gruneir A, et al. **Antipsychotic drugs and hyperglycemia** in older patients with diabetes. Arch Intern Med. 2009 Jul 27;169(14):1282-9.

Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and **fractures** in type 2 diabetes: a meta-analysis. CMAJ. 2009 Jan 6;180(1):32-9. Epub 2008 Dec 10. Long-term thiazolidinedione use doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes.

Loke Yoon Kong, Kwok Chun Shing, Singh Sonal. Comparative **cardiovascular effects of thiazolidinediones**: systematic review and meta-analysis of observational studies. BMJ 342:doi:10.1136/bmj.d1309 (17 Mar 2011)

Long JA, Jahnle EC, Richardson DM, Loewenstein G, Volpp KG. **Peer mentoring** and financial incentives to improve glucose control in african american veterans: a randomized trial. Ann Intern Med. 2012 Mar 20;156(6):416-24.

Lonn EM, Gerstein HC, Sheridan P, Smith S, Diaz R, Mohan V, Bosch J, Yusuf S, Dagenais GR; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) and **STARR** Investigators. Effect of ramipril and of rosiglitazone on carotid intima-media thickness in people with impaired glucose tolerance or impaired fasting glucose: STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone). J Am Coll Cardiol. 2009 Jun 2;53(22):2028-35. One thousand four hundred twenty-five people with IGT and/or IFG but without cardiovascular disease or diabetes were randomized to ramipril 15 mg/day or its placebo and to rosiglitazone 8 mg/day or its placebo with a 2 x 2 factorial design for 3years. In people with IGT and/or IFG without cardiovascular disease and diabetes, treatment with ramipril had a neutral effect on CIMT, whereas rosiglitazone modestly reduced CIMT progression.

Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for **polycystic ovary syndrome**. Cochrane Database Syst Rev. 2003;(3):CD003053.

Lorenzo C, Haffner SM. **Performance characteristics of the new definition of diabetes**: the insulin resistance atherosclerosis study. Diabetes Care. 2010 Feb;33(2):335-7. Epub 2009 Oct 30.

Louie JC, Markovic TP, Perera N, et al. A randomized controlled trial investigating the effects of a **low-glycemic index** diet on pregnancy outcomes in **gestational** diabetes mellitus. Diabetes Care. 2011 Nov;34(11):2341-6.

Lu ZX, Walker KZ, O'Dea K, Sikaris KA, Shaw JE. **A1C for screening and diagnosis** of type 2 diabetes in routine clinical practice. Diabetes Care. 2010 Apr;33(4):817-9. Epub 2010 Jan 12.

Lubowsky ND, Siegel R, Pittas AG. Management of glycemia in patients with **diabetes mellitus and CKD**. Am J Kidney Dis. 2007 Nov;50(5):865-79.

Ludvigsson Johnny, Krisky David, Casas Rosaura, **GAD65 Antigen Therapy** in Recently Diagnosed Type 1 Diabetes Mellitus. N Engl J Med 2012; 366:433-442. (not effective)

Lund SS, Tarnow L, Astrup AS, et al. Effect of adjunct **metformin** treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study. PLoS ONE. 2008;3(10):e3363. Epub 2008 Oct 9.

Lund Søren S, Tarnow Lise, Frandsen Merete, et al. Combining insulin with **metformin** or an insulin secretagogue (repaglinide) in non-obese patients with type 2 diabetes: 12 month, randomised, double blind trial. BMJ 2009;339:b4324, doi:10.1136/bmj.b4324 (Published 9 November 2009

Lung Derrick D., Olson Kent R.. Hypoglycemia in Pediatric **Sulfonylurea Poisoning**: An 8-Year Poison Center Retrospective Study. Pediatrics 2011; 127:6 e1558-e1564; ahead of print May 23, 2011, doi:10.1542/peds.2010-3235.

Luoto R, Kinnunen TI, Aittasalo M, Kolu P, Raitanen J, et al. (2011) Primary **Prevention of Gestational Diabetes Mellitus** and Large-for-Gestational-Age Newborns by **Lifestyle Counseling**: A Cluster-Randomized Controlled Trial.

TOP

PLoS Med 8(5): e1001036. doi:10.1371/journal.pmed.1001036
Macintosh MC, et al. **Perinatal mortality & congenital** anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ. 2006 Jul 22;333(7560):177. Epub 2006 Jun 16.
Malanda UL, Welschen LM, Riphagen II, et al. **Self-monitoring of blood glucose** in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database Syst Rev. 2012 Jan 18;1:CD005060. From this review, we conclude that when diabetes duration is over one year, the overall effect of self-monitoring of blood glucose on glycaemic control in patients with type 2 diabetes who are not using insulin is small up to six months after initiation and subsides after 12 months. Furthermore, based on a best-evidence synthesis, there is no evidence that SMBG affects patient satisfaction, general well-being or general health-related quality of life. More research is needed to explore the psychological impact of SMBG and its impact on diabetes specific quality of life and well-being, as well as the impact of SMBG on hypoglycaemia and diabetic complications.
Malik VS, Popkin BM, Bray GA, et al. **Sugar-sweetened beverages** and risk of metabolic syndrome and type 2 diabetes: A meta-analysis. Diabetes Care 2010: 33:2477-2483.
Mangione CM, et al. TRIAD Study Group. The association between quality of care and the intensity of diabetes **disease management programs**. Ann Intern Med. 2006 Jul 18;145(2):107-16. Summary for patients in: Ann Intern Med. 2006 Jul 18;145(2):I41.
Mann DM, Carson AP, Shimbo D, Fonseca V, Fox CS, Muntner P. Impact of **A1C screening criterion on the diagnosis of pre-diabetes** among U.S. adults. Diabetes Care. 2010 Oct;33(10):2190-5.
Manns BJ, Tonelli M, Zhang J, et al Enrolment in **primary care networks**: impact on outcomes and processes of care for patients with diabetes. CMAJ. 2012 Feb 7;184(2):E144-52.
Marshall SM, Flyvbjerg A. Prevention and early detection of **vascular complications** of diabetes. BMJ. 2006 Sep 2;333(7566):475-80.
Martin J, et al. **Cromium Picolinate** Supplementation Attenuates Body Weight Gain and Increases Insulin Sensitivity in Subjects With Type 2 Diabetes. Diabetes Care. Volume 29;8: 2006
Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of **enalapril and losartan in type 1** diabetes. N Engl J Med. 2009 Jul 2;361(1):40-51. Early blockade of the renin-angiotensin system in patients with type 1 diabetes did not slow nephropathy progression but slowed the progression of retinopathy.
Mauras N, Beck R, Xing D, et al. A randomized clinical trial to assess the efficacy and safety of **real-time continuous glucose monitoring** in the management of type 1 diabetes in **young children** aged 4 to <10 years. Diabetes Care. 2012 Feb;35(2):204-10.
May AL, Kuklina EV, Yoon PW. Prevalence of Cardiovascular Disease Risk Factors Among US **Adolescents**, 1999-2008. Pediatrics. 2012 May 21. (14% increase in prediabetes/diabetes)
Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes. (**CHICAGO**) A randomized trial. *JAMA* 2006; 298:doi:10.1001/jama.296.21.joc60158. Over an 18-month treatment period in patients with type 2 DM, pioglitazone slowed progression of CIMT compared with glimepiride.
McCall KL, Craddock D, Edwards K. Effect of **Angiotensin**-Converting Enzyme Inhibitors and **Angiotensin II** Type 1 Receptor Blockers on the Rate of New-Onset Diabetes Mellitus: A Review and Pooled Analysis. Pharmacotherapy. 2006 Sep;26(9):1297-306.
McCrimmon RJ, Ryan CM, Frier BM. Diabetes and **cognitive dysfunction**. Lancet. 2012 Jun 8.
McPherson R, Frohlich J, Fodor G, Genest J. **Canadian 2006** Cardiovascular Society position statement -- Recommendations for the diagnosis and treatment of **dyslipidemia** and prevention of cardiovascular disease. Can J Cardiol. 2006 Sep;22(11):913-27.
Medical Letter May 23,2005: **Pramlintide** for Diabetes.
Medical Letter Jan 30,2006: **Pioglitazone/Metformin** (Actoplus met)
Medical Letter Jan 1,2007: **Sitagliptin** (Januvia); Medical Letter. Sitagliptin/Metformin (Janumet) for Type 2 Diabetes. June 4,2007.
Medical Letter Jan 29,2007: **Pioglitazone/glimepiride** (Duetact)
Medical Letter. **Liraglutide** (Victoza) for Type 2 Diabetes. April 5,2010.
Medical Letter. **Continuous Glucose Monitoring**. May 2, 2011.
Megia A, Naf S, Herranz L, et al. The usefulness of **HbA1c in postpartum reclassification of gestational** diabetes. BJOG. 2012 Apr 24.
Menard J, Payette H, Baillargeon JP, Maheux P, et al. Efficacy of **intensive multitherapy** for patients with type 2 diabetes mellitus: a randomized controlled trial. CMAJ. 2005 Nov 17; [Epub ahead of print]
Meneilly GS. **Diabetes in the elderly**. Med Clin North Am. 2006 Sep;90(5):909-23.
Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. **Pioglitazone and risk of bladder cancer** among diabetic patients in France: a population-based cohort study. Diabetologia. 2012 Mar 31.
Miller ME, Bonds DE, Gerstein HC, et al. **ACCORD** Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010 Jan 8;340:b5444. doi: 10.1136/bmj.b5444.
Mingrone G, Panunzi S, De Gaetano A, et al. **Bariatric surgery versus conventional** medical therapy for type 2 **diabetes**. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200111.
Monami M, Dicembrini I, Antenore A, Mannucci E. **Dipeptidyl peptidase-4 inhibitors and bone fractures**: a meta-analysis of randomized clinical trials. Diabetes Care. 2011 Nov;34(11):2474-6. (May reduce fractures)
Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on **inpatient glycemic control**. *Endocr Pract* 2009;15:1-17.
Moghissi ES, Korytkowski MT, DiNardo M, et al.; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on **inpatient glycemic** control. Diabetes Care. 2009 Jun;32(6):1119-31. Epub 2009 May 8.
Mohamed Q, Gillies MC, Wong TY. Management of **diabetic retinopathy**: a systematic review. JAMA. 2007 Aug 22;298(8):902-16.
Moll E, et al. Effect of clomifene citrate plus metformin & **clomifene plus placebo** on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. BMJ. 2006 Jun 24;332(7556):1485. Epub 2006 Jun 12.
Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with **glyburide** in **gestational** diabetes: a randomized controlled trial. Obstet Gynecol. 2010 Jan;115(1):55-9.
Monami M, et al. **Three-year mortality** in diabetic patients treated with different **combinations of insulin secretagogues and metformin**. Diabetes Metab Res Rev. 2006 Apr 24; [Epub ahead of print]
Monami M, Colombi C, Balzi D, et al. **Metformin and Cancer** Occurrence in Insulin-treated type 2 diabetic patients. Diabetes Care. 2010 Oct 27. [Epub ahead of print]
Montori VM, Fernández-Balsells M. **Glycemic Control** in Type 2 Diabetes: **Time for an Evidence-Based About-Face**?. Ann Intern Med. 2009 Apr 20.
Moreland EC, et al. Use of a blood **glucose monitoring manual** to enhance monitoring adherence in adults with diabetes: a randomized controlled trial. Arch Intern Med. 2006 Mar 27;166(6):689-95.
Morrison JA, Glueck CJ, Horn PS, et al. **Childhood predictors** of adult type 2 diabetes at 9- and 26-year follow-ups. Arch Pediatr Adolesc Med. 2010 Jan;164(1):53-60.
Morrison F, Shubina M, Turchin A. **Encounter frequency** and serum glucose level, blood pressure, and cholesterol level control in patients with diabetes mellitus. Arch Intern Med. 2011;171(17):1542-1550.
Mozaffarian D, Kamineni A, Prineas RJ, Siscovick DS. **Metabolic syndrome** and mortality in older adults: the Cardiovascular Health Study. Arch Intern Med. 2008 May 12;168(9):969-78. These findings suggest limited utility of MetS for predicting total or CVD mortality in older adults compared with assessment of fasting glucose and blood pressure alone.
Mullan Rebecca J.; Montori Victor M.; Shah Nilay D.; et al. The Diabetes Mellitus Medication Choice **Decision Aid**: A Randomized Trial. Arch Intern Med. 2009;169(17):1560-1568.
Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ. 2008 Sep 25;337:a1680. doi: 10.1136/bmj.a1680. **Continuous glucose monitoring** during pregnancy is associated with improved glycaemic control in the third trimester, lower birth weight, and reduced risk of macrosomia.
Murphy CE. Review of the safety and efficacy of **exenatide once weekly** for the treatment of type 2 diabetes mellitus. Ann Pharmacother. 2012 Jun;46(6):812-21.
Nathan DM, et al. Management of hyperglycemia in type 2 diabetes: a **consensus algorithm** for the initiation and adjustment of therapy: a consensus statement from the **American Diabetes Association** and the **European Association** for the Study of Diabetes. Diabetes Care. 2006 Aug;29(8):1963-72.
Nathan DM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (**DCCT/EDIC**) Study Research Group. **Intensive diabetes treatment and cardiovascular disease in patients with type 1** diabetes. N Engl J Med. 2005 Dec 22;353(25):2643-53. (InfoPOEMs: This extension of the Diabetes Control and Complications Trial (DCCT) trial provides the first high-quality evidence that intensive treatment of Type 1 diabetes reduces the risk of adverse cardiovascular outcomes. Although the relative risk reduction was greater than 50%, the absolute risk reduction (0.42 per 100 patient years; NNT=25 over 10years) was modest. Note that this effect has not been shown in patients with Type 2 diabetes, although many patients and physicians believe otherwise, and data regarding all-cause mortality or adverse effects of intensive treatment (such as hypoglycemic episodes or traffic accidents) are not reported.. (LOE = 1b)) Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years' Duration: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). Arch Intern Med. 2009;169(14):1307-1316.
Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycaemia in type 2 diabetes mellitus: a **consensus algorithm** for the initiation and adjustment of therapy : A consensus statement from the American Diabetes Association (**ADA**) and the European Association for the Study of Diabetes. Diabetologia. 2008 Oct 22. http://care.diabetesjournals.org/misc/MedicalManagementofHyperglycemia.pdf
Nau KC. Lorenzetti RC, Cucuzzela M et al. **Glycemic control in Hospitalized Patents not in Intensive Care**: Beyond Sliding Scale. American Family Pysician. May 1, 2010.
NAVIGATOR Study Group, Effect of **Nateglinide** on the Incidence of Diabetes and Cardiovascular Events. N Engl J Med 2010 0: NEJMoa1001122.

TOP

NAVIGATOR Study Group, Effect of **Valsartan** on the Incidence of Diabetes and Cardiovascular Events. N Engl J Med 2010 0: NEJMoa1001121.
NICE recommends **liraglutide** for diabetes triple therapy Feb/10 http://www.nice.org.uk/newsroom/news/newsdiabetes.jsp http://www.nice.org.uk/nicemedia/live/13248/51313/51313.pdf
NICE: National Collaborating Centre for Chronic Conditions. **Type 2 diabetes**. The management of type 2 diabetes. London (UK): National Institute for Health and Clinical Excellence ; 2009 May.
NICE Mar 2011 Clinical Guideline 119. **Diabetic foot** - inpatient management of people with diabetic foot ulcers and infection. http://www.nice.org.uk/nicemedia/live/13416/53556/53556.pdf
Nichols GA, et al. **Normal fasting plasma glucose** and risk of type 2 diabetes diagnosis. Am J Med. 2008 Jun;121(6):519-24. The strong independent association between the level of normal fasting plasma glucose and the incidence of diabetes after controlling for other risk factors suggests that diabetes risk increases as fasting plasma glucose levels increase, even within the currently accepted normal range.
Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and Risks of Oral Diabetes Agents Compared With Insulin in Women With Gestational Diabetes: A Systematic Review. Obstet Gynecol. 2009 Jan;113(1):193-205. No substantial maternal or neonatal outcome differences were found with the use of glyburide or metformin compared with use of insulin in women with GDM.
Nahas R, Moher M. **Complementary and alternative medicine** for the treatment of type 2 diabetes. Can Fam Physician. 2009 Jun;55(6):591-6. Chromium, and possibly gymnema, appears to improve glycemic control. Fibre, green tea, and fenugreek have other benefits but there is little evidence that they substantially improve glycemic control. Further research on bitter melon and cinnamon is warranted. There is no complementary and alternative medicine research addressing microvascular or macrovascular clinical outcomes.
Naik Aanand D.; Palmer Nynikka; Petersen Nancy J.; et al. Comparative Effectiveness of **Goal Setting in Diabetes Mellitus Group Clinics**: Randomized Clinical Trial. *Arch Intern Med*. 2011;171(5):453-459.
Ning G, Bi Y, Wang T, Xu M, Xu Y, Huang Y, et al. Relationship of **urinary bisphenol A** concentration to risk for prevalent type 2 diabetes in Chinese adults. A cross-sectional analysis. Ann Intern Med. 2011;155:368-74.
Nissen SE, Wolski K, Topol EJ. Effect of **Muraglitazar** on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus JAMA. 2005;294:(doi:10.1001/jama.294.20.joc50147). Oct/05
Nissen SE, Nicholls SJ, Wolski K, et al.;for the **PERISCOPE** Investigators. Comparison of **Pioglitazone vs Glimepiride** on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes: The PERISCOPE Randomized Controlled Trial. JAMA. 2008 Mar 31; [Epub ahead of print] In patients with type 2 diabetes and coronary artery disease, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.
Noble D et al. **Risk models and scores for type 2 diabetes**: systematic review. BMJ. 2011 Nov 28;343:d7163.
Nordmann AJ, et al. Effects of **low-carbohydrate vs low-fat diets** on weight loss & cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Feb 13;166(3):285-93. (InfoPOEMs: People interested in weight loss can choose either a low-fat, reduced calorie diet or a low-carbohydrate, non-calorie-restricted diet to lose a small but sustained amount of weight. The effect on cardiovascular outcomes of either diet are not known, though each has different effects on lipid levels, which may or may not translate into an actual effect on patient-oriented outcomes that matter. (LOE = 1a))
Norris SL, Kansagara D, Bougatsos C, Fu R; U.S. Preventive Services Task Force. **Screening adults** for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008 Jun 3;148(11):855-68. Review. Summary for patients in: Ann Intern Med. 2008 Jun 3;148(11):I30. Direct evidence is lacking on the health benefits of detecting type 2 diabetes by either targeted or mass screening, and indirect evidence also fails to demonstrate health benefits for screening general populations. Persons with hypertension probably benefit from screening, because blood pressure targets for persons with diabetes are lower than those for persons without diabetes. Intensive lifestyle and pharmacotherapeutic interventions reduce the progression of prediabetes to diabetes, but few data examine the effect of these interventions on long-term health outcomes.
Nowicka P, Santoro N, Liu H, et al. Utility of **hemoglobin a1c for diagnosing prediabetes and diabetes** in obese children and adolescents. Diabetes Care. 2011 Jun;34(6):1306-11.
NPS – Australia – Sitagliptin / Januvia Review: http://www.nps.org.au/health_professionals/publications/nps_radar/issues/current/august_2008/sitagliptin
Ockrim Z, Yorston D. Managing diabetic **retinopathy**. BMJ. 2010 Oct 25;341:c5400. doi: 10.1136/bmj.c5400.
Ohara T, Doi Y, Ninomiya T, et al. **Glucose tolerance status** and **risk of dementia** in the community: The Hisayama Study. Neurology. 2011 Sep 20;77(12):1126-34.
Olansky L. Q: Do **incretin drugs** for type 2 diabetes increase the risk of **acute pancreatitis**? Cleve Clin J Med. 2010 Aug;77(8):503-5.
Olson DE, Rhee MK, Herrick K, et al. **Screening** for diabetes and pre-diabetes with proposed **A1C-based diagnostic criteria**. Diabetes Care. 2010 Oct;33(10):2184-9.
Onady G, Stolfi A. Insulin and oral agents for managing **cystic fibrosis**-related diabetes. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004730.
Orban T, Bundy B, Becker DJ, et al. the Type 1 Diabetes TrialNet **Abatacept** Study Group. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011 Jun 28.
Orchard TJ, et al.; **Diabetes Prevention Program** Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med. 2005 Apr 19;142(8):611-9 & ACP Journal Club . Summary for patients in: Ann Intern Med. 2005 Apr 19;142(8):I46.
ORIGIN trial investigators**. n-3 fatty acids** and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012.
ORIGIN Trial Investigators. **Basal insulin** (glargine) and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012 Jun 11
Oster RT, Johnson JA, Hemmelgarn BR, et al. Recent epidemiologic trends of diabetes mellitus **among status Aboriginal adults**. CMAJ. 2011 Sep 6;183(12):E803-8.
Palomba S, et al. A randomized controlled trial evaluating metformin pre-treatment and co-administration in non-obese insulin-resistant women with **polycystic ovary** syndrome treated with controlled ovarian stimulation plus timed intercourse or intrauterine insemination. Hum Reprod. 2005 Jun 15.
Palomba S, Orio F Jr, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate & metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005 Jul;90(7):4068-74. (InfoPOEMs: In nonobese women with polycystic ovary syndrome, metformin is more effective than clomiphene for improving the rate of conception. (LOE = 1b))
Pantalone KM, Kattan MW, Yu C, et al. The Risk of Overall Mortality in Patients with Type 2 Diabetes Receiving **Glipizide, Glyburide, or Glimepiride** Monotherapy: A Retrospective Analysis. Diabetes Care. 2010 Mar 9.
Papa G, et al. Safety of Type 2 Diabetes Treatment With **Repaglinide Compared With Glibenclamide in Elderly** People: A randomized, open-label, two-period, cross-over trial. Diabetes Care. 2006 Aug;29(8):1918-20.
Park K. How low to go with glucose control http://www.australianprescriber.com/magazine/32/2/30/1
Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the **ADVANCE** trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy. (InfoPOEMs: Perindopril (Aceon) plus indapamide (Lozol) is better than placebo in decreasing clinically relevant events in patients with type 2 diabetes who are at high risk of cardiovascular complications. Whether the combination is better than other medications -- like aspirin -- isn't addressed by this study. (LOE = 1b))
Paynter NP, Mazer NA, Pradhan AD, et al.. **Cardiovascular Risk Prediction** in Diabetic Men and Women Using **Hemoglobin A1c** vs Diabetes as a High-Risk Equivalent. Arch Intern Med. 2011 Jul 25.
Pearson ER, et al.; Neonatal Diabetes International Collaborative Group. Switching **from insulin to oral sulfonylureas** in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006 Aug 3;355(5):467-77.
Pedersen SD, Kang J, Kline GA. **Portion control plate** for weight loss in obese patients with type 2 diabetes mellitus: a controlled clinical trial. Arch Intern Med. 2007 Jun 25;167(12):1277-83.
Pergola Pablo E., Raskin Philip, Toto Robert D., et al. for the **BEAM** Study Investigators. **Bardoxolone** Methyl and Kidney Function in CKD with Type 2 Diabetes. June 24, 2011 (10.1056/NEJMoa1105351)
Perreault L, Pan Q, Mather KJ, et al., for the Diabetes Prevention Program Research Group. Effect of **regression from prediabetes to normal glucose** regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study (**DPPOS**) . Lancet 2012; online June 9.
Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Type 1 Diabetes TrialNet Anti-CD20 Study Group. **Rituximab**, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009 Nov 26;361(22):2143-52. Peterson K, et al. Management of **Type 2 diabetes inYouth**: An Update. Am Fam Physician 2007;76:658-64.
Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the Association of **Pioglitazone Use and Bladder Cancer** Through Drug Adverse Event Reporting. Diabetes Care. 2011 Apr 22
Pharmacist's Letter May 2006: Byetta (**Exenatide**) for **Weight Loss**.
Pharmacist's Letter July 2006: **Sitagliptin** (Januvia) and Vildagliptin (Galvus) for Diabetes. (see also Medical Letter Jan 1,2007 Sitagliptin) (see also Vildagliptin. Emerging Drug List CADTH Nov/06; (FDA:concern of skin toxicity in primates http://cws.huginonline.com/N/134323/PR/200611/1087811_5_2.html)
Pharmacist's Letter: **Treatment of type 2 diabetes mellitus**. Nov 2006
Pharmacist's Letter. Treatment of Diabetes in women who are **pregnant**. Sept 2007.
Pharmacist's Letter. Metformin-Induced **Vitamin B12 Deficiency**: Can it Lead to Peripheral Neuropathy? Aug,2009.
Pharmacist's Letter. **Fasting in the Patient with Diabetes**. July 2011.

TOP

Phung OJ; Scholle JM.; Talwar M; et al. Effect of **Noninsulin Antidiabetic Drugs Added to Metformin** Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes. JAMA. 2010;303(14):1410-1418.
Pickup JC. **Insulin-pump** therapy for type 1 diabetes mellitus. N Engl J Med. 2012 Apr 26;366(17):1616-24.
Pignone Michael, Alberts Mark J., Colwell John A., et al. **Aspirin for Primary Prevention of Cardiovascular Events in People With Diabetes**. A Position Statement of the American Diabetes Association (**ADA**), a Scientific Statement of the American Heart Association (**AHA**), and an Expert Consensus Document of the American College of Cardiology Foundation (ACCF). Circulation published May 27, **2010**, doi:10.1161/CIR.0b013e3181e3b133 http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181e3b133v1
Pimouguet, Clement, Le Goff, Melanie, Thiebaut, Rodolphe, et al. Effectiveness of **disease-management programs** for improving diabetes care: a meta-analysis. CMAJ 2011 183: E115-127.
Pinelli NR, Hurren KM. Efficacy and safety of long-acting **glucagon-like peptide-1 receptor agonists** compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Pharmacother. 2011 Jul;45(7-8):850-60.
Pi-Sunyer FX, et al. RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA. 2006 Feb 15;295(7):761-75. (InfoPOEMs: Rimonabant (Acomplia) is minimally effective for obese or overweight patients for achieving sustained weight loss. Less than half the subjects initially enrolled in this study completed the protocol at 1 year. Of those remaining in the study, only one fourth lost a clinically significant amount of weight (10% or more) and, as with other weight-loss drugs, the patients who stopped taking the medicine after 1 year regained the weight. (LOE = 1b-))
Porepa, Liane, Ray, Joel G, Sanchez-Romeu, Paula, Booth, Gillian L. Newly diagnosed diabetes mellitus as a risk factor for **serious liver disease**. CMAJ 2010 0: cmaj.092144.
Preiss D, Seshasai SR, Welsh P, et al. Risk of **incident diabetes with intensive-dose compared with moderate-dose statin** therapy. JAMA 2011; 305:2556-2564. (New onset diabetes NNH=498, Cardiovascular events NNT=155 per year)
Pratley RE, Nauck M, Bailey T, et al. for 1860-LIRA-DPP-4 Study Group. **Liraglutide versus sitagliptin** for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010 Apr 24;375(9724):1447-1456.
Qaseem A, Humphrey LL, Sweet DE, et al. for the Clinical Guidelines Committee of the American College of Physicians (**ACP**). **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus**: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-231.
Rajpathak SN, Kumbhani DJ, Crandall J, et al. **Statin** therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care. 2009 Oct;32(10):1924-9.
Ramachandran A, Riddle MC, et al. Relationship between **A1C and fasting plasma glucose in dysglycemia or type 2 diabetes**: an analysis of baseline data from the ORIGIN trial. Diabetes Care. 2012 Apr;35(4):749-53.
Rascati KL et al. **Progression to insulin** for patients with diabetes mellitus using the Texas medicaid database. Clin Ther. 2011 Dec;33(12):2016-20. (slower progression with metformin/TZD than sulfonylurea/TZD)
Ray JG, et al. **Breast size** and risk of type 2 diabetes mellitus. CMAJ. 2008 Jan 29;178(3):289-95. A large bra cup size at age 20 may be a predictor of type 2 diabetes mellitus in middle-aged women.
Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of **intensive control of glucose on cardiovascular outcomes** and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet 2009; 373: 1765-72.
Raz I, Wilson PW, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the **HEART2D** trial. Diabetes Care. 2009 Mar;32(3):381-6. Treating diabetic survivors of AMI with prandial versus basal strategies achieved differences in fasting blood glucose, less-than-expected differences in postprandial blood glucose, similar levels of A1C, and no difference in risk for future cardiovascular event rates.
Reboldi G, Gentile G, Angeli F, et al. Effects of **intensive blood pressure reduction on myocardial infarction and stroke in diabetes**: a meta-analysis in 73 913 patients. J Hypertens 2011; 29:1253-1269.
Reeds Dominic N., Patterson Bruce W., Okunade Adewole, et al. **Ginseng and Ginsenoside** Re Do Not Improve β-Cell Function or Insulin Sensitivity in Overweight and Obese Subjects With Impaired Glucose Tolerance or Diabetes. Diabetes Care May 2011 34:1071-1076; published ahead of print March 16, 2011, doi:10.2337/dc10-2299
Reis JP, Loria CM, Sorlie PD, et al. **Lifestyle factors** and risk for new-onset diabetes: a population-based cohort study. Ann Intern Med. 2011 Sep 6;155(5):292-9.
Retnakaran R, Zinman B. **Thiazolidinediones** and clinical outcomes in type 2 diabetes. *Lancet* 2009; DOI:10.1016/S0140-6736(09)61029-1.
Retnakaran, Ravi, Shah, Baiju R. **Mild glucose intolerance in pregnancy** and risk of cardiovascular disease: a population-based cohort study. CMAJ 2009 0: cmaj.090569
Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim Sh. **Rosiglitazone** for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006063. Eighteen trials which randomised 3888 people to rosiglitazone treatment were identified. Longest duration of therapy was four years with a median of 26 weeks. Published studies of at least 24 weeks rosiglitazone treatment in people with type 2 diabetes mellitus did not provide evidence that patient-oriented outcomes like mortality, morbidity, adverse effects, costs and health-related quality of life are positively influenced by this compound. Metabolic control measured by glycosylated haemoglobin A1c (HbA1c) as a surrogate endpoint did not demonstrate clinically relevant differences to other oral antidiabetic drugs. Occurrence of oedema was significantly raised (OR 2.27, 95% confidence interval (CI) 1.83 to 2.81). The single large RCT (ADOPT - A Diabetes Outcomes Progression Trial) indicated increased cardiovascular risk.
Richter B, Bandeira-Echtler E, et al.. **Pioglitazone** for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006060. Until new evidence becomes available, the benefit-risk ratio of pioglitazone remains unclear. Different therapeutic indications for pioglitazone of the two big U.S. and European drug agencies should be clarified to reduce uncertainties amongst patients and physicians.
Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors (**sitagliptin and vildagliptin**) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006739.
Ripsin CM, Kang H, Urban RJ. **Management of blood glucose in type 2 diabetes mellitus**. Am Fam Physician. 2009 Jan 1;79(1):29-36.
Robling M, McNamara R, Bennert K, et al. The effect of the **Talking Diabetes consulting skills intervention** on glycaemic control and quality of life in children with type 1 diabetes: cluster randomised controlled trial (**DEPICTED** study). BMJ 2012;344:e2359
Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: **Algorithm for Glycemic Control**. Endocr Pract. 2009 September-October 1;15(6):540-559.
Rodriguez BL, et al. Prevalence of cardiovascular disease risk factors in U.S. **children and adolescents** with diabetes: the **SEARCH** for diabetes in youth study. Diabetes Care. 2006 Aug;29(8):1891-6.
Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2006 Nov;8(6):650-60.
Roustit M, Blondel E, Villier C, Fonrose X, Mallaret MP. Symptomatic hypoglycemia associated with **trimethoprim/sulfamethoxazole and repaglinide** in a diabetic patient. Ann Pharmacother 44 (4): 764-7, 2010.
Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. **Metformin in Gestational Diabetes**: The Offspring Follow-Up (**MiG TOFU**): Body composition at 2 years of age. Diabetes Care. 2011 Oct;34(10):2279-84.
Roy MS, Affouf M. Six-year progression of **retinopathy** and associated risk factors in African american patients with type 1 diabetes mellitus: the new jersey 725. Arch Ophthalmol. 2006 Sep;124(9):1297-306.
Ruiter R et al. **Lower risk of cancer in patients on metformin** in comparison with those on sulfonylurea derivatives: Results from a large population-based follow-up study. Diabetes Care 2012 Jan; 35:119.
Russell-Jones D, Cuddihy RM, Hanefeld M, et al. **DURATION-4** Study Group. Efficacy and safety of **exenatide once weekly** versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2012 Feb;35(2):252-8.
Saenz A, Fernandez-Esteban I, Mataix A, et al. Metformin monotherapy for type 2 diabetes mellitus. **Cochrane** Database Syst Rev. 2005 Jul 20;(3):CD002966. CONCLUSIONS: Metformin may be the first therapeutic option in the diabetes mellitus type 2 with overweight or obesity, as it may prevent some vascular complications, and mortality. Metformin produces beneficial changes in glycaemia control, and moderated in weight, lipids, insulinaemia and diastolic blood pressure. Sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, insulin, and diet fail to show more benefit for glycaemia control, body weight, or lipids, than metformin.
Saito T, Watanabe M, Nishida J, et al; **Zensharen Study** for Prevention of Lifestyle Diseases Group. **Lifestyle modification and prevention** of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med. 2011;171(15):1352-1360.
Salas-Salvadó. J, Bullo M, Babio N et al. Reduction in the incidence of type 2 diabetes with the **Mediterranean Diet**: Results of the PREDIMED-Reus Nutrition Intervention Randomized trial. Diabetes Care 2011;34:14–19.
Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: **metformin** treatment in persons at **risk for diabetes mellitus**. Am J Med. 2008 Feb;121(2):149-157.e2. Using metformin to treat patients at risk for diabetes decreases their likelihood of developing diabetes over a 3-year period. Longer studies are needed to determine whether the likelihood of diabetes is truly decreased or simply delayed. We have no research to tell us whether, in the long run, patients live longer or live better if they are treated at this stage of (pre)diabetes. (LOE = 1a)
Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal **lactic acidosis with metformin** use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD002967. No evidence assoc. metformin with ↑lactic acidosis.
Sanyal, Arun J., Chalasani, Naga, Kowdley, Kris V., et al. the **NASH CRN, Pioglitazone**, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. N Engl J Med 2010 0: NEJMoa0907929.
Sattar N, McConnachie A, Shaper AG, et al. Can **metabolic syndrome** usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet. 2008 May 21. [Epub ahead of print] Metabolic syndrome and its components are associated with type 2 diabetes but have weak or no association with vascular risk in elderly populations, suggesting that attempts to define criteria that simultaneously predict risk for both cardiovascular disease and diabetes are unhelpful.

TOP

Sattar N, Preiss D, Murray HM, et al. **Statins** and risk of incident **diabetes**: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; DOI:10.1016/S0140-6736(09)61965-6.
Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using **self-monitoring** blood glucose and hemoglobin A1c. JAMA. 2006 Apr 12;295(14):1688-97.
Sauer WH, Cappola AR, Berlin JA, Kimmel SE. Insulin sensitizing pharmacotherapy for prevention of myocardial infarction in patients with diabetes mellitus. Am J Cardiol. 2006 Mar 1;97(5):651-4. Epub 2006 Jan 6.
Sawin G, Shaughnessy AF. **Glucose control in Hospitalized Patients**. American Family Pysician. May 1, 2010.
Schauer PR, Kashyap SR, Wolski K, et al. **Bariatric surgery versus intensive medical therapy** in obese patients with **diabetes**. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200225.

Scheen AJ, Finet al. **RIO-Diabetes** Study Group. Efficacy and tolerability of **rimonabant** (20mg/d)in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet. 2006 Nov 11;368(9548):1660-72. (n=1047 1yr) These data indicate that 20 mg/day rimonabant, in combination with diet and exercise, can produce a clinically meaningful reduction in bodyweight and improve HbA1c and a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes inadequately controlled by metformin or sulphonylureas.
Schmid R, Vollenweider P, Bastardot F, et al. Validation of **7 Type 2 Diabetes Mellitus Risk Scores** in a Population-Based Cohort: CoLaus Study. Arch Intern Med. 2012 Jan 23;172(2):188-9.
Schramm TK, Gislason GH, Vaag A, et al. **Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin** in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011 Aug;32(15):1900-8. Monotherapy with the most used ISs, including glimepiride, glibenclamide, glipizide, and tolbutamide, seems to be associated with increased mortality and cardiovascular risk compared with metformin. Gliclazide and repaglinide appear to be associated with a lower risk than other ISs.
Schwartz AV, et al. **Thiazolidinedione** use and **bone loss** in older diabetic adults. J Clin Endocrinol Metab. 2006 Sep;91(9):3349-54. Epub 2006 Apr 11.
Schwartz AV, Vittinghoff E, Bauer DC, et al. Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging, and Body Composition (Health ABC) Research Group. Association of **BMD and FRAX score with risk of fracture** in older adults with type 2 diabetes. JAMA. 2011 Jun 1;305(21):2184-92.
Schwing W, Hustak L, Taylor HC. Paradoxical Severe Decrease in HDL Cholesterol Due to **Rosiglitazone-Fenofibrate** Interaction. Endocr Pract. 2010 Jan 9:1-17. [Epub ahead of print]
Selvin E, Coresh J, Golden SH, et al. Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med. 2005 Sep 12;165(16):1910-6.
Selvin E, Bolen S, Yeh HC, et al.. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med. 2008 Oct 27;168(19):2070-80. Meta-analysis suggested that, compared with other oral diabetes agents and placebo, **metformin was moderately protective and rosiglitazone possibly harmful**, but lack of power prohibited firmer conclusions.
Selvin, Elizabeth, Steffes, Michael W., Zhu, Hong, et al. **Glycated Hemoglobin** (A1c), Diabetes, and Cardiovascular Risk in Nondiabetic Adults. (ARIC study) N Engl J Med 2010 362: 800-811.
Selvin E, Steffes MW, Gregg E, et al. Performance of **A1C for the classification and prediction of diabetes**. Diabetes Care. 2011 Jan;34(1):84-9.
Sen Gupta P, Green AN, Chowdhury TA. **Hypoglycaemia**. BMJ. 2011 Feb 16;342:d567. doi: 10.1136/bmj.d567.
Senthinathan A, Kelly V, Dzingina M et al. **Hyperglycaemia** in acute coronary syndromes: summary of NICE guidance. BMJ. 2011 Oct 26;343:d6646.
Shai I, Schwarzfuchs D, Henkin Y, et al. Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008 Jul 17;359(3):229-41. Mediterranean and low-carbohydrate diets may be effective alternatives to low-fat diets. The more favorable effects on lipids (with the low-carbohydrate diet) and on glycemic control (with the Mediterranean diet) suggest that personal preferences and metabolic considerations might inform individualized tailoring of dietary interventions. (Elhayany A, Lustman A, Abel R, et al. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. Diabetes Obes Metab. 2010 Mar;12(3):204-9.)
Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The Effect of **Oral Antidiabetic Agents on Glycated Hemoglobin Levels**: A Systematic Review and Meta-Analysis. Diabetes Care. 2010 May 18.
Sherifali D, Greb JL, Amirthavasar G, et al. Effect of **computer-generated tailored feedback** on glycemic control in people with diabetes in the community: a randomized controlled trial. Diabetes Care. 2011 Aug;34(8):1794-8.
Sherry N, Hagopian W, Ludvigsson J, et al. for the Protégé Trial Investigators. **Teplizumab** for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. Lancet. 2011 Jun 28.
Shojania KG, et al. Effects of **quality improvement strategies** for type 2 diabetes on glycemic control: a meta-regression analysis. JAMA. 2006 Jul 26;296(4):427-40.
Shurraw S, Hemmelgarn B, Lin M, et al; for the Alberta Kidney Disease Network. Association between **glycemic control and adverse outcomes** in people with diabetes mellitus and **chronic kidney disease**: a population-based cohort study. Arch Intern Med. 2011;171(21):1920-1927. {Lower A1C benefits renal function, but avoid A1Cs of <6.5%. e.g. U shaped curve for mortality (↑ mortality <6.5% & >9%)}
Shyangdan DS, Royle P, Clar C, et al. **Glucagon-like peptide analogues** (exenatide, liraglutide) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2011 Oct 5;10:CD006423. GLP-1 agonists are effective in improving glycaemic control.
Sieri S, Krogh V, Berrino F, et al. **Dietary glycemic load** and index and risk of coronary heart disease in a large italian cohort: the EPICOR study. Arch Intern Med. 2010 Apr 12;170(7):640-7.
Sillars B, Davis WA, Hirsch IB, et al. **Sulphonylurea-metformin combination therapy**, cardiovascular disease and all-cause mortality: the Fremantle Diabetes Study. Diabetes Obes Metab. 2010 Sep;12(9):757-65.
Silverman RA, Thakker U, Ellman T, et al. **Hemoglobin A1c as a screen** for previously undiagnosed prediabetes and diabetes in an acute-care setting. Diabetes Care. 2011 Sep;34(9):1908-12.
Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005 Jan;28(1):186-212.
Simmons D, McElduff A, McIntyre HD, et al. **Gestational Diabetes Mellitus**: **NICE for the U.S**.? A Comparison of the American Diabetes Association and the American College of Obstetricians and Gynecologists Guidelines With the U.K. National Institute for Health and Clinical Excellence Guidelines: Response to Holt et al. Diabetes Care. 2010 Mar;33(3):e48.
Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between **sulfonylurea drugs and mortality** in type 2 diabetes mellitus: a population-based cohort study. CMAJ. 2006 Jan 17;174(2):169-74. (Bell DS. Do sulfonylurea drugs increase the risk of cardiac events? CMAJ. 2006 Jan 17;174(2):185-6.) (Evans JM, et al. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia. 2006 Mar 9; [Epub ahead of print])
Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of **periodontal disease** for glycaemic control in people with diabetes. Cochrane Database Syst Rev. 2010 May 12;5:CD004714. There is some evidence of improvement in metabolic control in people with diabetes, after treating periodontal disease.
Simpson SH, Gamble JM, Mereu L, et al. Effect of **aspirin** dose on mortality and cardiovascular events in people with **diabetes**: a meta-analysis. J Gen Intern Med. 2011 Nov;26(11):1336-44.
Sinclair AJ, Paolisso G, et al. European Diabetes Working Party for Older People. **European** Diabetes Working Party for **Older People 2011 clinical guidelines** for type 2 diabetes mellitus. Executive summary. Diabetes Metab. 2011 Nov;37 Suppl 3:S27-38.
Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the **ACCORD, ADVANCE, and VADT diabetes trials**: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care. 2009 Jan;32(1):187-92. Epub 2008 Dec 17.
SMBG: Type 2 Diabetes and **Monitoring** your Blood Sugar –**Patient Pamphlet** . http://www.cadth.ca/media/pdf/smbg-nb_eng.pdf
Smith NL, et al. **New-onset diabetes** and risk of all-cause and **cardiovascular mortality**: the Cardiovascular Health Study. Diabetes Care. 2006 Sep;29(9):2012-7. Our findings indicate that there may be a mortality differential soon after diabetes onset in older adults and suggest that long-term macrovascular damage from atherosclerosis may not be primarily responsible for increased risk.
Smith S M, Paul G, Kelly A, et al. **Peer support** for patients with type 2 diabetes: cluster randomised controlled trial. *BMJ 342:doi:10.1136/bmj.d715 (Published 15 February 2011)*
Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Ad herence to **Mediterranean diet** and health status: meta-analysis. BMJ 2008;337:a1344.
Solomon Daniel H., Massarotti Elena, Garg Rajesh, et al. Association Between **Disease-Modifying Antirheumatic Drugs and Diabetes Risk** in Patients With Rheumatoid Arthritis and Psoriasis. JAMA. 2011;305(24):2525-2531.
Sosenko JM, Skyler JS, Mahon J, et al. **Validation of the Diabetes Prevention Trial-Type 1 Risk Score** in the TrialNet Natural History Study. Diabetes Care. 2011 Aug;34(8):1785-7.
Sorkin JD, et al.The relation of **fasting** & **2h postchallenge** plasma glucose concentrations to mortality:data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. Diabetes Care.2005Nov;28(11):2626-32. (InfoPOEMs: Higher fasting blood glucose levels or 2-hour postprandial blood glucose levels in middle-aged men are predictive of subsequent mortality. However, that doesn't necessarily mean that lowering their blood glucose with therapy reduces that mortality; this was not demonstrated in the United Kingdom Prospective Diabetes Study (UK Prospective Diabetes Study [UKPDS] Group. Lancet 1998;352:837-53). (LOE = 1b))
Soylemez Wiener R, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in **critically ill** adults: a meta-analysis. JAMA. 2008 Aug 27;300(8):933-44. In critically ill adult patients, tight glucose control is not associated with

TOP

significantly reduced hospital mortality but is associated with an increased risk of **hypoglycemia**.
Sperl-Hillen J, Beaton S, Fernandes O, et al. Comparative effectiveness of **patient education methods** for type 2 diabetes: a randomized controlled trial [published online October 10, 2011]. Arch Intern Med. doi:10.1001/archinternmed .2011.507.
Srinivasan S, et al. Randomized, controlled trial of metformin for obesity & insulin resistance in children & adolescents: improvement in body composition and fasting insulin. J Clin Endocrinol Metab. 2006 Jun;91(6):2074-80. Epub 2006 Apr 4. (InfoPOEMs: For obese 9- to 18-year-olds, metformin (1g twice daily) resulted in a mean weight loss of approximately 10 pounds at the end of 6 months of treatment. Larger and longer studies are needed to support the effectiveness and safety of this regimen. (LOE = 1b-))
Stankiewicz M, Norman R. Diagnosis and management of **polycystic ovary syndrome**: a practical guide. Drugs. 2006;66(7):903-12.
Stone MA, Camosso-Stefinovic J, Wilkinson J, de Lusignan S, Hattersley A, Khunti K. **Incorrect and incomplete coding and classification of diabetes**: a systematic review. Diabet Med 2010;27:491-7.
Strippoli GF, Craig MC, Schena FP, Craig JC. Role of blood pressure targets and specific antihypertensive agents used to prevent **diabetic nephropathy** and delay its progression. J Am Soc Nephrol. 2006 Apr;17 Suppl 2:S153-5. On the basis of available RCT evidence, ACEi are the only agents with proven renal benefit in patients who have diabetes with no nephropathy and the only agents with proven survival benefit in patients who have diabetes with nephropathy.
Strong WB, Malina RM, Blimkie CJ, et al. Evidence based **physical activity** for school-age **youth**. J Pediatr. 2005 Jun;146(6):732-7. (InfoPOEMs: Children should participate in at least 60 minutes of moderate to vigorous physical activity every day to avoid obesity and improve lipid levels and blood pressure. Encourage parents to turn off their child's television and find activities for them that are developmentally appropriate and fun. (LOE = 1a))
Stranges S, Marshall JR, Natarajan R, et al. Effects of Long-Term Selenium 200ug daily Supplementation on the Incidence of Type 2 Diabetes: A Randomized Trial. Ann Intern Med. 2007 Jul 9; [Epub ahead of print]
Selenium supplementation does not seem to prevent type 2 diabetes, and it may increase risk for the disease. (but this was a secondary analysis of the Nutritional Prevention of Cancer- NPC trial)
Strychar I. **Diet** in the management of weight loss. CMAJ. 2006 Jan 3;174(1):56-63.
Sun Qi; Spiegelman Donna; van Dam Rob M.; Miet al. White Rice, **Brown Rice**, and Risk of Type 2 Diabetes in US Men and Women. Arch Intern Med. 2010;170(11):961-969.
Sun JK, Keenan HA, Cavallerano JD, et al. Protection from **retinopathy** and other complications in patients with type 1 diabetes of extreme duration: the **joslin 50-year medalist study**. Diabetes Care. 2011 Apr;34(4):968-74.
Sundstrom J, et al. Clinical value of the **metabolic syndrome** for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. BMJ. 2006 Apr 15;332(7546):878-82. Epub 2006 Mar 1.
Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. **Prediabetes**: a high-risk state for diabetes development. Lancet. 2012 Jun 8.
Tang T, Lord JM, Norman RJ, et al. Insulin-sensitising drugs (**metformin**, rosiglitazone, pioglitazone, D-chiro-inositol) for women with **polycystic ovary syndrome**, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD003053. In agreement with the previous review, metformin is still of benefit in improving clinical pregnancy and ovulation rates.
Teeuw WJ, Gerdes VE, Loos BG. Effect of **periodontal treatment** on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes Care. 2010 Feb;33(2):421-7.
Thanabalasingham Gaya, Owen Katharine R. Diagnosis and management of **maturity onset diabetes of the young** (**MODY**). BMJ 2011;343:doi:10.1136/bmj.d6044 (Published 19 October 2011)
Tieu J, Middleton P, McPhee AJ, Crowther CA. **Screening** & subsequent management for **gestational diabetes** for improving maternal and infant health.Cochrane Database Syst Rev. 2010 Jul 7;7:CD007222. There was insufficient evidence to determine if screening for gestational diabetes, or what types ofscreening, can improve maternal and infant health outcomes.
Ting RZ, et al. Risk factors of **vitamin B12 deficiency** in patients receiving metformin. Arch Intern Med. 2006 Oct 9;166(18):1975-9. Our results indicate an increased risk of vitamin B(12) deficiency associated with current dose and duration of metformin use despite adjustment for many potential confounders
Tirosh A, Shai I, Tekes-Manova D, et al.; Israeli Diabetes Research Group. **Normal fasting plasma glucose** levels and type 2 diabetes in young men. N Engl J Med. 2005 Oct 6;353(14):1454-62.
TheHeart.org: Steno-2 news release: http://www.theheart.org/article/842047.do#
TheHeart.org: ACCORD – intensive glucose control arm halted early - news release: http://www.theheart.org/article/842113.do
Thomas D, Elliott EJ. Low **glycaemic index**, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006296. A low-GI diet can improve glycaemic control in diabetes without compromising hypoglycaemic events.
Thomas RL, Dunstan F, Luzio SD et al. Incidence of **diabetic retinopathy** in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. BMJ. 2012 Feb 22;344:e874.
Tirosh A et al. Adolescent **BMI trajectory and risk of diabetes versus coronary disease**. N Engl J Med 2011 Apr 7; 364:1315.
Tobe SW, Stone JA, Brouwers M, et al. **Harmonization of guidelines** for the prevention and treatment of cardiovascular disease: the **C-CHANGE Initiative**. CMAJ. 2011 Sep 12.
Tobias DK, Zhang C, van Dam RM, Bowers K, Hu FB. **Physical activity before and during pregnancy** and risk of gestational diabetes mellitus: a meta-analysis. Diabetes Care. 2011 Jan;34(1):223-9.
Tocci G, Paneni F, Palano F, et al. **Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers** and **Diabetes**: A Meta-Analysis of Placebo-Controlled Clinical Trials. Am J Hypertens. 2011 May;24(5):582-90.
TODAY Study Group. A clinical trial to maintain *glycemic control in youth* with type 2 diabetes. N Engl J Med 2012.
Tolman KG, Freston JW, Kupfer S, Perez A. **Liver Safety** in Patients with Type 2 Diabetes Treated with **Pioglitazone**: Results from a 3-Year, Randomized, Comparator-Controlled Study in the US. Drug Saf. 2009;32(9):787-800.
Tom WL, et al. The effect of short-contact topical **tretinoin** therapy for **foot ulcers** in patients with diabetes. Arch Dermatol. 2005 Nov;141(11):1373-7. (InfoPOEMs: This small study provides some support for a daily 10-minute application of 0.05% topical tretinoin to diabetic ulcers. (LOE = 1b-))
Tomova GS, Nimbal V, Horwich TB. Relation between **hemoglobin A1c and outcomes in heart failure** patients with and without diabetes mellitus. Am J Cardiol 2012.
Torpy Janet M., Golub Robert M.. **Diabetes patient page**. JAMA. 2011;305(24):2592.doi:10.1001/jama.2011.741.
Touma C, Pannain S. Does **lack of sleep cause diabetes**? Cleve Clin J Med. 2011 Aug;78(8):549-58.
Treatment Guidelines: **Drugs for Diabetes**. The Medical Letter: August, 2005; (3) pp. 57-62.
Tricco AC, Ivers NM, Grimshaw JM, et al. Eff ectiveness of **quality improvement strategies** on the management of diabetes: a systematic review and meta-analysis. Lancet 2012; online June 9.
Tzoulaki Ioanna, Molokhia Mariam, Curcin Vasa, et al. **Risk of cardiovascular disease** and all cause mortality among patients with type 2 diabetes prescribed **oral antidiabetes drugs**: retrospective cohort study using UK general practice research database. BMJ 2009;339:b4731, doi: 10.1136/bmj.b4731 (Published 3 December 2009)
Umpierre D, Ribeiro PB, Kramer CK, et al. Physical **Activity** Advice Only or Structured **Exercise** Training and Association With HbA1c Levels in Type 2 Diabetes: Systematic Review & Meta-analysis. JAMA.2011;305(17):1790-1799.
Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of **hyperglycemia in hospitalized patients** in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol 2012; 97:16-38.
UKPDS-34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. Lancet. 1998 Sep 12;352(9131):854-65. Erratum in: Lancet 1998 Nov 7;352(9139):1558.
Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of **diabetic ketoacidosis** at diagnosis of diabetes in children and young people: a systematic review. BMJ 2011;343:d4092.
U.S. Preventive Services Task Force. **Screening** for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008 Jun 3;148(11):846-54.
Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, Aviv A, Spector TD. Obesity, cigarette smoking, and telomere length in women. Lancet. 2005 Aug 20-26;366(9486):662-4.
van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes. A systematic review. JAMA 2005; 294:97-104. (InfoPOEMs Habitual coffee drinking is associated with a reduced risk for type 2 diabetes. The lowest risk reduction occurred among individuals consuming 6 or more cups of filtered coffee daily. Decaffeinated and caffeinated brews are equally effective. (LOE = 2a-):)
Van de Laar FA, Lucassen PL, Akkermans RP, et al. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD003639 & ACP Journal Club . AUTHORS' CONCLUSIONS: It remains unclear whether alpha-glucosidase inhibitors influence mortality or morbidity in patients with type 2 diabetes. Conversely, they have a significant effect on glycemic control and insulin levels, but no statistically significant effect on lipids and body weight. These effects are less sure when alpha-glucosidase inhibitors are used for a longer duration. Acarbose dosages higher than 50 mg TID offer no additional effect on glycated hemoglobin but more adverse effects instead. Compared to sulphonylurea, alpha-glucosidase inhibitors lower fasting and post-load insulin levels and have an inferior profile regarding glycemic control and adverse effects.
van der Heijden AA, Ortegon MM, Niessen LW, et al. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. Diabetes Care. 2009 Nov;32(11):2094-8. The use of the Framingham function for prediction of the first CHD event is likely to overestimate an individual`s absolute CHD risk. In CHD prevention, application of the **SCORE and UKPDS** functions might be useful in the absence of a more valid tool.
van Dieren S, Beulens JW, Kengne AP, et al. **Prediction models for the risk of cardiovascular disease** in patients with type 2 diabetes: a systematic review. Heart. 2011 Dec 18.
Van Gaal LF, Rissanen AM, Scheen AJ, et al. **RIO-Europe** Study Group. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet. 2005 Apr 16-22;365(9468):1389-97. Erratum in: Lancet. 2005 Jul 30-Aug 5;366(9483):370.
Vetter ML, Cardillo S, Rickels MR, Iqbal N. Narrative review: effect of **bariatric surgery** on type 2 diabetes mellitus. Ann Intern Med. 2009 Jan 20;150(2):94-103.

TOP

Vigersky RA, Fonda SJ, Chellappa M, et al. Short- and long-term effects of **real-time continuous glucose monitoring** in patients with type 2 diabetes. Diabetes Care. 2012 Jan;35(1):32-8.
Vijan Sandeep. **In the Clinic: Type 2 Diabetes**. *Ann Intern Med* March 2, 2010 152:ITC3-1; doi:10.1059/0003-4819-152-5-201003020-01003.
Vause TD, Cheung AP, Sierra S, Claman P, Graham J, Guillemin JA, Lapensée L, Steward S, Wong BC. Ovulation induction in polycystic ovary syndrome. J Obstet Gynaecol Can. 2010 May;32(5):495-502. Ovulation Induction in **Polycystic Ovary Syndrome SOGC-2010** http://sogc.org/guidelines/documents/gui242CPG1005E.pdf
Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial: **lifestyle modification & pharmacotherapy** for obesity. N Engl J Med 2005;353:2111-20. Combo of sibutramine & group lifestyle modifications resulted in more weight loss (**12.1 kg** at 1yr) then either alone.
Wahrenberg H, Hertel K, Leijonhufvud BM, Persson LG, Toft E, Arner P. Use of **waist circumference** to predict insulin resistance: retrospective study. BMJ. 2005 Jun 11;330(7504):1363-4. Epub 2005 Apr 15.
Walker EA, et al. **Adherence** to preventive medications: predictors and outcomes in the Diabetes Prevention Program. Diabetes Care. 2006 Sep;29(9):1997-2002.
Wang Amy T, McCoy Christopher P, Murad Mohammad Hassan, Montori Victor M. Association between **industry affiliation** and position on cardiovascular risk with **rosiglitazone**: cross sectional systematic review. BMJ 2010;340:c1344, doi: 10.1136/bmj.c1344 (Published 18 March 2010).
Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic Syndrome vs **Framingham Risk Score** for Prediction of Coronary Heart Disease, Stroke, and Type 2 Diabetes Mellitus. Arch Intern Med. 2005 Dec 26;165(22):2644-50.
Wannamethee S. Goya; Shaper A. Gerald; Whincup Peter H.; et al. Impact of Diabetes on **Cardiovascular Disease Risk and All-Cause Mortality in Older Men**: Influence of Age at Onset, Diabetes Duration, and Established and Novel Risk Factors. *Arch Intern Med*. 2011;171(5):404-410.
Wasko MC, Hubert HB, Lingala VB, et al. **Hydroxychloroquine and risk of diabetes** in patients with rheumatoid arthritis. JAMA. 2007 Jul 11;298(2):187-93.
Waugh N, Cummins E, Royle P, et al. Newer agents for blood glucose control (glucagon-like peptide-1 (GLP-1) analogue **exenatide**; dipeptidyl peptidase-4 (DPP-4) inhibitors **sitagliptin** and **vildagliptin**; the long-acting insulin analogues, **glargine** and **detemir**) in type 2 diabetes: systematic review and economic evaluation. Health Technol Assess. 2010 Jul;14(36):1-248.
Waugh N, Royle P, Clar C, et al. **Screening for hyperglycaemia in pregnancy**: a rapid update for the National Screening Committee. Health Technol Assess. 2010 Sep;14(45):1-183. The evidence base has improved since the last HTA review in 2002. There is now good evidence for treatment of oral drugs instead of insulin and it looks increasingly as if FPG could be the test of choice.
Weinger K, Beverly EA, Lee Y, Sitnokov L, Ganda OP, Caballero AE. The effect of a **structured behavioral intervention** on poorly controlled diabetes: a randomized controlled trial [published online October 10, 2011]. Arch Intern Med.
Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. Diabetes Care 2005; 28:1510-17. (InfoPOEMs: Intensive monitoring of blood glucose in patients with type 2 diabetes not using insulin results in a small decrease in hemoglobin A1c (HbA1c) levels but does not change fasting blood glucose levels. Urine glucose monitoring works just as well. More casual monitoring of blood glucose, such as once a day, has not been studied. There is a strong possibility that the weak study design was largely responsible for the difference seen in the study. Blood glucose monitoring is expensive: At the intense level of monitoring used in some of these studies (6 times a day), the cost of the monitoring strips alone can be $2000 US per year. (LOE = 1a))
Wen CP, et al. Increased mortality risks of pre-diabetes (**impaired fasting glucose**) in Taiwan. Diabetes Care. 2005 Nov;28(11):2756-61. CONCLUSIONS: There was an overall J-shaped relationship between all-cause mortality and FBG. IFG, when defined as 110-125 mg/dl, is an independent risk factor and should be aggressively treated as a disease because its subsequent mortality risks for CVD and diabetes were significantly increased. The newly defined IFG at 100-125 mg/dl did not have the predictive power for later increases in CVD or diabetes mortality.
Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomized parallel-group trial. Lancet. 2008 May 4;371(9626):1753-1760. Early intensive insulin therapy in patients with newly diagnosed type 2 diabetes has favourable outcomes on recovery and maintenance of beta-cell function and protracted glycaemic remission compared with treatment with oral hypoglycaemic agents.
Wernicke JF, et al. A randomized controlled trial of **duloxetine** in diabetic peripheral **neuropathic** pain. Neurology. 2006 Oct 24;67(8):1411-20. (InfoPOEMs: In this study, duloxetine (Cymbalta) 60 mg daily was more effective than placebo in reducing pain from neuropathy in pts with diabetes. Higher doses of duloxetine didn't provide much additional benefit. The biases in this study favor treatment, so it is likely that the real benefit is less than what these investigators observed. Finally, we don't know if duloxetine is any more effective than other treatments used for painful diabetic neuropathy. (LOE = 2b-))
Wherrett DK, Bundy B, Becker DJ, et al, and the Type 1 Diabetes TrialNet GAD Study Group. Antigen-based therapy with **glutamic acid decarboxylase (GAD) vaccine** in patients with recent-onset type 1 diabetes: a randomised double-blind trial. Lancet 2011; published online June 27. DOI:10.1016/S0140-6736(11)60895-7.
White NH, Sun W, Cleary PA, et al. Effect of Prior Intensive Therapy in Type 1 Diabetes Mellitus on 10-year Progression of **Retinopathy** in the **DCCT/EDIC**: Comparison of Adults and Adolescents. Diabetes. 2010 Feb 11.
Wilding JP, Hardy K. **Glucagon-like peptide-1 analogues** for type 2 diabetes. BMJ. 2011 Feb 16;342:d410. doi: 10.1136/bmj.d410.
Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, et al. Long-term efficacy of **dapagliflozin** in patients with type 2 diabetes mellitus receiving high doses of insulin. A randomized trial. Ann Intern Med. 2012;156: 405-15.
Wile DJ and Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care 2010 Jan; 33:156. (depressed **vitamin B12,** cobalamin levels)
Wilson Jennifer F. **In the Clinic: Diabetic Ketoacidosis**. Ann Intern Med January 5, 2010 152:ITC1-1; doi:10.1059/0003-4819-152-1-201001050-01001.
Wright AD, Cull CA, Macleod KM, Holman RR; for the UKPDS Group. Hypoglycemia in Type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications. 2006 Nov-Dec;20(6):395-401. More on basal insulin reported hypoglycemia (3.8% per year) than diet (0.1%), sulfonylurea (1.2%), or metformin (0.3%) therapy, but less than on basal and prandial insulin (5.3%) (all P<.0001). **Low hypoglycemia rates** seen during the first 6 years of intensive glucose lowering therapy in Type 2 diabetes are unlikely to have a major impact on attempts to achieve guideline glycemic targets when sulfonylurea, metformin, or insulin are used as monotherapy.
Wright A, Burden AC, Paisey RB, Cull CA, Holman RR; U.K. Prospective Diabetes Study Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (**UKPDS 57**). Diabetes Care. 2002 Feb;25(2):330-6.
Wu SS, Yen HH. Images in clinical medicine. Pneumatosis cystoides intestinalis (due to **acarbose**). N Engl J Med. 2011 Aug 25;365(8):e16.
Yamaoka K, Tango T. Efficacy of **lifestyle education** to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2005 Nov;28(11):2780-6.
Yang X, So WY, Ma RC, et al. Low HDL Cholesterol, **Metformin Use and Cancer** Risk in Type 2 Diabetes – the Hong Kong Diabetes Registry. Diabetes Care. 2010 Oct 27.
Yeung Wing-Chi G, Rawlinson William D, Craig Maria E. **Enterovirus infection** and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies. BMJ 2011;342:doi:10.1136/bmj.d35 (3 Feb 2011)
Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after **screening** for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA. 2009 Apr 15;301(15):1547-55.
Yu CH. "Safety" technology: a hidden cause of **diabetic ketoacidosis**. CMAJ. 2012 Mar 20;184(5):557-8.
Yuqian Bao, Xiaojing Ma, Huating Li et al. **Glycated haemoglobin A1c** for **diagnosing diabetes** in Chinese population: cross sectional epidemiological survey; BMJ 2010;340.
Zeller M, Danchin N, Simon D, et al. French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction investigators. Impact of Type of Preadmission **Sulfonylureas** on Mortality and Cardiovascular Outcomes in Diabetic Patients with Acute Myocardial Infarction. J Clin Endocrinol Metab. 2010 Aug 11.
Zhang C, et al. A prospective study of pregravid physical activity and **sedentary behaviors** in relation to the risk for **gestational** diabetes mellitus. Arch Intern Med. 2006 Mar 13;166(5):543-8.
Zhang ZJ, Zheng ZJ, Kan H, et al. **Reduced risk of colorectal cancer with metformin** therapy in patients with type 2 diabetes: a meta-analysis. Diabetes Care. 2011 Oct;34(10):2323-8.
Zhang Xinzhi; Saaddine Jinan B.; Chou Chiu-Fang; et al. Prevalence of **Diabetic Retinopathy** in the United States, 2005-2008. JAMA. 2010;304(6):649-656.
Zhang ZJ, Zheng ZJ, Shi R, Su Q, Jiang Q, Kip KE. **Metformin for Liver Cancer Prevention** in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2012 Apr 20.
Zhou X, Pang Z, Gao W, et al. Performance of an A1C and **Fasting Capillary Blood Glucose** Test for Screening Newly Diagnosed Diabetes and Pre-Diabetes Defined by an Oral Glucose Tolerance Test in Qingdao, China. Diabetes Care. 2010 Mar;33(3):545-50. Epub 2009 Dec 10.
Ziegler D, Low PA, Litchy WJ, et al. Efficacy and safety of antioxidant treatment with **α-lipoic acid** over 4 years in **diabetic polyneuropathy**: the **NATHAN 1** trial. Diabetes Care. 2011 Sep;34(9):2054-60.
Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with **rosiglitazone and metformin** to prevent type 2 diabetes mellitus (**CANOE** trial): A double-blind randomised controlled study. Lancet 2010; DOI: 10.1016/S0140-6736(10)60746-5.
Zoungas S et al. **Severe hypoglycemia** and risks of vascular events and death (**Advance**). N Engl J Med 2010 Oct 7; 363:1410. During a median follow-up period of 5 years, 231 patients (2.1%) had at least one severe hypoglycemic episode; 150 had been assigned to intensive glucose control (**2.7%** of the 5571 patients in that group), and 81 had been assigned to standard glucose control (1.5% of the 5569 patients in that group).

AHRQ-USA: Patients Summary: http://www.effectivehealthcare.ahrq.gov/ehc/products/155/721/OralMedT2Diab_consumer.pdf
Mayo Clinic – **Shared Decision Making** – diabetes tools: http://dev.shareddecisions.mayoclinic.org/decision-aids-for-diabetes/diabetes-medication-management/

Health Canada – Advisory on rosiglitazone (Avandia) (June 01, 2007) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_4_e.html

Important Advice for Managing Your Patients

In Canada, Avandia® is NOT approved for use:
- with insulin therapy
- with the combination of metformin AND a sulfonylurea
- in patients with pre-diabetes.

Avandia® is contraindicated in patients with NYHA Class III and IV cardiac status.
Avandia® should be used with caution in any patient with NYHA Class I and II cardiac status.
All patients should be monitored for signs and symptoms of fluid retention, edema, and rapid weight gain.

The dose of Avandia® used in combination with a sulfonylurea should not exceed 4mg daily.

More links, information and a RxFiles Q&A Summary available at: http://www.rxfiles.ca/Rosiglitazone-CV-Controversy.htm

TOP

Background considerations:

- Weighing the benefits & risks of intensive therapy: [See also Diabetes - Landmark Outcome Trials Chart[24]]
  - The results of clinical trials evaluating outcomes of intensive glycemic control have been somewhat disappointing. Achieving an A1C of less than 6.5% may ↓ microvascular endpoints, but over 100,000 patient years of RCT data have failed to show a benefit on CV endpoints.[25] {The 10 year observational follow-up to the UKPDS suggests CV benefit of intensive glycemic control (FBG <6; mean baseline A1Cs 7.9% vs 8.5%) especially with metformin.[26]}
  - Individualization of antihyperglycemic therapy has become a common theme[27,28] as some evidence & experience suggests that some patients may do worse with more intensive regimens (e.g. ↑ mortality (NNH=95/3.5yrs) in the ACCORD RCT n=10,251 in patients randomized to achieve an intensive A1c of 6% vs 7 - 8%; actual A1c achieved was 6.4% vs 7.5%)[29].
  - Although an A1C of <7% is suggested for most, individual patient & treatment regimen factors may result in acceptance of less aggressive targets. For example the American Geriatric Society[30] noted that an A1C of 8% may be more suitable in frail elderly & those with a life expectancy <5yrs.
  - A recent observational cohort trial found a "U" shaped curve for mortality related to A1C. An A1C of 7.5% was associated with the lowest mortality, with higher mortality seen at higher and lower A1C values.[31]

- CADTH Exec Summary: Within the limitations of available evidence, this report concludes:
  - Use of SMBG appears to be associated with improvements in glycemic control among patients with insulin-treated type 2 diabetes. Evidence was limited and of low quality.
  - Few studies compared different frequencies of SMBG for patients with either type 1 or insulin-treated type 2 diabetes, and the evidence from these studies was of low quality. Well-designed studies may prove beneficial in optimizing SMBG frequency for these individuals.
  - Use of SMBG in patients with type 2 diabetes who are not using insulin is associated with a statistically significant, albeit clinically modest, improvement in glycemic control. Performing SMBG may reduce the number of symptomatic hypoglycemic events in patients using sulfonylureas. There was little or no evidence that SMBG provides other benefits, such as improved quality of life, or greater patient satisfaction. Longer-term studies are needed to determine whether or not SMBG reduces diabetes related clinical endpoints (e.g., blindness, reduction in myocardial infarctions, end-stage renal disease) or mortality. Studies of specific subgroups within this population who may be more likely to benefit from SMBG are also warranted.
  - The effect of using SMBG in women with gestational diabetes requires further investigation.
- Estimated 40 year NNTs for SMBG in non-insulin T2DM: 266 for MI; 500 for stroke; 1,389 for end stage renal disease[15]

Comparison: CADTH & Canadian Diabetes Association (CDA).

- CADTH review includes detailed systematic review of the clinical evidence as well as cost evaluation. Significant effort goes into limiting, minimizing the possible effects of, and acknowledging conflicts of interest.
- CDA guidelines include clinical evidence only. Conflicts of interest are more extensive; however they are acknowledged.

Other Major Meta-analysis Reviews

- Poolsup et al SMBG Meta-analysis: suggests that SMBG in non-insulin T2DM may benefit those with a baseline A1C of >8%, but not < 8%.[32]
- St John meta-analysis: suggests similar ↓ in A1C of -0.22 (95% CI: -0.34—0.11). St John A, Davis WA, Price CP, Davis TM. The value of self-monitoring of blood glucose: a review of recent evidence. J Diabetes Complications. 2009 Feb 19.
- Gomes T, Juurlink DN, Shah BR, Paterson JM, Mamdani MM. Blood Glucose Test Strip Use: Patterns, Costs and Potential Cost Reduction Associated with Reduced Testing. ICES Investigative Report. Toronto: Institute for Clinical Evaluative Sciences; 2009. Accessed Feb 11, 2010 at http://www.ices.on.ca/file/Blood%20Glucose%20Test%20Strip_Dec2009.pdf Outlines strip costs for elderly in ON; found potential for reduce costs by $26 million - $302 million if less testing in low-risk.

Health Canada Related Alerts

- Possible interference of icodextrin, intravenous immunoglobulins, galactose and d-xylose with certain blood glucose meters - Notice to Hospitals http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/gluc_met_nth-aah-eng.php

Reagents: NOTE: (Adapted from Hamilton Family Health Team – Table)

Why consideration of reagants in test strips is important -e.g., peritoneal dialysis - use meters that are not affected by GDH-PQQ Rationale: drug products or therapies that contain certain non-glucose sugars, such as maltose, galactose, and xylose will produce falsely elevated glucose result if measuring your glucose using a GDH-PQQ test strip. This could result in insulin dosing errors or not detecting low (hypoglycemic) readings. Avoid use of these test strips in patients using interfering drug products or therapies. Glucose oxidase – may be important at certain altitudes, although very rare.

[A] Strips with glucose dehydrogenase (GDH) pyrroloquinolinequinone (PQQ) will have cross-reactivity with maltose, galactose or xylose but are unaffected by pO2.

[B] Strips with glucose oxidase are affected by pO2 in the blood but not by maltose, galactose and xylose

[C] Strips with glucose dehydrogenase (GDH) Flavin adenine dinucleotide (FAD) can be affected by xylose but unaffected by pO2, maltose and galactose.

Maltose: found in IV solutions (i.e. immunoglobulin) and other solutions containing dialysate icodextrin

Alternate site testing: not recommended if hypoglycemia suspected, especially if prone to hypoglycemic confusion. In these cases, the finger tip method is the best way to get an accurate result.

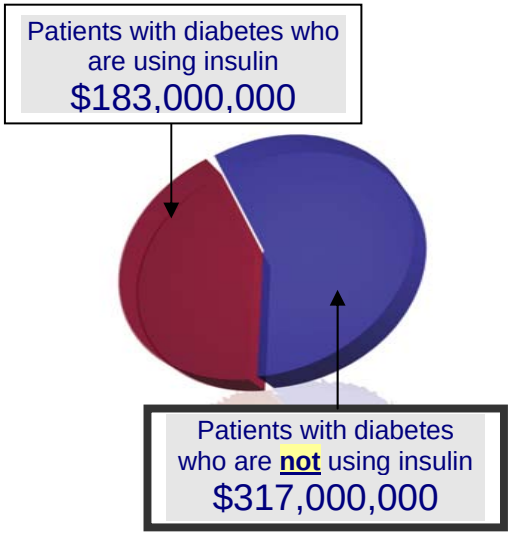
If practice changes to reflect the evidence, $450 million to $1.2 billion* could be freed up between 2012 and 2015 for spending on antidiabetes interventions that are proven effective. Patient health would not be affected negatively.

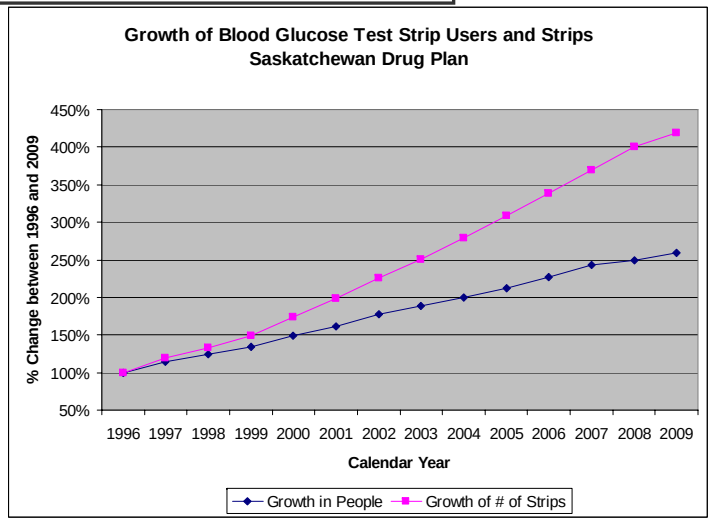
http://www.cadth.ca/media/compus/pdf/C1109-Prescribing-Aid-Web-e.pdf?&utm_source=c1109&utm_medium=vo2-issue-8&utm_campaign=communique-03-13-12 Revised March 2012

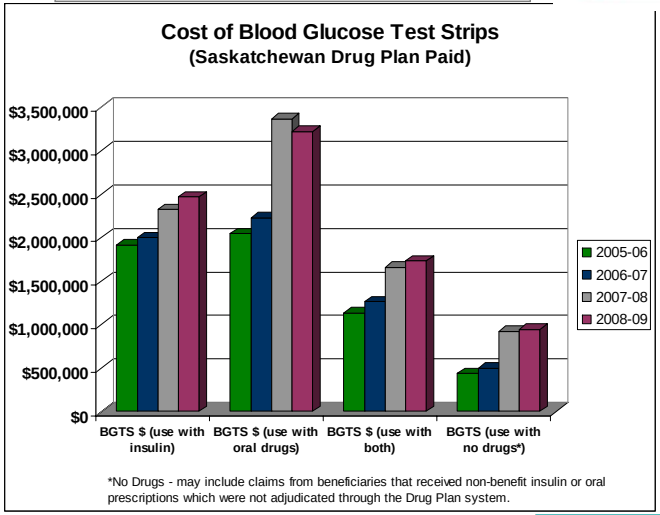
[These results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public and Private Drug Plans Databases, 2000-2011]

- Cost to drug plans public+private = $330 million 2006 Canadian data
- Cost per QALY (quality adjusted life year) is estimated at $113,643 for routine use of SMBG (at least 1 strip each day on average).
- Annual cost per patient: $165 - $2,400 (see Table below).

Thanks to CADTH-COMPUS for assistance the development of this document.







Data provided from Saskatchewan Health; used by permission.

TOP

References

[1] Cameron C, Coyle D, Ur E, Klarenbach S. Cost-effectiveness of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin. CMAJ. 2010 Jan 12;182(1):28-34. {Summary also in DailyPOEMs: 01Apr2010; https://www.essentialevidenceplus.com/content/poem/120401 }

[2] Kolb H, Kempf K, Martin S, Stumvoll M, Landgraf R. On what evidence-base do we recommend self-monitoring of blood glucose? Diabetes Res Clin Pract. 2010 Feb;87(2):150-156.

[3] O'Kane MJ, Pickup J. Self-monitoring of blood glucose in diabetes: is it worth it? Ann Clin Biochem. 2009 Jul;46(Pt 4):273-82.

[4] Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, Craven A, Goyder L, Holman RR, Mant D, Kinmonth AL, Neil HA; DiGEM Trial Group. Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial. Health Techno Assess. 2009 Feb;13(15):iii-iv, ix-xi, 1-50.

[5] Varanauskiene E. Can blood glucose self-monitoring improve treatment outcomes in type 2 diabetes? Diabetes Res Clin Pract. 2008 Dec 15;82 Suppl 2:S112-7.

[6] Towfigh A, Romanova M, Weinreb JE, Munjas B, Suttorp MJ, Zhou A, Shekelle PG. Self-monitoring of blood glucose levels in patients with type 2 diabetes mellitus not taking insulin: a meta-analysis. Am J Manag Care. 2008 Jul;14(7):468-75.

[7] Majumdar SR. Self-monitoring of blood glucose was not cost-effective in non-insulin-treated type 2 diabetes. ACP J Club. 2008 Nov-Dec;149(4):4-5.

[8] French DP, Wade AN, Yudkin P, Neil HA, Kinmonth AL, Farmer AJ. Self-monitoring of blood glucose changed non-insulin-treated Type 2 diabetes patients' beliefs about diabetes and self-monitoring in a randomized trial. Diabet Med. 2008 Oct;25(10):1218-28. {No change in diabetes-related health behaviours.}

[9] O'Kane MJ, Pickup J. Self-monitoring of blood glucose in diabetes: is it worth it? Ann Clin Biochem. 2009 Jul;46(Pt 4):273-82.

[10] Mansell K, Blackburn D, Eurich D. Do postprandial glucose levels add important clinical information when fasting glucose levels are near normal in non-insulin-dependent patients with type 2 diabetes? CPJ 2010;142(6):298-302. Accessed on line Feb 11, 2010 at http://www.cpjournal.ca/perlserv/?request=get-document&doi=10.3821%2F1913-701X-142.6.298&ct=1

[11] Malanda UL, Welschen LM, Riphagen II, et al. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database Syst Rev. 2012 Jan 18;1:CD005060. {From this review, we conclude that when diabetes duration is over one year, the overall effect of self-monitoring of blood glucose on glycaemic control in patients with type 2 diabetes who are not using insulin is small up to six months after initiation and subsides after 12 months. Furthermore, based on a best-evidence synthesis, there is no evidence that SMBG affects patient satisfaction, general well-being or general health-related quality of life. More research is needed to explore the psychological impact of SMBG and its impact on diabetes specific quality of life and well-being, as well as the impact of SMBG on hypoglycaemia and diabetic complications.}

[12] O'Kane MJ, Bunting B, Copeland M, Coates VE; ESMON study group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. BMJ. 2008;336(7654):1174-7.

[13] Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A; Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. BMJ. 2008 May 24;336(7654):1177-80.

[14] Parkin CG, Hinnen D, Campbell RK, Geil P, Tetrick DL, Polonsky WH. Effective use of paired testing in type 2 diabetes: practical applications in clinical practice. Diabetes Educ. 2009 Nov-Dec;35(6):915-27.

[15] Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. [Internet]. 2008 Sep [cited 2008 Jan 17];32(Suppl 1): S168-S180. Available from: http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
Note: see Diabetes and Pregnancy Recommendations, *page s170 and s174*

[16] COMPUS Optimal Therapy Report: Cost Effectiveness of Blood Glucose Test Strips in the Management of Adult Patients with Diabetes Mellitus. May 2009. Accessed Feb 04, 2010 at http://www.cadth.ca/media/pdf/BGTS_Consolidated_Economic_Report.pdf

[17] Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A; Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. BMJ. 2008 May 24;336(7654):1177-80.

[18] COMPUS Optimal Therapy Report: Systematic Review of Use of Blood Glucose Test Strips for the Management of Diabetes Mellitus. May 2009. Accessed Feb 04, 2010 at http://www.cadth.ca/media/pdf/BGTS_SR_Report_of_Clinical_Outcomes.pdf

[19] Canadian Diabetes Association. Your guide 2009/10. Accessed Feb 23, 2010 at: http://www.diabetes.ca/documents/about-diabetes/CDA_ConsmrGuide.pdf

[20] Canadian Pharmacist's Letter Detail Document #260220, February 2010 on Blood Glucose Meters.

[21] Consumer Reports: Blood Glucose Meter Ratings. Dec 2009. Accessed online at: Features: http://www.consumerreports.org/health/healthy-living/home-medical-supplies/blood-glucose-meters/blood-glucose-meter/ratings/blood-glucose-meter-features.htm; Ratings Overview: http://www.consumerreports.org/health/healthy-living/home-medical-supplies/blood-glucose-meters/blood-glucose-meter/ratings/blood-glucose-meter-ratings.htm

[22] Company Websites: www.onetouch.ca; www.accu-check.ca; www.novacares.ca; http://www.oraclediabetes.com/; www.homediagnostics.com; www.bayerdiabetes.ca

[23] Gaurdian RTS: Accessed online at: http://www.minimed.com/products/guardian/index.html

[24] RxFiles Diabetes – Glucose Control- Landmark Trials and Links. Accessed online at: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

[25] Regier L, Jensen B. RxFiles Diabetes Glucose Control – Landmark Trials & Links. Access online at: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

[26] Holman R, Sanjoy P, Bethel MA, Matthews D, Neil A. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. (UKPDS-80). N Engl J Med 2008;359:1-13.

[27] Canadian 2008 Guidelines (Sept 2008). Accessed at http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
{Also, Bhattacharyya OK, Estey EA, Cheng AY; Canadian Diabetes Association 2008. Update on the Canadian Diabetes Association 2008 clinical practice guidelines. Can Fam Physician. 2009 Jan;55(1):39-43.}

[28] Nauck MA, El-Ouaghlidi A, Vardarli I. Self-monitoring of blood glucose in diabetes mellitus: arguments for an individualized approach. Dtsch Arztebl Int. 2009 Sep;106(37):587-94.

[29] RxFiles ACCORD Trial Summary: Accessed online at: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf

[30] Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc. 2003 May;51(5 Suppl Guidelines):S265-80.

[31] Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010 Jan 26. [Epub ahead of print]

[32] Poolsup N, Suksomboon N, Rattanasookchit S. Meta-analysis of the benefits of self-monitoring of blood glucose on glycemic control in type 2 diabetes patients: an update. Diabetes Technol Ther. 2009 Dec;11(12):775-84.

Extras:

CDC: Note from the Field: Deaths from Acute Hepatitis B Virus Infection Associated with Assisted Blood Glucose Monitoring in an Assisted-Living Facility --- North Carolina, August--October 2010 MMWR February 18, 2011 / 60(06);182. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6006a5.htm?s_cid=mm6006a5_x

Decision Tool for SMBG in Non-insulin T2DM. Diabetes Care Program of Nova Scotia (DCPNS) & Dalhousie Academic Detailing Service. Apr 2010. http://cme.medicine.dal.ca/files/dcpNS_tool.pdf
Supporting Video: How to use the SMBG Decision Tool: http://www.diabetescareprogram.ns.ca/SMBG_Decision_Tool.asp

Additional articles:

Battelino T et al. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011; 34:795.

Bergenstal RM et al. Effectiveness of sensor-augmented insulinpump therapy in type 1 diabetes. N Engl J Med 2010; 363:311.

Blevins TC et al. Statement by the American Association of Clinical Endocrinologists Consensus Panel on Continuous Glucose Monitoring. Endocr Pract 2010; 16:730.

Butalia S. Rabi D. To test or not to test? Self-monitoring blood glucose in patients with type 2 diabetes managed without insulin. Open Medicine, North America, 4, may. 2010.

Cameron, C., Viranti, A., Dean, H., et al. Utilization and Expenditure on Blood Glucose Test Strips in Canada. Canadian Journal of Diabetes. 2010;34(1):34-40.

CADTH Rapid Response: Blood Glucose Monitors and Test Strips: A Review of the Comparative Clinical Evidence and Cost-Effectiveness. Apr 2011. Accessed at: http://www.cadth.ca/media/pdf/htis/april-2011/L0256%20SMBG%20Test%20Strips%20and%20Monitors%20Final.pdf

Canadian Diabetes Association (CDA) plans to launch a compassionate use program to assist people with diabetes who have difficulty covering the costs of blood glucose monitoring supplies http://www.diabetes.ca/

Farmer AJ, Perera R, Ward A, et al. Meta-analysis of individual patient data in randomised trials of self monitoring of blood glucose (SMBG) in people with non-insulin treated type 2 diabetes. BMJ. 2012 Feb 27;344:e486. {SMBG does not appreciably improve control in T2DM patients not on insulin. ↓A1C only marginally 8.3%⇨8.05%.}

FDA Aug/10 and CDC have noted a progressive increase in the reports of bloodborne infection transmission over the past 10 to 15 years (primarily hepatitis B virus), resulting from shared use of fingerstick and point-of-care [POC] blood testing devices.

Franciosi M, Lucisano G, Pellegrini F, et al. ROSES Study Group. Role of self-monitoring of blood glucose and intensive education in patients with Type 2 diabetes not receiving insulin. A pilot randomized clinical trial. Diabet Med.2011Jul;28(7):789-96.

Gillett M., Dallosso H. M., Dixon S., et al. Delivering the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes:cost effectiveness analysis.BMJ 2010;341:c4093

JDRF CGM Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008; 359:1464.

Lau, D. The Cost of Diabetes: A Game Changer. Canadian Journal of Diabetes, Mar '10.

Mcintosh B., Yu C., Lal A. et al. Efficacy of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin: a systematic review and meta-analysis. Open Medicine, North America, 4, may. 2010. Also article in CPJ, Sep 2010 @ http://www.cpjournal.ca/doi/pdf/10.3821/1913-701X-143.5.218; Commentary by Johnson in CPJ, Sep 2010 @ http://www.cpjournal.ca/doi/pdf/10.3821/1913-701X-143.5.216.

Medical Letter. Continuous Glucose Monitoring. May 2, 2011.

Pickup John C, Freeman Suzanne C, Sutton Alex J. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:doi:10.1136/bmj.d3805 (7 July 2011)

Rabi, D., Johnson, J., Edwards, J. Self-monitoring of blood glucose for individuals with type 2 diabetes not using insulin: Leaving no cornerstone unturned. Canadian Journal of Diabetes, March 2010. Accessed June 24 2010 at:
SMBG: Type 2 Diabetes and Monitoring your Blood Sugar –Patient Pamphlet. http://www.cadth.ca/media/pdf/smbg-nb_eng.pdf

Vigersky RA, Fonda SJ, et al. Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care. 2012 Jan;35(1):32-8.

Woo, V., Cheng, A., Hanna, A., et al. Self-monitoring of Blood Glucose in Individuals with Type 2 Diabetes Not Using Insulin: Commentary. Canadian Journal of Diabetes, March 2010. Accessed June 24 2010.

Acknowledgements: Contributors & Reviewers: Ann Colbourne, MD, FRCPC, FACP (Department of Medicine, U of A, Edmonton), Tessa Laubscher (CCFP, College of Medicine, U of S, Saskatoon), M Jin PharmD, CDE (Hamilton), Henry Halapy (PharmD, CDE; SMH, Toronto), Arlene Kuntz (Pharmacist, DES, CDA; Regina); Derek Jorgenson (PharmD, College of Medicine, U of S. Saskatoon), Karen MdDermaid (Pharmacist CDE, RQHR, SK), Kristen Chelak BSc(Pharm), MSc, RPh (COMPUS, Ottawa) & the RxFiles Advisory Committee. Prepared by: *L. Regier* BSP, BA, *B. Jensen* BSP

TOP

Extras

Recently Discontinued Insulin Devices (within last 3 years): HumaPen Ergo (discontinued 2007) & Novolin-Pen 3

AutoPen 24 (3ml penfill) A) green – up to 21 units 1-21 units in 1 unit increments B) blue – up to 42 units 2-42 units in 2 unit increments		**LANTUS** (glargine) ◆ free with Lantus insulin	◆ has side-mounted injection button ◆ small white numbers on a dark background; does not have number window (e.g. number not magnified.) ◆ does NOT have dial back capabilities, dose must be wasted if overdialed ◆ if insufficient insulin in cartridge, number remaining on dial will show remaining dose to be given

References: CPS product monographs 2008 (e-CPS accessed 12 Sep, 2008); *Product information leaflets. See also RxFiles Drug Comparison Charts / BOOK – diabetes pages 24-26 (www.RxFiles.ca).*

Additional References:

Errors Associated with Pen Injectors. Pharmacist's Letter Nov 2008.

Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Curr Med Res Opin. 2010 Jun;26(6):1519-30.

Hofman PL, Behrensdorf Derraik JG, et al. Defining the ideal injection techniques when using 5-mm needles in children and adults. Diabetes Care. 2010 Jun 28.

Israel-Bultman Harma, Hyllested-Winge Jacob, Kolaczynski Marcin, et al. Comparison of Preference for NovoPen(R) 4 With Previous Insulin Pen Treatments After 12 Weeks in Adult Patients With Type 1 and Type 2 Diabetes: A Multicenter Observational Study, Clinical Therapeutics, Volume 33, Issue 3, March 2011, Pages 346-357

Jet injectors (eg. AdvantaJet, Medi-Jector) avoid the use of needles, are expensive, & require frequent cleaning.

TOP

INSULIN Comparison Chart

1. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003 May 7;289(17):2254-64.
2. Drug Information Handbook 10TH edition. Lacy CF et al (editors). American Pharmaceutical Association. Lexi-Comp Inc, Hudson Ohio, 2002-2003 edition.
3. Boctor, MA. Diabetes Mellitus in Therapeutic Choices (3rd edition). Gray, Jean (editor). Canadian Pharmacists Association. Web-com Ltd, Ottawa, ON, 2000.
4. Micromedex 2010 computer drug data base.
5. Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized controlled trial. (FINFAT STUDY) Ann Intern Med 1999;130:389-96.
6. Meltzer S, Leiter L, Daneman D. et al 1998 Clinical practice guidelines for the management of diabetes in **Canada**. CMAJ **1998**;159 (8 Suppl).
7. Hermann LS. Optimizing therapy for insulin-treated Type 2 Diabetes Mellitus. Drugs & Aging 2000;17(4):283-94.
8. Insulin glargine (Lantus), a new long-acting insulin. Med Lett Drugs Ther. 2001 Aug 6;43(1110):65-6.
9. Insulin aspart, a new rapid-acting insulin. Med Lett Drugs Ther. 2001 Oct 15;43(1115):89-90.
10. American Diabetes Association: Clinical Practice Recommendations 2003, Diabetes Care 2003 26:Supplement 1
11. Writing Team For The Diabetes Control And Complications Trial/Epidemiology Of Diabetes Interventions And Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA. 2003 Oct 22;290(16):2159-67.
12. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977-986.
13. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.
14. Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med. 1999 Mar 2;130(5):389-96.
15. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR; U.K. Prospective Diabetes Study Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care. 2002 Feb;25(2):330-6.
16. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995 May;28(2):103-17.
17. Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care. 2001 Apr;24(4):631-6.
18. New Drugs: Lantus (insulin glargine injection). in Pharmacists Letter Mar 2005;21(3):210319.
19. Mayfield JA, White RD. Insulin therapy for type 2 diabetes: rescue, augmentation, and replacement of beta-cell function. Am Fam Physician. 2004 Aug 1;70(3):489-500. Erratum in: Am Fam Physician. 2004 Dec 1;70(11):2079-80.
20. Harjutsalo V, Podar T, Tuomilehto J. Cumulative incidence of type 1 diabetes in 10,168 siblings of Finnish young-onset type 1 diabetic patients. Diabetes 2005; 54:563-69. (InfoPOEMs- The cumulative risk of type 1 diabetes up to ages 10, 20, 30, 40, and 50 years in brothers and sisters of patients with childhood-onset diabetes is 1.5%, 4.1%, 5.5%, 6.4%, and 6.9%, respectively. A young age at diagnosis of diabetes in the index case is the strongest predictor of the risk of type 1 diabetes in siblings. The risk in siblings is also increased with increasing maternal and paternal age at birth and male sex. (LOE = 1b))
21. Hirsch IB. Insulin analogues. N Engl J Med. 2005 Jan 13;352(2):174-83.
22. **Treatment Guidelines**: Drugs for Diabetes. **The Medical Letter**: August, **2005**; (3) pp. 57-62.
23. Rosenstock J, Zinman B, Murphy LJ, et al. **Inhaled insulin** improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2005 Oct 18;143(8):549-58. CONCLUSIONS: Inhaled insulin improved overall glycemic control and hemoglobin A1c level when added to or substituted for dual oral agent therapy with an insulin secretagogue and sensitizer. Consistent with other insulin therapies, hypoglycemia and mild weight gain occurred. Pulmonary function showed no between-group differences.
24. Comparison of insulins Pharmacist's Letter/Prescriber's Letter 2006;22(2):220217
25. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F,et al. Intensive insulin therapy in the **critically ill patients**. N Engl J Med. 2001 Nov 8;345(19):1359-67.
26. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the **medical ICU**. N Engl J Med. 2006 Feb 2;354(5):449-61. CONCLUSIONS: Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy. Further studies are needed to confirm these preliminary data. (InfoPOEMs: Intensive insulin treatment of patients in the medical intensive care unit (ICU) is helpful if patients spend at least 3 days in the unit. Unfortunately, those with a shorter stay may be harmed, and physicians were unable to accurately predict who would actually stay 3 or more days (36% of those predicted to stay at least 3 days were discharged sooner in this study). (LOE = 1b))
27. Nathan DM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (**DCCT/EDIC**) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005 Dec 22;353(25):2643-53. (InfoPOEMs: This extension of the Diabetes Control and Complications Trial (DCCT) trial provides the first high-quality evidence that intensive treatment of Type 1 diabetes reduces the risk of adverse cardiovascular outcomes. Although the relative risk reduction was greater than 50%, the absolute risk reduction (0.42 per 100 patient years; NNT=25 over 10years) was modest. Note that this effect has not been shown in patients with Type 2 diabetes, although many patients and physicians believe otherwise, and data regarding all-cause mortality or adverse effects of intensive treatment (such as hypoglycemic episodes or traffic accidents) are not reported.. (LOE = 1b))
28. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64:1348-53.
29. Fiallo-Scharer R, Horner B, McFann K, Walravens P, Chase HP. **Mixing rapid-acting** insulin analogues with insulin **glargine** in children with type 1 diabetes mellitus. J Pediatr. 2006 Apr;148(4):481-4. There were no significant differences in glycemic control between children who mixed IG in the same syringe with a RAI analogue compared with children who took separate injections.
30. Garg S, Rosenstock J, et al. Efficacy & safety of preprandial human **insulin inhalation** powder versus injectable insulin in pts with type 1 diabetes. Diabetologia. 2006 May;49(5):891-9. Epub 2006 Feb 28.
31. Barnett AH, et al. An open, randomized, parallel-group study to compare the efficacy and safety profile of **inhaled human insulin (Exubera) with metformin** as adjunctive therapy in patients with type 2 diabetes poorly controlled on a sulfonylurea. Diabetes Care. 2006 Jun;29(6):1282-7.
32. Hermansen K, et al. A 26-week, randomized, parallel, treat-to-target trial **comparing insulin detemir with NPH** insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006 Jun;29(6):1269-74. In both groups, 70% of participants achieved an A1C < or =7.0%, but the proportion achieving this without hypoglycemia was higher with insulin detemir than with NPH insulin (26 vs. 16%, P = 0.008). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47% (P < 0.001) and nocturnal hypoglycemia by 55% (P < 0.001). Mean weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH insulin (P < 0.001), and the difference in baseline-adjusted final weight was -1.58 (P < 0.001).
33. Siebenhofer A, et al. **Short acting insulin analogues versus regular** human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003287.
34. Cheung NW, Wong VW, McLean M. The hyperglycemia: intensive insulin infusion in infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care. 2006 Apr;29(4):765-70. (InfoPOEMs: Intensive control of blood glucose in patients with known diabetes or in patients with hyperglycemia at the time of admission for acute myocardial infarction (AMI) does not decrease either short-term or long-term mortality. (LOE = 1b-))
35. Inhaled insulin (**Exubera**). Med Lett Drugs Ther. 2006 Jul 17;48(1239):57-8. {dry powder, rapid acting, not yet in Canada; no difference in HbA1c from regular/NPH based regimens; pts may prefer over sc; CI in COPD, smoking; long term lung safety unknown; $$$$}
36. Pearson ER, et al. Neonatal Diabetes International Collaborative Group. Switching **from insulin to oral sulfonylureas** in pts with diabetes due to Kir6.2 mutations. N Engl J Med. 2006 Aug 3;355(5):467-77.
37. Babenko AP, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med. 2006 Aug 3;355(5):456-66.
38. Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. Ann Intern Med. 2006 Jul 18;145(2):125-34.
39. Health Canada Insulin Products update Sept/06 http://www.hc-sc.gc.ca/iyh-vsv/alt_formats/cmcd-dcmc/pdf/insulin_e.pdf

TOP

40. Ballani P, Tran MT, Navar MD, Davidson MB. Clinical experience with **U-500 regular insulin** in obese, markedly insulin-resistant type 2 diabetic patients. Diabetes Care. 2006 Nov;29(11):2504-5.
41. Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of **inhaled insulin** therapy in adults with diabetes mellitus. Ann Intern Med. 2006 Nov 7;145(9):665-75.
42. Budnitz DS, et al. National surveillance of emergency department visits for outpatient **adverse drug events**. JAMA. 2006 Oct 18;296(15):1858-66. In an analysis of routine surveillance data from 63 US hospitals, adverse drug events accounted for an estimated 2.5% of emergency department visits for unintentional injury and 0.6% of visits for all causes. About a third were allergic reactions and another third were unintentional overdoses, particularly of drugs that need regular monitoring such as digoxin and warfarin. Insulin and warfarin were implicated in over a quarter of all serious events. Insulin, warfarin, and digoxin accounted for more than 40% of serious events among people aged over 65.
43. Dunn C, Curran MP. **Inhaled human insulin** (Exubera): a review of its use in adult patients with diabetes mellitus. Drugs. 2006;66(7):1013-32.
44. Shapiro AM, et al. International trial of the **Edmonton protocol** for **islet transplantation**. N Engl J Med. 2006 Sep 28;355(13):1318-30. Out of the 36 patients given transplants in an uncontrolled trial, 16 had stopped using insulin by the end of the first year, but only five were still independent of insulin a year later. Only one was cured for the full three years of the trial.
45. Barnett AH, et al. An open, randomized, parallel-group study to compare the efficacy and safety profile of **inhaled human insulin** (Exubera) with glibenclamide as adjunctive therapy in patients with type 2 diabetes poorly controlled on metformin. Diabetes Care. 2006 Aug;29(8):1818-25.
46. Cheung NW, et al. The Hyperglycemia: **Intensive Insulin Infusion in Infarction** (**HI-5**) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care. 2006 Apr;29(4):765-70.
47. Martin CL, et al. **DCCT/EDIC** Research Group. **Neuropathy** among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care. 2006 Feb;29(2):340-4.
48. Skyler JS, Jovanovic L, Klioze S, Reis J, Duggan W; Inhaled Human Insulin Type 1 Diabetes Study Group. Two-year safety and efficacy of inhaled human insulin (**Exubera**) in adult patients with type 1 diabetes. Diabetes Care. 2007 Mar;30(3):579-85. Treatment group differences in lung function between EXU and s.c. insulin in adult patients with type 1 diabetes are small, develop early, and are nonprogressive for up to 2 years of therapy.
49. McMahon GT, Arky RA. **Inhaled insulin** for diabetes mellitus. N Engl J Med. 2007 Feb 1;356(5):497-502.
50. Taylor R, Davison JM. **Type 1 diabetes and pregnancy**. BMJ. 2007 Apr 7;334(7596):742-5.
51. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; (**DCCT/EDIC**) Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med. 2007 May 3;356(18):1842-52. **No evidence of substantial long-term declines in cognitive function** was found in a large group of patients with type 1 diabetes who were carefully followed for an average of 18 years, despite relatively high rates of recurrent severe hypoglycemia. Forty percent of the cohort reported having had at least one hypoglycemic coma or seizure.
52. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005613. Our analysis suggests, if at all only a minor clinical benefit of treatment with long-acting insulin analogues for patients with diabetes mellitus type 2 treated with "basal" insulin regarding symptomatic nocturnal hypoglycaemic events. Until long-term efficacy and safety data are available, we suggest a cautious approach to therapy with **insulin glargine or detemir**.
53. Gandhi GY, Nuttall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med. 2007 Feb 20;146(4):233-43. Intensive insulin therapy during cardiac surgery does not reduce perioperative death or morbidity. The increased incidence of death and stroke in the intensive treatment group raises concern about routine implementation of this intervention.
54. Pharmacist's Letter. Treatment of Diabetes in women who are **pregnant**. Sept 2007.
55. Bryden KS, et al. Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. Diabetes Care. 1999 Dec;22(12):1956-60.
56. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, et al.; the **4-T Study** Group. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. (4T) N Engl J Med. 2007 Sep 21; [Epub ahead of print] A single analogue-insulin formulation added to metformin and sulfonylurea resulted in a glycated hemoglobin level of 6.5% or less in a minority of patients at 1 year. The addition of biphasic or prandial insulin aspart reduced levels more than the addition of basal insulin detemir but were associated with greater risks of hypoglycemia and weight gain. (InfoPOEMs: Patients choosing biphasic or prandial insulin regiments should be prepared to gain approximately **10 pounds to 12 pounds** and expect **4 to 8 moderate or severe episodes of hypoglycemia per year**. Basal insulin was a bit less effective as measured by the change in glycated hemoglobin (Hb A1C), but resulted in less weight gain & much less hypoglycemia. Of course, we don't know whether any of these regiments improve long-term clinical outcomes in these patients. If you are going to add insulin for a patient with poorly controlled Type 2 diabetes, it makes sense to start with a single dose of basal insulin for most patients, and to focus primarily on those patients with an initial Hb A1C of more than 8.5%. (LOE = 1b))

    Holman, Rury R., Farmer, Andrew J., Davies, Melanie J., et al. the 4-T Study Group, **Three-Year** Efficacy of Complex Insulin Regimens in Type 2 Diabetes.N Engl J Med 2009 0: NEJMoa0905479. Patients who added a basal or prandial insulin-based regimen to oral therapy had better glycated hemoglobin control than patients who added a biphasic insulin-based regimen. Fewer hypoglycemic episodes and less weight gain occurred in patients adding basal insulin.
57. Pharmacists Letter. Exubera. Oct 2007.
58. Norris JM, Yin X, Lamb MM, Barriga K, et al. **Omega-3** polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA. 2007 Sep 26;298(12):1420-8. Dietary intake of omega-3 fatty acids is associated with reduced risk of IA in children at increased genetic risk for type 1 diabetes.
59. Weston C, Walker L, Birkhead J; National Audit of Myocardial Infarction Project, National Institute for Clinical Outcomes Research. Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an **acute coronary syndrome**. Heart. 2007 Dec;93(12):1542-6. Epub 2007 May 13. In non-diabetic patients with acute coronary syndrome and hyperglycaemia, treatment with insulin was associated with a reduction in the relative risk of death, evident within 7 days of admission, which persists at 30 days.
60. Datta S, Qaadir A, Villanueva G, Baldwin D. Once-daily insulin glargine versus 6-hour sliding scale regular insulin for control of hyperglycemia after a bariatric surgical procedure: a randomized clinical trial. Endocr Pract 2007;13(3):225-31.
61. Yeldandi RR, Lurie A, Baldwin D. Comparison of once-daily glargine insulin with twice-daily NPH/regular insulin for control of hyperglycemia in inpatients after cardiovascular surgery. Diabetes Technology & Therapeutics 2006;8(6):609-16.
62. Hofman PL, Lawton SA, Peart JM, et al. An angled insertion technique using 6-mm needles markedly reduces the risk of intramuscular injections in children and adolescents. Diabetic Medicine 2007;74(12):1400-1405. (InfoPOEMs: A pinched technique with angled insertion using 6-mm needles most reliably results in the appropriately placed subcutaneous injection of insulin in children with diabetes. This same needle-size used in the abdominal site also resulted in the least amount of injection pain. (LOE = 2b))
63. Goebel-Fabbri AE, Fikkan J, et al. **Insulin restriction and associated morbidity and mortality** in women with type 1 diabetes. Diabetes Care. 2008 Mar;31(3):415-9. Epub 2007 Dec 10. Our data demonstrate that insulin restriction is associated with increased rates of diabetes complications and increased mortality risk. Mortality associated with insulin restriction appeared to occur in the context of eating disorder symptoms, rather than other psychological distress.
64. Hassan K, Rodriguez LM, Johnson SE, et al. A randomized, controlled trial comparing twice-a-day insulin glargine mixed with rapid-acting insulin analogs versus standard neutral protamine Hagedorn (NPH) therapy in newly diagnosed type 1 diabetes. Pediatrics. 2008 Mar;121(3):e466-72. Epub 2008 Feb 25. Glycemic control with insulin glargine mixed with a rapid-acting insulin analog given twice daily seems significantly more effective than the standard therapy in newly diagnosed type 1 diabetes. Furthermore, it decreases pain and burden of injections for children with diabetes by allowing patients to **mix glargine with rapid**-acting insulin analog.
65. Coustan DR. Pharmacological management of **gestational diabetes**: an overview. Diabetes Care. 2007 Jul;30 Suppl 2:S206-8. Review. Erratum in: Diabetes Care. 2007 Dec;30(12):3154.
66. Bretzel RG, Nuber U, Landgraf W, et al. **Once-daily basal insulin glargine** versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet. 2008 Mar 29;371(9618):1073-84. A therapeutic regimen involving the addition of either basal or prandial insulin analogue is equally effective in lowering hae

TOP

A(1c). We conclude that insulin glargine provides a simple and effective option that is more satisfactory to patients than is lispro for early initiation of insulin therapy, since it was associated with a lower risk of hypoglycaemia, fewer injections, less blood glucose self monitoring, and greater patient satisfaction than was insulin lispro.
67. Lopez X, Castells M, Ricker A, Velazquez EF, Mun E, Goldfine AB. **Human insulin analog--induced lipoatrophy**. Diabetes Care. 2008 Mar;31(3):442-4. Epub 2007 Dec 27. Tryptase-positive/chymase-postitive mast cells, known to be sensitive to sodium cromolyn, may contribute to the destructive immune process mediated in response to exogenous insulin. Mast cell stabilizing therapy with topical **cromolyn** may reverse early and prevent new **lipoatrophic** lesions.
68. Cope JU, Morrison AE, Samuels-Reid J. Adolescent use of **insulin** and patient-controlled analgesia **pump** technology: a 10-year Food and Drug Administration retrospective study of adverse events. Pediatrics. 2008 May;121(5):e1133-8. A total of 1674 reports were identified: 1594 for insulin pumps and 53 for patient-controlled analgesic pumps. In reports of insulin pump events, there were 13 reported deaths, 2 reports that indicated possible suicide attempts, and several additional reports indicating severe hypoglycemic or hyperglycemic events that seemed to be device-related.
69. Guideline Development Group. Management of diabetes from **preconception to the postnatal** period: summary of NICE guidance. BMJ. 2008 Mar 29;336(7646):714-7.
70. Crowther CA, Hiller JE, Moss JR, et al. Australian Carbohydrate Intolerance Study in Pregnant Women (**ACHOIS**) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005 Jun 16;352(24):2477-86. Epub 2005 Jun 12.
71. Rowan JA, Hague WM, Gao W, Battin MR, et al; **MiG** Trial Investigators. **Metformin** versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008 May 8;358(19):2003-15. In women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin.
72. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of **glyburide and insulin** in women with gestational diabetes mellitus. N Engl J Med. 2000 Oct 19;343(16):1134-8. In women with gestational diabetes, glyburide is a clinically effective alternative to insulin therapy.
73. Gangemi A, Salehi P, Hatipoglu B, Martellotto J, Barbaro B, Kuechle JB, Qi M, Wang Y, Pallan P, Owens C, Bui J, West D, Kaplan B, Benedetti E, Oberholzer J. **Islet transplantation** for brittle type 1 diabetes: the UIC protocol.Am J Transplant. 2008 Jun;8(6):1250-61. Epub 2008 Apr 29. Four subjects (Group 1) received the Edmonton immunosuppression regimen (daclizumab, sirolimus, tacrolimus). Six subjects (Group 2) received the University of Illinois protocol (etanercept, exenatide and the Edmonton regimen).Combined treatment of etanercept and exenatide improves islet graft function and facilitates achievement of insulin-independence with less islets.
74. Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD006297. Long acting insulin preparations seem to exert a beneficial effect on nocturnal glucose levels. Their effect on the overall diabetes control is clinically unremarkable. Their use as a basal insulin regimen for type 1 diabetes mellitus warrants further substantiation.
75. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, et al. A randomised, 52-week, treat-to-target trial comparing **insulin detemir with insulin glargine** when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia. 2008 Jan 16; [Epub ahead of print] Supplementation of oral agents with detemir or glargine achieves clinically important improvements in glycaemic control with low risk of hypoglycaemia. Non-inferiority was demonstrated for detemir using higher insulin doses (mainly patients on twice daily dosing); weight gain was somewhat reduced with once daily insulin detemir.
76. Soylemez Wiener R, Wiener DC, Larson RJ. Benefits and risks of **tight glucose control in critically ill** adults: a meta-analysis. JAMA. 2008 Aug 27;300(8):933-44. In critically ill adult patients, tight glucose control is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia.
77. de Boer IH, Kestenbaum B, Rue TC, et al. Diabetes Control and Complications Trial (**DCCT**)/Epidemiology of Diabetes Interventions and Complications (**EDIC**) Study Research Group. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med. 2008 Sep 22;168(17):1867-73. Hyperglycemia is a risk factor for incident hypertension in type 1 diabetes, and intensive insulin therapy reduces the long-term risk of developing hypertension.
78. Qayyum R, Bolen S, Maruthur N, et al. Systematic Review: Comparative Effectiveness and Safety of Premixed Insulin Analogues in Type 2 Diabetes. Ann Intern Med. 2008 Sep 15. [Epub ahead of print]
79. Murphy HR, Rayman G, Lewis K, et al; Effectiveness of **continuous glucose monitoring** in pregnant women with diabetes: randomised clinical trial. BMJ. 2008 Sep 25;337:a1680. doi: 10.1136/bmj.a1680. Continuous glucose monitoring during pregnancy is associated with improved glycaemic control in the third trimester, lower birth weight, and reduced risk of macrosomia.
80. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, et al. **Continuous glucose monitoring** and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76. Epub 2008 Sep 8.
81. Weng J et al. Effect of **intensive insulin** therapy on β-cell function and glycaemic control in patients with **newly diagnosed** type 2 diabetes: A multicentre randomised parallel-group trial. Lancet 2008 May 24; 371:1753.
82. Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycemic control and beta-cell function in **newly diagnosed** type 2 diabetes with severe hyperglycemia after short-term **intensive insulin** therapy. Diabetes Care. 2008 Oct;31(10):1927-32. Epub 2008 Jun 12. n=50. A 6-month course of insulin therapy, compared with OAD treatment, could more effectively achieve adequate glycemic control and significant improvement of beta-cell function in new-onset type 2 diabetic patients with severe hyperglycemia.
83. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycaemia in type 2 diabetes mellitus: a **consensus algorithm** for the initiation and adjustment of therapy : A consensus statement from the American Diabetes Association (**ADA**) and the European Association for the Study of Diabetes. Diabetologia. 2008 Oct 22. http://care.diabetesjournals.org/misc/MedicalManagementofHyperglycemia.pdf
84. Ludvigsson J, Faresjo M, Hjorth M, et al. **GAD treatment** and insulin secretion in recent-onset type 1 diabetes. N Engl J Med. 2008 Oct 30;359(18):1909-20. Epub 2008 Oct 8.
85. Arabi YM, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical **critically ill patients**. Crit Care Med. 2008 Dec;36(12):3190-7. Intensive insulin therapy was not associated with improved survival among medical surgical intensive care unit patients and was associated with increased occurrence of hypoglycemia. Based on these results, we do not advocate universal application of intensive insulin therapy in intensive care unit patients.
86. Esposito K, Ciotola M, Maiorino MI, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. Ann Intern Med. 2008 Oct 21;149(8):531-9. Similar glycemic control occurred with the addition of NPL or glargine insulin to oral regimens in patients with poorly controlled type 2 diabetes. Hypoglycemia was similar in the 2 groups, but sample size limited the ability to make a definite safety assessment.
87. Hollander P, Cooper J, Bregnhøj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing **insulin detemir with insulin glargine** in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. Clin Ther. 2008 Nov;30(11):1976-87. When used as indicated as part of a basal-bolus regimen in patients with T2DM who had previously received other insulin and/or OAD regimens, detemir was noninferior to glargine in its effects on overall glycemic control. Both basal insulins were associated with clinically relevant reductions in hyperglycemia. Both were well tolerated, with no significant difference in the frequency of hypoglycemia or AEs.
88. Pharmacist's Letter. **How Much Insulin is Too Much**? Jan 2009.
89. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. Diabet Med. 2006 Aug;23(8):879-86.
90. Ashwell SG, Gebbie J, Home PD. Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times. Diabet Med. 2006 Jan;23(1):46-52.
91. Lund SS, Tarnow L, Astrup AS, et al. Effect of adjunct **metformin** treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study. PLoS ONE. 2008;3(10):e3363. Epub 2008 Oct 9.
92. NeedleAid Ensures: injection at the proper angle & depth & shields the needle. Useful for visually impaired. http://www.needleaid.com/
93. Hirsch IB. **Sliding scale** insulin--time to stop sliding. JAMA. 2009 Jan 14;301(2):213-4.
94. Singh SR, Ahmad F, Lal A, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180(4):385-97. Online at: http://www.cmaj.ca/cgi/reprint/180/4/385 Rapid-and long-acting insulin analogues offer little benefit relative to conventional insulins in terms of glycemic control or reduced hypoglycemia. Long-term, high-quality studies are needed to determine whether insulin analogues reduce the risk of long-term complications of diabetes.
95. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitis. CMAJ 2009;180(4):400-7. http://www.cmaj.ca/cgi/reprint/180/4/400 . The cost-effectiveness of insulin analogues depends on the type of insulin analogue and whether the patient receiving the treatment has type 1 or type 2 diabetes. With the exception of rapid-acting insulin analogues in type 1 diabetes, routine use of insulin analogues, especially

TOP

analogues in type 2 diabetes, is unlikely to represent an efficient use of finite health care resources.
96. Siebenhofer-Kroitzsch A, Horvath K, Plank J. Insulin analogues: too much noise about small benefits. CMAJ. 2009 Feb 17;180(4):369-70. http://www.cmaj.ca/cgi/reprint/180/4/369
97. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al. **Early insulin therapy in very-low-birth-weight infants.** N Engl J Med. 2008 Oct 30;359(18):1873-84.
98. **NICE-SUGAR** Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, et al. **Intensive** versus conventional glucose control in **critically ill** patients. N Engl J Med. 2009 Mar 26;360(13):1283-97. Epub 2009 Mar 24. In this large, international, randomized trial, we found that intensive glucose control **increased mortality** among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.
Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009 Apr 14;180(8):821-7. Epub 2009 Mar 24.
99. Montori VM, Fernández-Balsells M. **Glycemic Control** in Type 2 Diabetes: **Time for an Evidence-Based About-Face**?. Ann Intern Med. 2009 Apr 20.
100. Ray KK, Seshasai SR, et al. Effect of **intensive control of glucose on cardiovascular outcomes** and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet 2009; 373: 1765-72.
101. Perez, Norma, Moisan, Jocelyne, Sirois, Caroline, Poirier, Paul, Gregoire, Jean-Pierre. **Initiation of insulin** therapy in elderly patients taking oral antidiabetes drugs. CMAJ 2009 180: 1310-1316.
102. Glargine & cancer: FDA Jul/09 : Early Communication About Safety of Lantus (insulin glargine): http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169722.htm ; http://www.diabetologia-journal.org/cancer.html ; Related links: http://www.medscape.com/viewarticle/705198?src=mp&spon=34&uac=93517FV ; http://www.nationalpost.com/life/health/story.html?id=4578946f-1f50-426e-b92a-bc0f7dd86eed ; http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_115-eng.php ; http://www.endo-society.org/advocacy/policy/upload/Statement-for-Patients-on-Insulin-Glargine.pdf
Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009 Jul 2. [Epub ahead of print]
Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia. 2009 Jun 30. [Epub ahead of print]
Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdóttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia. 2009 Jul 9. [Epub ahead of print]
Ruiter R, Visser LE, van Herk-Sukel MP, et al. Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: results from a large population-based follow-up study. Diabetologia. 2011 Sep 29.
103. Pérez N, Moisan J, Sirois C, Poirier P, Grégoire JP. **Initiation of insulin** therapy in elderly patients taking oral antidiabetes drugs. CMAJ. 2009 Jun 23;180(13):1310-6
104. Bolli GB, Kerr D, Thomas R, et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. Diabetes Care. 2009 Jul;32(7):1170-6. Epub 2009 Apr 23. In unselected people with type 1 diabetes naive to CSII or insulin glargine, glycemic control is no better with the more expensive CSII therapy compared with glargine-based MDI therapy.
105. Lingvay I, Legendre JL, Kaloyanova PF, et al. **Insulin-Based** versus Triple Oral Therapy for Newly-Diagnosed Type 2 Diabetes: Which is Better? Diabetes Care. 2009 Jul 10. [Epub ahead of print] When compared with a clinically equivalent treatment regimen, insulin-based therapy is effective, did not cause greater weight gain or hypoglycemia, nor decrease compliance, treatment satisfaction, or QoL. Insulin is safe, well-accepted, and effective for ongoing treatment of patients with newly-diagnosed type 2 diabetes.
106. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin **Glargine** Safety in **Pregnancy**: a Transplacental Transfer Study. Diabetes Care. 2009 Oct 6. [Epub ahead of print]
107. Dejgaard A, Lynggaard H, Råstam J, Krogsgaard Thomsen M. No evidence of increased risk of **malignancies** in patients with diabetes treated with insulin **detemir**: a meta-analysis. Diabetologia. 2009 Oct 17.
108. Van den Berghe G, Mesotten D, Vanhorebeek I. Intensive insulin therapy in the intensive care unit. CMAJ. 2009 Apr 14;180(8):799-800. Epub 2009 Mar 24.
109. Pescovitz MD, Greenbaum CJ, et al. Type 1 Diabetes TrialNet Anti-CD20 Study Group. **Rituximab**, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009 Nov 26;361(22):2143-52.
110. Wilson Jennifer F. **In the Clinic: Diabetic Ketoacidosis**. Ann Intern Med January 5, 2010 152:ITC1-1; doi:10.1059/0003-4819-152-1-201001050-01001.
111. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (**CSII**) **versus multiple insulin** injections for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD005103.
112. Hernández-Díaz S, Adami HO. Diabetes therapy and **cancer risk**: causal effects and other plausible explanations. Diabetologia. 2010 Feb 23.
113. Hovorka R, Allen JM, Elleri D, et al. Manual **closed-loop insulin delivery** in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet. 2010 Feb 27;375(9716):743-51.
114. Egi M et al. **Hypoglycemia** and outcome in critically ill patients. Mayo Clin Proc 2010 Mar; 85:217.
115. Barton AL, Gilbertson HR, Donath SM and Cameron FJ. Is bedtime **supper** necessary for older children with diabetes using **glargine insulin** in multiple daily injection regimens?. Diabet Med. 2010 Feb;27:238-41.
116. Gibney MA, Arce CH, et al. Skin & subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections:implications for **needle length** recommendations. Curr Med Res Opin.2010Jun;26(6):1519-30.
117. Nguyen TM, Renukuntla VS, Heptulla RA. **Mixing Insulin Aspart With Detemir** Does Not Affect Glucose Excursion In Children With Type 1 Diabetes Mellitus. Diabetes Care. 2010 May 26.
118. Giovannucci, Edward, Harlan, David M., Archer, Michael C., et al. **Diabetes and Cancer**: A Consensus Report. CA Cancer J Clin 2010 0: caac.20078.
119. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet. 2010 Feb 27;375(9716):743-51.
120. Rosenstock Julio, Lorber Daniel L, Gnudi Luigi, et al., Prandial inhaled insulin plus basal insulin glargine versus twice daily biaspart insulin for type 2 diabetes: a multicentre randomised trial, The Lancet, Volume 375, Issue 9733, 26 June 2010-2 July 2010, Pages 2244-2253
121. Bergenstal, Richard M., Tamborlane, William V., Ahmann, Andrew, et al. the **STAR 3** Study Group, Effectiveness of **Sensor-Augmented Insulin-Pump** Therapy in Type 1 Diabetes. N Engl J Med 2010 0: NEJMoa1002853.
122. Miser William F., Arakaki R, Jiang H et al., Randomized, open-label, parallel-group evaluations of **basal-bolus therapy versus** insulin lispro **premixed** therapy in patients with type 2 diabetes mellitus failing to achieve control with starter insulin treatment and continuing oral antihyperglycemic drugs: A noninferiority intensification substudy of the DURABLE trial, Clinical Therapeutics, Volume 32, Issue 5, May 2010, Pages 896-908.
123. Hofman PL, Behrensdorf Derraik JG, et al. Defining the ideal injection techniques when using **5-mm needles** in children and adults. Diabetes Care. 2010 Jun 28.
124. Campbell PT, Deka A, Jacobs EJ, et al. Prospective study reveals associations between **colorectal cancer** and type 2 diabetes mellitus or insulin use in men. Gastroenterology. 2010 Oct;139(4):1138-46.
125. Grimaldi-Bensouda L, Marty M, Pollak M.; et al. The international study of insulin and cancer (**ISICA**). Lancet. 2010 Sep 4;376(9743):769-70.
126. Zhao YT, Weng CL, Chen ML, et al. Comparison of **glucose-insulin-potassium and insulin-glucose** as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials. Heart. 2010 Oct;96(20):1622-6. Current evidence suggests that GIK with insulin does not reduce mortality in patients with AMI. However, studies of glycaemia are inconclusive & it remains possible that glycaemic control is beneficial.
127. Knip Mikael, Virtanen Suvi M, Seppä Karri, et al.. for the Finnish TRIGR Study Group. **Dietary Intervention** in Infancy and Later Signs of Beta-Cell Autoimmunity. N Engl J Med 2010; 363:1900-1908.
128. Frid A, Hirsch L, Gaspar R, et al. Scientific Advisory Board for the Third Injection Technique Workshop. **New injection recommendations** for patients with diabetes. Diabetes Metab. 2010 Sep;36 Suppl 1:S3-18.
129. Pharmacist's Letter. Insulin **Pump Therapy**. Dec 2010.
130. Dhulkotia JS, Ola B, Fraser R, et al. **Oral hypoglycemic agents vs insulin in management of gestational diabetes**: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010 Nov;203(5):457.e1-9.
131. Pollex E, Moretti ME, Koren G,et al. Safety of Insulin **Glargine Use in Pregnancy**: A Systematic Review and Meta-Analysis (January). Ann Pharmacother.2011 Jan 4.
132. Kansagara Devan, Fu Rongwei, Freeman Michele, et al. **Intensive Insulin Therapy in Hospitalized Patients**: A Systematic Review. Ann Intern Med February 15, 2011 154:268-282.
133. Qaseem Amir, Humphrey Linda L., Chou Roger, et al. and for the Clinical Guidelines Committee of the American College of Physicians. Use of **Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients**: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med February 15, 2011 154:260-267.
134. Zinman Bernard, Fulch e Greg r, Rao Paturi V. **Insulin degludec**, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. The Lancet, Early Online Publication, 10 March 2011. doi:10.1016/S0140-6736(10)62305-7
135. Morgan CL, Evans M, Toft AD, et al. Clinical Effectiveness of Biphasic Insulin **Aspart 30:70** Vs Biphasic Human Insulin 30 in UK General Clinical Practice: A Retrospective Database Study. Clin Ther.2011Jan;33(1):27-35.
136. Hovorka R, Kumareswaran K, Harris J, Allen JM, Elleri D, Xing D, et al. **Overnight closed loop insulin delivery (artificial pancreas)** in adults with type 1 diabetes: crossover randomised controlled studies. BMJ 2011;342:1855.
137. Buse JB, Wolffenbuttel BH, Herman WH, et al. **DURAbility** of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) Trial: Comparing the durability of lispro mix 75/25 and glargine. Diabetes Care. 2011 Feb;34(2):249-55.
138. Hamaty M. **Insulin treatment for type 2 diabetes**: When to start, which to use *Cleveland Clinic Journal of Medicine* 2011; 78(5):332-342; doi:10.3949/ccjm.78a.10051.
139. Korownyk C, Ivers N, Allan GM. Strategies for **initiating insulin** in type 2 diabetes. Can Fam Physician. 2011 May;57(5):562.

TOP

140. Umpierrez GE, Hor T, Smiley D, et al. Comparison of inpatient insulin regimens with **detemir plus aspart versus neutral protamine Hagedorn plus regular** in medical patients with type 2 diabetes. (DEAN) J Clin Endocrinol Metab 2009; 94:564–569.
141. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011; 34:256–261.
142. Umpierrrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diabetes Care 2007; 30:2181–2186.
143. Umpierez GE, How to manage type 2 diabetes in **medical and surgical patients in the hospital**. Cleveland Clinic Journal of Medicine 2011; 78(6):379-384; doi:10.3949/ccjm.78gr.11001.
144. Rogal SS, Ukomadu C, Levy BD, Loscalzo J. Clinical problem-solving. A sweet source of abdominal pain. (Glycogenic hepatopathy) N Engl J Med. 2011 May 5;364(18):1762-7.
145. Ajay Varanasi, Natalie Bellini, Deepti Rawal, et al. **Liraglutide** as Additional Treatment in Type 1 Diabetes *Eur J Endocrinol* 2011 EJE-11-0330.
146. Levin Philip A., Zhang Quanwu, Mersey James H., et al. Glycemic Control With Insulin **Glargine Plus Insulin Glulisine** Versus Premixed Insulin Analogues in Real-World Practices: A Cost-Effectiveness Study With a Randomized Pragmatic Trial Design, Clinical Therapeutics, In Press, Corrected Proof, Available online 30 June 2011.
147. Pickup John C, Freeman Suzanne C, Sutton Alex J. Glycaemic control in type 1 diabetes during real time **continuous glucose monitoring** compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:doi:10.1136/bmj.d3805 (7 July 2011)
148. Zachariah S, Sheldon B, Shojaee-Moradie F, et al. **Insulin detemir reduces weight gain** as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care. 2011 Jul;34(7):1487-91.
149. Petznick A. **Insulin management** of type 2 diabetes mellitus. Am Fam Physician. 2011 Jul 15;84(2):183-90.
150. Cohen D. The prickly problem of **access to insulin**. BMJ. 2011 Sep 14;343:d5782. doi: 10.1136/bmj.d5782.
151. Blair JC, Peak M, Gregory JW. What is the best way to deliver subcutaneous **insulin to infants, children, and young people** with type 1 diabetes mellitus? BMJ. 2011 Sep 2;343:d5221.
152. Ruiter R, Visser LE, van Herk-Sukel MP, et al. Risk of **cancer in patients on insulin glargine and other insulin analogues** in comparison with those on human insulin: results from a large population-based follow-up study. Diabetologia. 2011 Sep 29.
153. Rascati KL, Richards KM, Lopez D, et al. **Progression to Insulin** for Patients with Diabetes Mellitus Using the Texas Medicaid Database. Clin Ther. 2011 Nov 17.
154. Bellolio MF, Gilmore RM, Stead LG. **Insulin for** glycaemic control in acute **ischaemic stroke**. Cochrane Database Syst Rev. 2011;(9): CD005346. Starting intravenous insulin within the first 24 hours of acute ischemic stroke to maintain normoglycemia does not reduce death or dependency but increases the risk for hypoglycemia.
155. Gray CS,Hildreth AJ, Sandercock PA, et al;GISTTrialists Collaboration. **Glucose-potassium-insulin infusions** in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;6:397-406.
156. Tibaldi JM. Intensifying insulin therapy in type 2 diabetes mellitus: dosing options for **insulin analogue premixes**. Clin Ther. 2011 Nov;33(11):1630-42.
157. Rascati KL et al. **Progression to insulin** for patients with diabetes mellitus using the Texas medicaid database. Clin Ther. 2011 Dec;33(12):2016-20. (slower progression with metformin/TZD than sulfonylurea/TZD)
158. Lee P, Chang A, Blaum C, Vlajnic A, Gao L, Halter J. Comparison of safety and efficacy of **insulin glargine and neutral protamine hagedorn** insulin in older adults with type 2 diabetes mellitus: results from a pooled analysis. J Am Geriatr Soc. 2012 Jan;60(1):51-9.
159. Ng KW, Allen ML, Desai A et al. **Cardioprotective effects of insulin**: how intensive insulin therapy may benefit cardiac surgery patients. Circulation. 2012 Feb 7;125(5):721-8.
160. Heller S, Buse J, Fisher M, et al, on behalf of the **BEGIN Basal-Bolus Type 1** Trial Investigators. **Insulin degludec**, an ultra-longacting basal insulin, **versus insulin glargine** in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379: 1489–97.
161. Garber AJ, King AB, Del Prato S, et al, on behalf of the NN1250–3582 (BEGIN BB T2D) Trial Investigators. **Insulin degludec**, an ultra-longacting basal insulin, **versus insulin glargine** in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (**BEGIN Basal-Bolus Type 2**): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379: 1498–507.
162. Lau AN, Tang T, Halapy H, Thorpe K, Yu CH. **Initiating insulin** in patients with type 2 diabetes. CMAJ. 2012 Apr 2.
163. Pickup JC. **Insulin-pump** therapy for type 1 diabetes mellitus. N Engl J Med. 2012 Apr 26;366(17):1616-24.
164. Donner T, Muñoz M. **Update on insulin** therapy for type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1405-13.
165. Lasserson D, Fox R, Farmer A. **Late onset type 1 diabetes**. BMJ. 2012 Apr 30;344:e2827.
166. Mauras N, Beck R, Xing D, et al. A randomized clinical trial to assess the efficacy and safety of **real-time continuous glucose monitoring** in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Care. 2012 Feb;35(2):204-10.
167. Aschner PJ, Chan J, Owens DR, et al, **EASIE** investigators. **Insulin glargine versus sitagliptin** in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised, open-label trial. Lancet 2012; online June 9.
168. **ORIGIN** Trial Investigators. Basal insulin (glargine) and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012 Jun 11; [e-pub ahead of print].
169. Gale EA. **Post-marketing studies** of new insulins: sales or science? BMJ. 2012 Jun 12;344:e3974.

Insulin Analogues Systematic Review (COMPUS) Jan 2009: http://cadth.ca/media/pdf/compus_IA_OT_rec_report.pdf
CDR / CEDAC Final Recommendation for Insulin Glulisine (Apidra) – Feb 19, 2009: http://www.cadth.ca/media/cdr/complete/cdr_complete_Apidra_February-19-2009.pdf
CADTH: Starting Insulin in T2DM: http://www.cadth.ca/media/pdf/c1109-guide-to-starting-insulin-final-e.pdf

TOP

Temporary Extras:

◆{Pen devices:↑'d portability, convenience & ease of use; but ↑ potential for contamination, needle sticks, malfunction & cost}

◆T1DM: A1c difference between SAIA and HI is less than 1/10th of the difference between intensive and conventional tx groups in the DCCT; based on this, expected NNT for 1 less retinopathy = 650 / year

◆Epidural Corticosteroids: expect ↑BG levels for a few days Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. Spine 2012;37(1):E46-50.

◆Insulin Pump (CSII): may allow for ↓A1C by 0.3-0.6%; ↓ insulin dose by 10-20%; potentially useful if ↑ A1C despite best attempt with MDI &/or who have continued disabling hypoglycemia. Also of use in 1st trimester of pregnancy, or before, if A1C <6.1% not achieved.

Acknowledgements: Contributors & Reviewers: Sue Pedersen, MD, FRCPC (Specialist in Endocrinology & Metabolism, Calgary), Tessa Laubscher (CCFP, College of Medicine, U of S, Saskatoon), Henry Halapy (PharmD, CDE; SMH, Toronto), Arlene Kuntz (Pharmacist, DES, CDA; Regina), G. Casper-Bell (Endocrinology, SHR, Saskatoon), M. Dahl (MD, FRCPC, Associate Professor, Endocrinology, U of BC, Vancouver; COMPUS-CERC member – Insulin Analogues), Mike Allen MD (Dalhousie-Continuing Professional Learning; COMPUS-CERC member – Insulin Analogues), Derek Jorgenson (PharmD, College of Medicine, U of S. Saskatoon), Karen MdDermaid (Pharmacist CDE, RQHR, SK), L. Cruickshank (MEDEC, Regina), (T. Arneson (Endocrinology, Saskatoon – SHR/UofS), Debbie Bunka (Pharmacist, Calgary Health Region), Kyle McNair (Pharmacist-PRISM, Manitoba) the RxFiles Advisory Committee. Prepared by: *M Jin* PharmD, CDE *(Hamilton); L. Regier* BSP, BA, B. *Jensen* BSP

References – Insulin Management: Evidence Tips & Pearls www.RxFiles.ca

[1] Building Competency in Diabetes Education: The Essentials, Canadian Diabetes Association

[2] Weng J et al. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: A multicentre randomised parallel-group trial. *Lancet* 2008 May 24; 371:1753.

Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. Diabetes Care. 2008 Oct;31(10):1927-32. Epub 2008 Jun 12. n=50. A 6-month course of insulin therapy, compared with OAD treatment, could more effectively achieve adequate glycemic control and significant improvement of beta-cell function in new-onset type 2 diabetic patients with severe hyperglycemia.

[3] Fiallo-Scharer R, Horner B, McFann K, Walravens P, Chase HP. Mixing rapid-acting insulin analogues with insulin glargine in children with type 1 diabetes mellitus. J Pediatr. 2006 Apr;148(4):481-4.

[4] Kaplan W, Rodriguez LM, Smith OE, Haymond MW, Heptulla RA. Effects of mixing glargine and short-acting insulin analogs on glucose control. Diabetes Care. 2004 Nov;27(11):2739-40.

[5] Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Sept 2008, 32(1). Accessed online at: http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf

Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD003395.

Serlin D., et al. Diagnosis and Management of Gestational Diabetes Mellitus. Am Fam Physician. 2009; 80 (1):57-62.

Landon MB et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009 Oct 1; 361:1339.

Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2010 Jan;115(1):55-9.

Biggio JR Jr et al. Fetal anomalies in obese women: The contribution of diabetes. Obstet Gynecol 2010 Feb; 115:290.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care March 2010 33:676-682

Simmons D, McElduff A, McIntyre HD, et al. Gestational Diabetes Mellitus: NICE for the U.S.? A Comparison of the American Diabetes Association and the American College of Obstetricians and Gynecologists Guidelines With the U.K. National Institute for Health and Clinical Excellence Guidelines: Response to Holt et al. Diabetes Care. 2010 Mar;33(3):e48.

Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. BMJ. 2010 Apr 1.

Getahun Darios, Fassett Michael J., Jacobsen Steven J. Gestational diabetes: risk of recurrence in subsequent pregnancies. Available online 14 July 2010. American Journal of Obstetrics & Gynecology DOI: 10.1016/j.ajog.2010.05.032.

Tieu J, Middleton P, McPhee AJ, Crowther CA. Screening and subsequent management for gestational diabetes for improving maternal and infant health. Cochrane Database Syst Rev. 2010 Jul 7;7:CD007222. There was insufficient evidence to determine if screening for gestational diabetes, or what types of screening, can improve maternal and infant health outcomes.

Agarwal MM, Dhatt GS, Shah SM. Gestational diabetes mellitus: simplifying the international association of diabetes and pregnancy diagnostic algorithm using fasting plasma glucose. (IADPSG) Diabetes Care. 2010 Sep;33(9):2018-20.

Dhulkotia JS, Ola B, Fraser R, et al. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010 Nov;203(5):457.e1-9.

Tobias DK, Zhang C, van Dam RM, Bowers K, Hu FB. Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis. Diabetes Care. 2011 Jan;34(1):223-9.

Brisson D, Perron P, Guay SP, Gaudet D, Bouchard L. The "hypertriglyceridemic waist" phenotype and glucose intolerance in pregnancy. CMAJ. 2010 Oct 19;182(15):E722-5.

Luoto R, Kinnunen TI, Aittasalo M, Kolu P, Raitanen J, et al. (2011) Primary Prevention of Gestational Diabetes Mellitus and Large-for-Gestational-Age Newborns by Lifestyle Counseling: A Cluster-Randomized Controlled Trial. PLoS Med 8(5): e1001036. doi:10.1371/journal.pmed.1001036

Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU): Body composition at 2 years of age. Diabetes Care. 2011 Oct;34(10):2279-84.

Louie JC, Markovic TP, Perera N, et al. A randomized controlled trial investigating the effects of a low-glycemic index diet on pregnancy outcomes in gestational diabetes mellitus. Diabetes Care. 2011 Nov;34(11):2341-6.

Malanda UL, Welschen LM, Riphagen II, et al. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database Syst Rev. 2012 Jan 18;1:CD005060. From this review, we conclude that when diabetes duration is over one year, the overall effect of self-monitoring of blood glucose on glycaemic control in patients with type 2 diabetes who are not using insulin is small up to six months after initiation and subsides after 12 months. Furthermore, based on a best-evidence synthesis, there is no evidence that SMBG affects patient satisfaction, general well-being or general health-related quality of life. More research is needed to explore the psychological impact of SMBG and its impact on diabetes specific quality of life and well-being, as well as the impact of SMBG on hypoglycaemia and diabetic complications.

Megia A, Naf S, Herranz L, et al. The usefulness of HbA1c in postpartum reclassification of gestational diabetes. BJOG. 2012 Apr 24.

[6] Siebenhofer A, Plank J, Berghold A, Jeitler K, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003287.

[7] Horvath K, Jeitler K, Berghold A, Ebrahim SH, et al. Long-acting insulin analogues versus NPH insulin for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007 Apr 18;:CD005613. {Also: http://www.medscape.com/viewarticle/578042 }

[8] Canadian Optimal Medication Prescribing & Utilization Service (COMPUS), 2008; Current Topics, Diabetes: http://cadth.ca/index.php/en/compus/current-topics/-dm1 (www.cadth.ca)

{Long-acting IAs: Metaanalysis of Clinical Outcomes: http://cadth.ca/media/compus/reports/compus_Long-Acting-Insulin-Analogs-Report_Clinical-Outcomes.pdf }

{Rapid Acting IAs: Metaanalysis of Clinical Outcomes: http://cadth.ca/media/compus/reports/compus_Rapid-Acting-Insulin-Analogues-Report_Clinical=Outcomes.pdf }

{Optimal Therapy Recommendations for Prescribing and Use of Insulin Analogues: http://cadth.ca/media/pdf/compus_IA_OT_rec_report.pdf Final Report: January 2009}

{Grade Evidence Profiles of Long and Rapid Acting Insulin Analogues: http://cadth.ca/media/compus/reports/compus_GRADE-REPORT.pdf }

[9] Schooff MD, Gupta L. Are long-acting insulin analogues better than isophane insulin? Am Fam Physician. 2008;15:447-9.

TOP

EXTRAS Page

Upcoming Trials in Diabetes/CV Risk Prevention:

- **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)- NEJM Mar/10; **TRANSCEND** (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease); **RAPSODI** (rimonabant in diabetes prevention); **CANOE** (rosiglitazone 2mg bid & metformin 500mg bid in diabetes prevention);

Prediabetes [ADA]:

- Includes: 1) Impaired Fasting Glucose {8hr fasting BG between 5.6-6.9mmol/L) & 2) Impaired glucose tolerance {Postprandial BG of 7.8-11.0mmol/L 2hrs post 75g oral glucose challenge}
- Risk factors: family hx, obesity – especially around waist, age >45, hypertension, gestational diabetes hx, sedentary lifestyle. Screening recommendations vary; USPSTF recommends screening particularly if BP >135/80. Oral Glucose Challenge most recommended, but A1c screen also advocated by some.
- QDScore diabetes risk calculator: (UK Prediction Calculator for T2DM): http://www.qdscore.org/

Insulin Analogues Systematic Review/Reports, 2008: http://www.cadth.ca/index.php/en/compus/insulin-analogs/reports

Tight glucose control in critically ill hospitalized pts may ↑mortality & ↑↑risk of hypoglycemia. JAMA'08; 31 Nice-Sugar NNH=38/90day

---

Q&A: Limitations & Unanswered Questions Regarding A1C Control and Clinical Outcome - Benefits or Risks

There are some important qualifiers on the commonly quoted observational data that "with every 1 % drop in A1C the risk of developing long-term diabetes complications decreases". (Concept originally based on observational data driven by an eye related microvascular endpoint in the UKPDS). **RCT evidence does not support this assumption**!

- Most recently the **ACCORD** trial (established, higher risk T2DM) was halted after looking at whether a A1C target of <6% would result in beneficial clinical outcomes compared to 7-7.9%. According to the preliminary results still awaiting publication, it would appear from this RCT, in this population group, the extra 1.1% drop in A1C seen in the intensive group was actually associated with increased all cause death compared to the standard group. Explanations for this are still pending; some possibilities noted with 5yr follow-up discussion below.
  (See also; http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf).
  - 5 year ACCORD[7b] follow-up results published [Mar 2011 NEJM]: A1C lowering intensiveness relaxed for balance of study period; participants continued in BP or lipid lowering arms; A1C at 5 yrs ~ 7.2% vs 7.6%.
    1) ↑ death sustained in intensive glucose lowering group 5.5% vs 4.5% [NNH=100/5yr];
    2) ↓ non-fatal MI, but fatal CV ↑;
    3) severe hypoglycaemia equivalent in follow-up period;
    4) those most at risk of ↑ death were those with baseline A1C > 8%;
    5) possible explanations for harm with intensive glucose lowering:
    A) different outcomes associated with different drugs or drug combinations?: **B)** impact of ↑ wt gain?; **C)** impact of intense BG lowering.
- With the current RCT evidence with rosiglitazone, there is some concern that lowering A1C does not necessarily result in CV event reductions? With the limited evidence, it appears to at best be neutral, and at worst, harmful in RCTs/durations studied so far (e.g. up to 5.5 year RCTs.) Patients studied, agents used & study limitations [e.g. dropouts] may affect the benefit/risk balance.
- The UKPDS-33, ~ 10 year trial saw reductions predominantly in the microvascular events (predominantly photocoagulation), with stroke and heart related endpoints not significant, but trending favorably and contributing to the composite endpoint benefit. (Exception: metformin had all-cause death reduction in obese T2DM in UKPDS-34)
- In UKPDS 34,[p860] which noted a mortality benefit for metformin in obese T2DM, there is inconsistency in the association of A1C & outcomes (less A1C difference but more benefit [UKPDS34 VS 33])
- In UKPDS 34 Metformin + Sulfonylurea combination led to a lower A1C than Sulf alone (7.7 vs 8.2) but had higher incidence of DM death and all cause death (perhaps due to design issues and a several year delay in moving to combination therapy) .
- The UKPDS epidemiologic evidence for the 1% drop in A1C did not control for obesity/BMI/waist circumference. [UKPDS 35]
- In ADOPT, rosiglitazone decreased A1C more that metformin or glyburide, but glyburide had the lowest rate of CV outcomes.
- In VADT, a 1.5% reduction (6.9% [intensive] vs 8.4% [standard]) in A1C for an average follow-up of 5.6 years resulted in no benefit (microvascular or macrovascular) but increased serious adverse events (predominantly hypoglycaemia).

- **Meta-analysis [2011] of Intensive ↓ BG RCTs in T2DM**: 13 trials, n=34,500. Endpoints: mortality, no difference [(RR=1.04, 99%CI 0.91-1.19)]; CV death, no difference [(RR=1.11;0.86-1.43)]; non-fatal MI: ↓ (RR=0.85, [0.74-0.96]);
  Severe hypoglycaemia: ↑↑ (RR=2.33, [1.62-3.36]) 1.9-6.6% of patients required tx for severe hypoglycaemia over 5 years. If only high quality studies included, no longer a ↓ in non-fatal MI & there was an ↑ in HF.
  Microvascular effects: no difference, but heterogeneity; rate of retinopathy (0.85, 0.71-1.03); photocoagulation (0.91, 0.71-1.17), ↓ vision or blindness (1.00); neuropathy 0.99, 0.95-1.03); renal failure or 2x SCR (1.03, 0.98-1.08).
  Microalbuminuria: ↓ (0.90, 0.85-0.96), ARR 0.7%-3.1%; NNT=142-32. OVERALL: for hard clinical endpoints, no benefit, but increased severe hypoglycaemia requiring tx. However, note heterogeneity in trials, different tx approaches, different definitions of "intensive lowering", etc. Nevertheless, the more trials, the more evidence that just lowering BG does not equate automatically to beneficial clinical outcomes, but does carry hypoglycaemia risk.

There is some disconcordence between randomized trial outcome evidence and the frequently reported "1% A1C..." benefit. One thing that has growing certainty is that the risks and benefits of drug regimens that lower A1C is more complex than what was previously commonly accepted. While a high A1C is not good, some methods of lowering A1C in some patient groups, are also harmful. While we do not want to be lazy in addressing glucose control, the evidence suggests that we not assume a net benefit for all A1C lowering interventions in all Type 2 diabetes patients. {*Let the target serve the patient, and not the patient the target.*}

See also: Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. BMJ. 2011 Dec 28;343:d7995. http://www.bmj.com/content/343/bmj.d7995

TOP

Multfactorial intervention - blood pressure, lipids, possibly ASA, lifestyle – in addition to glucose control, is essential in reducing macrovascular endpoints!

See also RxFiles Landmark Trials Chart: Summary of Lipid, BP & ASA diabetes related trials: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-DIABETES-Landmark-Trials-Non-Glucose.pdf

References - Diabetes Trials: Landmark Outcome and Prevention (www.RxFiles.ca)

[1] DCCT Reasearch Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30;329(14):977-86.

[2] Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005 Dec 22;353(25):2643-53.

de Boer IH, Kestenbaum B, Rue TC, et al. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med. 2008 Sep 22;168(17):1867-73. Hyperglycemia is a risk factor for incident hypertension in type 1 diabetes, and intensive insulin therapy reduces the long-term risk of developing hypertension.

{Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years' Duration: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). Arch Intern Med. 2009;169(14):1307-1316.}

White NH, Sun W, Cleary PA, et al. Effect of Prior Intensive Therapy in Type 1 Diabetes Mellitus on 10-year Progression of Retinopathy in the DCCT/EDIC: Comparison of Adults and Adolescents. Diabetes. 2010 Feb 11.

Albers JW, Herman WH, Pop-Busui R, et al. for the DCCT/EDIC Research Group. Effect Of Prior Intensive Insulin Treatment During The Diabetes Control And Complications Trial (DCCT) On Peripheral Neuropathy In Type 1 Diabetes During The Epidemiology Of Diabetes Interventions, And Complications (EDIC) Study. Diabetes Care. 2010 Feb 11.

de Boer Ian H.; Rue Tessa C.; Cleary Patricia A.; et al.; for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term Renal Outcomes of Patients With Type 1 Diabetes Mellitus and Microalbuminuria: An Analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort DCCT/EDIC. Arch Intern Med. 2011;171(5):412-420.

DCCT/EDIC Research Group. Intensive Diabetes Therapy and Glomerular Filtration Rate in Type 1 Diabetes. N Engl J Med. 2011; 365:2366.

[3] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.

[4] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. Erratum.

[5] Ohkubo Y, Kishikawa H, Araki E, Miyata T,et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995 May;28(2):103-17. (Kumamoto study)

[6] Dormandy JA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study. (PROspective pioglitAzone Clinical Trial in macroVascular Events): a RCT. Lancet. 2005; 366: 1279-1289. {InfoPOEMs Aug 2008: Pioglitazone (Actos), unlike its chemical cousin rosiglitazone (Avandia), does not seem to increase the likelihood of cardiovascular events (N Engl J Med. 2007;356:2457-2471). The researchers conducting this study stretched -- and broke -- the scientific method when claiming benefit, but any claims of benefit are specious. (LOE = 1a-)}

[7] Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59. {RxFiles Trial Summary: ACCORD }

Miller ME, Bonds DE, Gerstein HC, et al. ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010 Jan 8;340:b5444. doi: 10.1136/bmj.b5444.

ACCORD Study Group and ACCORD Eye Study Group, Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 0: NEJMoa1001288.

Ismail-Beigi F, Craven T, Banerji MA. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: analysis of ACCORD randomised trial.The Lancet, Early Online, 29June10 doi:10.1016/S0140-6736(10)60576-4.

[7b]: ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011 Mar 3; 364:818.

ACCORD Anderson RT, Narayan KM, Feeney P, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Investigators. Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial. Diabetes Care. 2011 Apr;34(4):807-12.

Launer LJ, Miller ME, Williamson JD, et al; ACCORD MIND. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes: a randomised open-label substudy. Lancet Neurol. 2011 Nov;10(11):969-77.

[8] ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.

Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. {RxFiles Trial Summary: ADVANCE http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-ADVANCE-trial.pdf }

Zoungas S, de Galan BE, Ninomiya T, et al. the ADVANCE Collaborative Group. The combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes; new results from ADVANCE. Diabetes Care. 2009 Aug 3. [Epub ahead of print] The effects of routine blood pressure lowering and intensive glucose control were independent of one another and when combined produced additional reductions in clinically relevant outcomes.

Zoungas S et al. Severe hypoglycemia and risks of vascular events and death (Advance). N Engl J Med 2010 Oct 7; 363:1410. During a median follow-up period of 5 years, 231 patients (2.1%) had at least one severe hypoglycemic episode; 150 had been assigned to intensive glucose control (2.7% of the 5571 patients in that group), and 81 had been assigned to standard glucose control (1.5% of the 5569 patients in that group).

[9] Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. (STENO-2) N Engl J Med. 2008 Feb 7;358(6):580-91.

[10] UGDP.

[11] Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med. 2008 Dec 17. (VADT study) Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications. {InfoPOEMs Mar09: Like the ACCORD and ADVANCE studies, this trial provides additional evidence that intensive glucose control does not improve outcomes in patients with type 2 diabetes mellitus. It is important to note that these patients had well-controlled hypertension (mean blood pressure = 126/68) and well-controlled hyperlipidemia (mean low-density lipoprotein = 80 mg/dL).}

Anderson RJ, Bahn GD, Moritz TE, et al.; for the VADT Study Group. Blood Pressure and Cardiovascular Disease risk in the Veterans Affairs Diabetes Trial (VADT) Diabetes Care. 2010 Nov 8. DBP <70 mmHg elevated CVD risk.

[12] Holman R, Sanjoy P, Bethel MA, Matthews D, Neil A. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. (UKPDS-80). N Engl J Med 2008;359:1-13. {(SU/Insulin vs control: ↓ MI 19.6⇨16.8 per 1000 patient-yrs RR=0.85 (CI: 0.74-0.97); ↓ Death 30.3⇨26.8 per 1000 patient-yrs RR=0.87 (CI: 0.79-0.96)); (MF vs control: ↓ MI, 21.1⇨14.8 per 1000 patient-yrs RR=0.67 (CI: 0.51-0.89); ↓ Death 33.1⇨25.9 per 1000 patient-yrs RR=0.73 (CI: 0.59-0.89)). {Daily POEM: "The advantages of tight blood sugar control seen in the United Kingdom Prospective Diabetes Study (UKPDS) trial were maintained and to some extent extended during a 10-year nonrandomized follow-up period, even though all patients quickly had similar glycohemoglobin levels. The benefit was most pronounced with metformin. Note that patients in the "intensive therapy" group had a mean glycohemoglobin of approximately 8% at the end of the randomized portion of the study, and the recent ACCORD study found that more aggressive control offered no benefit and may be harmful (N Engl J Med 2008;358:2545-59, POEM #100825). (LOE = 2b)"}

[13] Lindstrom J, Ilanne-Parikka P, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. The Lancet. 2006; 368:1673-1679.

Uusitupa M, Peltonen M, Lindström J, et al. 2009 Ten-Year Mortality and Cardiovascular Morbidity in the Finnish Diabetes Prevention Study—Secondary Analysis of the Randomized Trial. PLoS ONE 4(5): e5656. doi:10.1371/journal.pone.0005656.

[14] Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med 2008;121:149-157.e2. {InfoPOEMS: Using metformin to treat patients at risk for diabetes decreases their likelihood of developing diabetes over a 3-year period. Longer studies are needed to determine whether the likelihood of diabetes is truly decreased or simply delayed. We have no research to tell us whether, in the long run, patients live longer or live better if they are treated at this stage of (pre)diabetes. (LOE = 1a)}

[15] Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med. 2007 May 21; [Epub ahead of print] http://content.nejm.org/cgi/content/full/NEJMoa072761

[16] DeFronzo Ralph A., Tripathy Devjit, Schwenke Dawn C., et al. for the ACT NOW Study. Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance. N Engl J Med 2011; 364:1104-1115.

ACT-NOW: ↓progression to T2DM (annual incidence of diabetes was 2.1 vs 7.6%/yr; NNT=19/yr) but ↑weight (3.9kg vs 0.77kg) & edema (12.9 vs 6.4%).

TOP

Loke Yoon Kong, Kwok Chun Shing, Singh Sonal. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 342:doi:10.1136/bmj.d1309
[17] Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. BMJ 2007;28;334(7599):882-4. Accessed online: http://www.bmj.com/cgi/content/extract/334/7599/882
[18] Weng J et al. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: A multicentre randomised parallel-group trial. *Lancet* 2008 May 24; 371:1753.
[19] Knowler WC, Barret-Connor E, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. (DPP trial) N Engl J Med. 2002; 346: 393-403.
Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009 Nov 14;374(9702):1677-86.
[20] Knowler WC, Hamman RF, Edelstein SL, et al. Prevention of type 2 diabetes with troglitazone in the diabetes prevention program. Diabetes. 2005; 54: 1150-1156.
[21] Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). Diabetologia. 2006 Feb;49(2):289-97. Epub 2006 Jan 4. n=531 over 2.5yrs
Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, Seeli AC, Shetty AS. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). Diabetologia. 2009 Mar 10. [Epub ahead of print]
[22] Chiasson JL, Josse RG, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. The Lancet. 2002; 359: 2072-2077.
[23] Chiasson JL, Josse RG, Gomis R, et al. Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients with Impaired Glucose Tolerance: The STOP-NIDDM Trial. JAMA 2003; 290(4): 486-494.
[24] Torgerson JS, Boldrin MN, et al. XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. Diabetes Care. 2004; 27: 155-161.
[25] DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105. Erratum in: Lancet 2006;18;368:1770.
DREAM On (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up) Investigators. Long-term effect of rosiglitazone and/or ramipril on the incidence of diabetes. Diabetologia. 2010 Nov.
Holman RR, Zinman B, Yusuf S, Sheridan PM, Anand SS, Bosch JJ, Conget I, et al. Incidence of Diabetes Following Ramipril or Rosiglitazone Withdrawal. (DREAM) trial. Diabetes Care. 2011 Apr 22.
[26] DREAM Trial Investigators; Bosch J, Yusuf S, Gerstein HC, et al.Effect of ramipril on the incidence of diabetes. N Engl J Med. 2006 Oct 12;355(15):1551-62. Epub 2006 Sep 15.
Holman RR, Zinman B, Yusuf S, Sheridan PM, Anand SS, Bosch JJ, Conget I, et al. Incidence of Diabetes Following Ramipril or Rosiglitazone Withdrawal. (DREAM) trial. Diabetes Care. 2011 Apr 22.
[27] NAVIGATOR Study Group, Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events. N Engl J Med 2010 0: NEJMoa1001122. NAVIGATOR Study Group, Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events. N Engl J Med 2010 0: NEJMoa1001121.
[28] AACE: THE DIAGNOSIS AND MANAGEMENT OF PRE-DIABETES IN THE CONTINUUM OF HYPERGLYCEMIA. July 2008. Accessed online at: http://www.aace.com/meetings/consensus/hyperglycemia/hyperglycemia.pdf
[29] Canadian Optimal Medication Prescribing & Utilization Service (COMPUS), Current Topics, Diabetes: http://cadth.ca/index.php/en/compus/current-topics/-dm1 (www.cadth.ca)
[30] Montori V, Fernandez-Balsells M. Glycemic Control in Type 2 Diabetes: Time for an Evidence-Based About Face? Ann Int Med 2009; 150(11). Available at: http://www.annals.org/cgi/content/full/0000605-200906020-00118v1 on 2009 Apr 21.
[31] Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008 Aug 27;300(8):933-44. In critically ill adult patients, tight glucose control is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia.
Arabi YM, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008 Dec;36(12):3190-7.
NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97. Epub 2009 Mar 24. In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.
[31] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 20;373(9681):2125-35. {Commentary & limitations: http://www.medscape.com/viewarticle/704038 }
Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. Eur Heart J 2010; DOI: 10.1093/eurheartj/ehp604.
Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125-2135.
Avenell A, Cook JA, MacLennan GS, McPherson GC; RECORD trial group. Vitamin D supplementation and type 2 diabetes. Age Ageing. 2009;38(5):606-609.
[32] Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Eff ect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe):a cluster-randomised trial. Lancet 2011; published online June 25

Additional References

ADA-American Diabetes Association Guidelines- Standards of Medical Care in Diabetes—2010 http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html
ADA, ACC & AHA Position Statement - Intensive Glycemic Control & the prevention of CV Events - Jan/2009 Implications of ACCORD, ADVANCE & VA Diabetes Trials (ePublished - accessed Dec 30, 2008) http://care.diabetesjournals.org/misc/finaldc9026.pdf
American College of Sports Medicine, American Diabetes Association. **Exercise and type 2 diabetes**: American College of Sports Medicine and the American Diabetes Association: joint position statement. Med Sci Sports Exerc 2010 Dec;42(12):2282-303.
Andrews RC, Cooper AR, Montgomery AA, et al. **Diet or diet plus physical activity versus usual care** in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet 2011; June 25.
BMJ 2009;338:b800. Mar 2009. Editorials: **Tight contro**l of blood glucose in long standing type 2 diabetes. Accessed at http://www.bmj.com/cgi/content/full/338/mar05_2/b800?ct
Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of **intensive glucose lowering treatment on all cause mortality, cardiovascular death**, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.
Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009;26:142-8. {InfoPOEMs Apr09: This meta-analysis found no evidence to support the contention that diabetes alone is a coronary heart disease (CHD) risk equivalent to a history of prior myocardial infarction (MI). The blanket use of aspirin and statins for patients with type 2 diabetes, regardless of their lipid levels, is not supported by the evidence. (LOE = 2a)}
Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review & meta-analysis. Arch Intern Med. 2012;172 (10):761-769
Collins GS, Altman DG. External validation of QDSCORE((R)) for predicting the 10-year risk of developing Type 2 diabetes. Diabet Med. 2011 May;28(5):599-607. doi: 10.1111/j.1464-5491.2011.03237.x
Coppell KJ, Kataoka M, Williams SM, et al. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial. BMJ 2010;341:c3337.
Defronzo RA, Banerji M, Bray GA, et al. Actos Now for the prevention of diabetes (ACT NOW) study. BMC Endocr Disord. 2009 Jul 29;9:17. (pioglitazone)
DeFronzo Ralph A., Tripathy Devjit, Schwenke Dawn C., et al. for the ACT NOW Study. Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance. N Engl J Med 2011; 364:1104-1115.
Elhayany A, Lustman A, Abel R, et al. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. Diabetes Obes Metab. 2010 Mar;12(3):204-9.
Franks, Paul W., Hanson, Robert L., Knowler, William C., et al. Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death. N Engl J Med 2010 362: 485-493.
Haynes RB, Haynes GA. What does it take to put an ugly fact through the heart of a beautiful hypothesis? Evid Based Med. 2009 Jun;14(3):68-9. http://ebm.bmj.com/cgi/content/full/14/3/68?linkType=FULL&journalCode=ebmed&resid=14/3/68
Heianza Y, Hara S, Arase Y, et al. HbA(1c) 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet. 2011 Jun 24.

TOP

Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD008143. DOI: 10.1002/14651858.CD008143.pub2. The included trials did not show significant differences for all-cause mortality and cardiovascular mortality when targeting intensive glycaemic control compared with conventional glycaemic control. Targeting intensive glycaemic control reduced the risk of microvascular complications while increasing the risk of hypoglycaemia. Furthermore, intensive glycaemic control might reduce the risk of non-fatal myocardial infarction in trials exclusively dealing with glycaemic control in usual care settings.

Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ. 2011 Nov 24;343:d6898.

Hippisley-Cox J, Coupland C, Robson J, Sheikh A, Brindle P. Predicting risk of type 2 diabetes in England and Wales: prospective derivation and validation of QDScore. BMJ. 2009 Mar 17;338:b880. doi: 10.1136/bmj.b880.

Holman, Rury R., Farmer, Andrew J., Davies, Melanie J., et al. the 4-T Study Group, Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes.N Engl J Med 2009 0: NEJMoa0905479.

Ismail-Beigi Faramarz, Moghissi Etie, Tiktin Margaret, et al. Individualizing Glycemic Targets in Type 2 Diabetes Mellitus: Implications of Recent Clinical Trials. Ann Intern Med April 19, 2011 154:554-559.

Johnston Stephen S., Conner Christopher, Aagren Mark, et al. Evidence Linking Hypoglycemic Events to an Increased Risk of Acute Cardiovascular Events in Patients With Type 2 Diabetes. Diabetes Care May 2011 34:1164-1170.

Kahn HS, Cheng YJ, Thompson TJ, Imperatore G, Gregg EW. Two risk-scoring systems for predicting incident diabetes mellitus in U.S. adults age 45 to 64 years. Ann Intern Med. 2009 Jun 2;150(11):741-51. Basic information identified adults at high risk for diabetes. Additional data from fasting blood tests better identified those at extreme risk.

Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors (DPP-4) for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369.

Kawamori R, Tajima N, et al. Voglibose Ph-3 Study Group. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet. 2009 May 9;373(9675):1607-14.

Li R, Zhang P, Barker LE, et al. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010 Aug;33(8):1872-94.

Lilly M, Godwin M. Treating prediabetes with metformin: systematic review and meta-analysis. Can Fam Physician. 2009 Apr;55(4):363-9. Metformin decreases the rate of conversion from prediabetes to diabetes. This was true at higher dosage (850 mg twice daily) & lower dosage (250 mg twice or 3 times daily); in people of varied ethnicity; & even when a sensitivity analysis was applied to the data. The number needed to treat was between 7 & 14 for treatment over a 3-year period.

Lind M, Bounias I, Olsson M, Gudbjörnsdottir S, et al. Glycaemic control and incidence of heart failure in 20 985 patients with type 1 diabetes: an observational study. Lancet 2011; published online June 25.

Loke Yoon Kong, Kwok Chun Shing, Singh Sonal. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 342:doi:10.1136/bmj.d1309

Look AHEAD Group. Long-term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals With Type 2 Diabetes Mellitus: Four-Year Results of the Look AHEAD Trial. Arch Intern Med. 2010;170(17):1566-1575.

Luoto R, Kinnunen TI, Aittasalo M, Kolu P, Raitanen J, et al. (2011) Primary Prevention of Gestational Diabetes Mellitus and Large-for-Gestational-Age Newborns by Lifestyle Counseling: A Cluster-Randomized Controlled Trial. PLoS Med 8(5): e1001036. doi:10.1371/journal.pmed.1001036

Montori V, Fernandez-Balsells M. Glycemic Control in Type 2 Diabetes: Time for an Evidence-Based About Face? Ann Int Med 2009; 150(11). Available at: http://www.annals.org/cgi/content/full/0000605-200906020-00118v1 on 2009 Apr 21.

Mozaffarian D, Kamineni A, Carnethon M, et al. Lifestyle risk factors and new-onset diabetes mellitus in older adults. Arch Intern Med 2009; 169:798-807.

Perreault L, Pan Q, Mather KJ, et al., for the Diabetes Prevention Program Research Group. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. Lancet 2012; online June 9.

Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet 2009; 373: 1765-72.

Reis JP, Loria CM, Sorlie PD, et al. Lifestyle factors and risk for new-onset diabetes: a population-based cohort study. Ann Intern Med. 2011 Sep 6;155(5):292-9.

Rosenstock J, Klaff LJ, Schwartz S, et al. Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Prediabetes. Diabetes Care. 2010 Mar 23. n=152 over 24weeks.

Saito T, Watanabe M, Nishida J, et al; Zensharen Study for Prevention of Lifestyle Diseases Group. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med. 2011;171(15):1352-1360.

Saitz R. How Much Evidence Do We Need to Change Practices in Which We Firmly Believe? Enough already! Randomized trials show that tight glucose control in patients with long-standing type 2 diabetes isn't beneficial. *http://general-medicine.jwatch.org/cgi/content/full/2009/730/1#R9*

Shurraw S, Hemmelgarn B, Lin M, et al; for the Alberta Kidney Disease Network. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. Arch Intern Med. 2011;171(21):1920-1927.

Tocci G, Paneni F, Palano F, et al. Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers and Diabetes: A Meta-Analysis of Placebo-Controlled Clinical Trials. Am J Hypertens. 2011 May;24(5):582-90.

TODAY Study Group. A clinical trial to maintain *glycemic control in youth* with type 2 diabetes. N Engl J Med 2012.

Zinman B, Harris SB, Gerstein HC, Young TK, Raboud JM, Neuman J, Hanley AJ. Preventing type 2 diabetes using combination therapy: design and methods of the CAnadian Normoglycaemia Outcomes Evaluation (CANOE) trial. Diabetes Obes Metab. 2006 Sep;8(5):531-7.

Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone & metformin to prevent type 2 diabetes mellitus (CANOE): A double-blind randomised controlled study. Lancet 2010; DOI: 10.1016/S0140-6736(10)60746-5.

TOP

[10] Rolla A. Pharmacokinetic and pharmacodynamic advantages of insulin analogues and premixed insulin analogues over human insulins: impact on efficacy and safety. Am J Med. 2008 Jun;121(6 Suppl):S9-S19.
[11] Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA, Robertson LI. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. Diabet Med. 2007 Jun;24(6):635-42.
[12] Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia. 2008 Mar;51(3):408-16. {582 patients were randomly assigned to supplemental OD detemir (55% went on to require BID dosing) or OD glargine. Improvement in A1c and rates of hypoglycaemia were similar, but OD detemir had less weight gain than glargine (1.6kg difference). In those patients who required BID detemir: the benefit of decreased weight gain was lost and a higher daily dose was required. Average daily dose required was: glargine od 0.4 unit/kg, detemir od 0.52 unit/kg & detemir bid 1 unit/kg (Overall average detemir dose 0.78 unit/kg). More discontinuations occurred due to injection site reactions with detemir (4.5% vs 1.4%.}
[13] Derived from CADTH HTA reports: http://cadth.ca/media/compus/reports/compus_Rapid-Acting-Insulin-Analogues-Report_Clinical=Outcomes.pdf ; http://cadth.ca/media/compus/reports/compus_Long-Acting-Insulin-Analogs-Report_Clinical-Outcomes.pdf
[14] COMPUS An economic evaluation of insulin analogues for the treatment of patients with Type1 and Type 2 diabetes Mellitus in Canada. Optimal therapy report 2008;2(4).: http://cadth.ca/media/compus/reports/compus_Economic_IA_Report.pdf
[15] DECODE; Lancet 1999; 354(9179) 617-21.
[16] Tibaldi J. Initiating and intensifying insulin therapy in type 2 diabetes mellitus. Am J Med. 2008 Jun;121(6 Suppl):S20-9.
[17] Odeh M. Oliven A. Bassan H. Transient atrial fibrillation precipitated by hypoglycemia. [Case Reports. Journal Article] Annals of Emergency Medicine. 19(5):565-7, 1990 May.
[18] O'Kane MJ, Bunting B, Copeland M, Coates VE, for the ESMON study group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomized controlled trial. BMJ 2008;336:1174-1177.
[19] Welschen, LMC; Bloemendal, E; Nijpels, G; Dekker, JM; Heine, RJ; Stalman, WAB; Bouter, LM; Welschen, Laura. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin (Cochrane Review). In: The Cochrane Library 2007 Issue 1. Chichester, UK: John Wiley and Sons, Ltd.
[20] *Farmer* A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 2007;335:132.
Gomes, Tara, Juurlink, David N, Shah, Baiju R, et al. Blood glucose test strips: options to reduce usage. CMAJ 2009 0: cmaj.091017.
Cameron, Chris, Coyle, Doug, Ur, Ehud, Klarenbach, Scott. Cost-effectiveness of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin. CMAJ 2009 0: cmaj.090765.
[21] Rohlfing CL, Wiedmeyer HM, Little RR, et al. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and $HbA_{(1c)}$ in the Diabetes Control and Complications Trial. *Diabetes Care* 2002;25(2):275-8.
Kuenen JC, Borg R, Kuik DJ, et al. ADAG Study Group. Does glucose variability influence the relationship between mean plasma glucose and HbA1c levels in type 1 and type 2 diabetic patients? Diabetes Care. 2011 Aug;34(8):1843-7.
[22] Manley SE. Estimated average glucose derived from HbA1c eAG: report from European Association for the Study of Diabetes (EASD), Amsterdam 2007. [Consensus Development Conference. Journal Article] Diabetic Medicine. 25(2):126-8, 2008 Feb.
[23] Seltzer HS. Drug-induced hypoglycemia. A review of 1418 cases. Endocrinol Metab Clin North Am. 1989 Mar;18(1):163-83.
Cryer PE, Axelrod L, Grossman AB, et al.; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.
[24] Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008 Aug 27;300(8):933-44. In critically ill adult patients, tight glucose control is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia.
Arabi YM, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008 Dec;36(12):3190-7.
NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97. Epub 2009 Mar 24. In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.
Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009 Apr 14;180(8):821-7. Epub 2009 Mar 24.
Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. Diabetes Care. 2009 Jul;32(7):1153-7. Hypoglycemia is common in diabetic patients hospitalized in the general ward. Patients with hypoglycemia have increased LOS and higher mortality both during and after admission. Measures should be undertaken to decrease the frequency of hypoglycemia in this high-risk patient population.
Van den Berghe G, Mesotten D, Vanhorebeek I. Intensive insulin therapy in the intensive care unit. CMAJ. 2009 Apr 14;180(8):799-800. Epub 2009 Mar 24.
COIITSS Study Investigators, Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA. 2010 Jan 27;303(4):341-8.
Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. Chest. 2010 Mar;137(3):544-51. Epub 2009 Dec 16.
Zhao YT, Weng CL, Chen ML, et al. Comparison of glucose-insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials. Heart. 2010 Oct;96(20):1622-6.
Kavanagh Brian P, McCowen Karen C, Glycemic Control in the ICU. N Engl J Med 2010; 363:2540-2546.
Kansagara Devan, Fu Rongwei, Freeman Michele, et al. Intensive Insulin Therapy in Hospitalized Patients: A Systematic Review. Ann Intern Med February 15, 2011 154:268-282.
ADA- American Diabetes Association. Standards of Medical Care in Diabetes—2011 Diabetes Care January 2011 34:S11-S61; doi:10.2337/dc11-S011. http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html
Qaseem Amir, Humphrey Linda L., Chou Roger, et al. and for the Clinical Guidelines Committee of the American College of Physicians. Use of Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med February 15, 2011 154:260-267.
Egi M, Finfer S, Bellomo R. Glycemic control in the ICU. Chest. 2011 Jul;140(1):212-20.
Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol 2012; 97:16-38.
Senthinathan A, Kelly V, Dzingina M et al. Hyperglycaemia in acute coronary syndromes: summary of NICE guidance. BMJ. 2011 Oct 26;343:d6646.

[25] Dr. H. Gerstein, oral presentation to family physicians, nurse practitioners, nurses, and pharmacists, Burlington, Ontario, May 2008. (see also CPS: Avandia & Actos)
[26] Building Competency in Diabetes Education: Advancing Practice
[27] Addapted in part from: http://www.calgaryhealthregion.ca/healthinfo/library/pdf/ProceduresTreatments/606288_Diet_and_Insulin_Adjustment_For_Medical_Procedures_2004-08.pdf; http://findarticles.com/p/articles/mi_m0MDR/is_4_9/ai_n13784023 ; http://www.massgeneral.org/GASTROENTEROLOGY/docs/Prep_Colon_Fleet.pdf ; http://www.med.umich.edu/1libr/aha/umegd.htm
Pharmacist's Letter. Fasting in the Patient with Diabetes. July 2011.
[28] Wilson RD, Johnson JA, Wyatt P, Allen V, Gagnon A, Langlois S, Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada and The Motherrisk Program. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2007 Dec;29(12):1003-26.

CKS-NHS-UK – Link: http://www.cks.library.nhs.uk/diabetes_type_2

Additional references (Post Nov 2008):

[29] Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and Risks of Oral Diabetes Agents Compared With Insulin in Women With Gestational Diabetes: A Systematic Review. Obstet Gynecol. 2009 Jan;113(1):193-205. No substantial maternal or neonatal outcome differences were found with the use of glyburide or metformin compared with use of insulin in women with GDM.
[30] Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008 May 8;358(19):2003-15. In women with gestational

TOP

diabetes mellitus, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment.

[31] BWH: Managing Diabetes in Hospitalized Patients: http://www.brighamandwomens.org/pharmacoepid/Research/EduMaterials/Diabetes%20Management%20in%20Hospitalized%20Pts%20May%202003%20(5).pdf

[32] Insulin Analogues Systematic Review (COMPUS) Jan 2009: http://cadth.ca/media/pdf/compus_IA_OT_rec_report.pdf; http://www.cadth.ca/media/pdf/C1109-Gaps-and-KM-Report-final.pdf;
Economic Review Draft: http://www.cadth.ca/media/pdf/compus_Draft_BGTS_Consolidated_Econ_Report.pdf

[33] Hirsch IB. Sliding scale insulin--time to stop sliding. JAMA. 2009 Jan 14;301(2):213-4.

[34] Singh SR, Ahmad F, Lal A, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180(4):385-97. Online at: http://www.cmaj.ca/cgi/reprint/180/4/385

[35] Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitis. CMAJ 2009;180(4):400-7. http://www.cmaj.ca/cgi/reprint/180/4/400 .

[36] Siebenhofer-Kroitzsch A, Horvath K, Plank J. Insulin analogues: too much noise about small benefits. CMAJ. 2009 Feb 17;180(4):369-70. http://www.cmaj.ca/cgi/reprint/180/4/369

[37] CDR / CEDAC Final Recommendation for Insulin Glulisine (Apidra) – Feb 19, 2009: http://www.cadth.ca/media/cdr/complete/cdr_complete_Apidra_February-19-2009.pdf

ADA-American Diabetes Association Guidelines- Standards of Medical Care in Diabetes—2010 http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html

ADA- American Diabetes Association. Standards of Medical Care in Diabetes—**2011** Diabetes Care January 2011 34:S11-S61; doi:10.2337/dc11-S011. http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html

ACCORD Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4 year follow up of glycemic treatment in the ACCORD. Diabetes Care 2010; 33:983-990.

Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD003395.

Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009 May 23;373(9677):1773-1779.

Bihan H, Fysekidis M, Harbuz V, Reach G, Cohen R. False-positive blood glucose and ketone values with lightening cream. Ann Intern Med. 2011 Nov 1;155(9):649.

Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909, (Published 8 Jan 2010)

Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA1c in insulin-treated diabetes (MITRE Study). . Diabet. Med. 2009 May;26:540–7.

Donner T, Muñoz M. Update on insulin therapy for type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1405-13.

FDA Aug/09 Patients with diabetes who take therapeutic products containing nonglucose sugars (e.g., peritoneal dialysis solution and some immunoglobulins) can have falsely elevated readings from blood glucose test strips that use glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) technology, according to an FDA public health notification. The strips are in wide use, and we have provided a link to a listing of the affected products. The FDA cites 13 deaths associated with hypoglycemia not detected by the test strips, which cannot distinguish between lucose and other sugars such as maltose and xylose. Ten patients were receiving icodextrin peritoneal dialysis solution. The FDA advises physicians to avoid using GDH-PQQ test strips in health care facilities and to rely, instead, on laboratory assays of glucose — especially in patients taking the therapeutic products listed in the alert. Interfering products containing nonglucose sugars include icodextrin peritoneal dialysis solution, certain immunoglobulins, abatacept (Orencia, Bristol-Myers Squibb), tositumomab (Bexxar, GlaxoSmithKline), and any product containing or metabolized into maltose, galactose, or xylose. Several test strips and associated monitors use GDH-PQQ methodology: *ACCU-CHEK* (Roche), *FreeStyle* (Abbott Diabetes Care), *TRUEtest* (Home Diagnostics), *CoZmonitor* blood glucose module (for use with the *Deltec Cozmo* insulin pump, Smiths Medical MD), and *OmniPod* insulin management system (Insulet).

Frid A, Hirsch L, Gaspar R, et al. Scientific Advisory Board for the Third Injection Technique Workshop. New injection recommendations for patients with diabetes. Diabetes Metab. 2010 Sep;36 Suppl 1:S3-18.

Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Curr Med Res Opin. 2010 Jun;26(6):1519-30.

Giovannucci, Edward, Harlan, David M., Archer, Michael C., et al. Diabetes and Cancer: A Consensus Report. CA Cancer J Clin 2010 0: caac.20078.

Goldenberg RM, Cheng AYY, Punthakee Z, Clement M. CDA Position statement: use of glycated hemoglobin (A1C) in the diagnosis of type 2 diabetes mellitus in adults. Can J Diabetes 2011;35:247-9.

Hardikar PS, Joshi SM, Bhat DS, et al. Spuriously high prevalence of prediabetes diagnosed by HbA(1c) in young indians partly explained by hematological factors and iron deficiency anemia. Diabetes Care. 2012 Apr;35(4):797-802.

Hamaty M. Insulin treatment for type 2 diabetes: When to start, which to use. Cleveland Clinic Journal of Medicine 2011; 78(5):332-342; doi:10.3949/ccjm.78a.10051.

Hofman PL, Behrensdorf Derraik JG, et al. Defining the ideal injection techniques when using 5-mm needles in children and adults. Diabetes Care. 2010 Jun 28.

Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, et al.; the 4-T Study Group. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. (4T) N Engl J Med. 2007 Sep 21; [Epub ahead of print] A single analogue-insulin formulation added to metformin and sulfonylurea resulted in a glycated hemoglobin level of 6.5% or less in a minority of patients at 1 year. The addition of biphasic or prandial insulin aspart reduced levels more than the addition of basal insulin detemir but were associated with greater risks of hypoglycemia and weight gain. (InfoPOEMs: Patients choosing biphasic or prandial insulin regiments should be prepared to gain approximately 10 pounds to 12 pounds and expect 4 to 8 moderate or severe episodes of hypoglycemia per year. Basal insulin was a bit less effective as measured by the change in glycated hemoglobin (Hb A1C), but resulted in less weight gain & much less hypoglycemia. Of course, we don't know whether any of these regiments improve long-term clinical outcomes in these patients. If you are going to add insulin for a patient with poorly controlled Type 2 diabetes, it makes sense to start with a single dose of basal insulin for most patients, and to focus primarily on those patients with an initial Hb A1C of more than 8.5%. (LOE = 1b))

Holman, Rury R., Farmer, Andrew J., Davies, Melanie J., et al. the 4-T Study Group, Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes.N Engl J Med 2009 0: NEJMoa0905479. Patients who added a basal or prandial insulin-based regimen to oral therapy had better glycated hemoglobin control than patients who added a biphasic insulin-based regimen. Fewer hypoglycemic episodes and less weight gain occurred in patients adding basal insulin.

Hovorka R, Kumareswaran K, Harris J, Allen JM, Elleri D, Xing D, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. BMJ 2011;342:1855.

Ijas H, Vaarasmaki M, Morin-Papunen L, et al. Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. BJOG. 2011 Jun;118(7):880-5.

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study JDRF Group, Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76. Epub 2008 Sep 8.

Korownyk C, Ivers N, Allan GM. Strategies for initiating insulin in type 2 diabetes. Can Fam Physician. 2011 May;57(5):562.

Lee JM, Wu EL, Tarini B, et al. Diagnosis of diabetes using hemoglobin A1c: should recommendations in adults be extrapolated to adolescents?. J Pediatr. 2011 Jun;158(6):947-952.e1-3.

Lu ZX, Walker KZ, O'Dea K, Sikaris KA, Shaw JE. A1C for screening and diagnosis of type 2 diabetes in routine clinical practice. Diabetes Care. 2010 Apr;33(4):817-9. Epub 2010 Jan 12.

Malanda UL, Welschen LM, Riphagen II, et al. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database Syst Rev. 2012 Jan 18;1:CD005060. From this review, we conclude that when diabetes duration is over one year, the overall effect of self-monitoring of blood glucose on glycaemic control in patients with type 2 diabetes who are not using insulin is small up to six months after initiation and subsides after 12 months. Furthermore, based on a best-evidence synthesis, there is no evidence that SMBG affects patient satisfaction, general well-being or general health-related quality of life. More research is needed to explore the psychological impact of SMBG and its impact on diabetes specific quality of life and well-being, as well as the impact of SMBG on hypoglycaemia and diabetic complications.

Mann DM, Carson AP, Shimbo D, Fonseca V, Fox CS, Muntner P. Impact of A1C screening criterion on the diagnosis of pre-diabetes among U.S. adults. Diabetes Care. 2010 Oct;33(10):2190-5.

Miller ME, Bonds DE, Gerstein HC, et al. ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010 Jan 8;340:b5444. doi: 10.1136/bmj.b5444.

Montori VM, Fernández-Balsells M. Glycemic Control in Type 2 Diabetes: Time for an Evidence-Based About-Face?. Ann Intern Med. 2009 Apr 20.

TOP

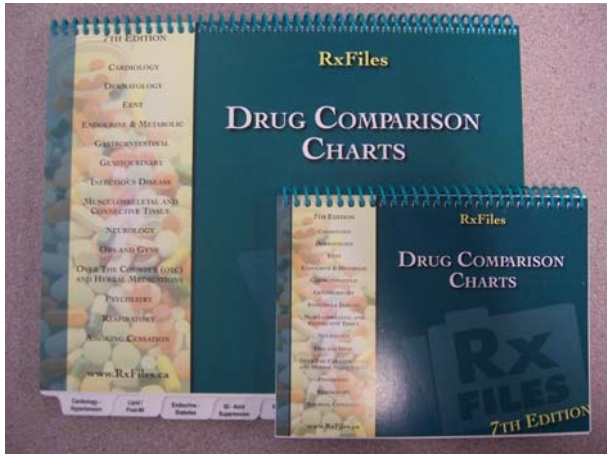
Nau KC. Lorenzetti RC, Cucuzzela M et al. Glycemic control in Hospitalized Patents not in Intensive Care: Beyond Sliding Scale. American Family Pysician. May 1, 2010.
Newman SP, Cooke D, Casbard A, et al. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technol Assess. 2009 May;13(28):iii-iv, ix-xi, 1-194.
Nowicka P, Santoro N, Liu H, et al. Utility of hemoglobin a1c for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes Care. 2011 Jun;34(6):1306-11.
Olson DE, Rhee MK, Herrick K, et al. Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. Diabetes Care. 2010 Oct;33(10):2184-9.
Petznick A. Insulin management of type 2 diabetes mellitus. Am Fam Physician. 2011 Jul 15;84(2):183-90.
Ramachandran A, Riddle MC, et al. Relationship between A1C and fasting plasma glucose in dysglycemia or type 2 diabetes: an analysis of baseline data from the ORIGIN trial. Diabetes Care. 2012 Apr;35(4):749-53.
Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet 2009; 373: 1765-72.
Nau KC. Lorenzetti RC, Cucuzzela M et al. Glycemic control in Hospitalized Patents not in Intensive Care: Beyond Sliding Scale. American Family Pysician. May 1, 2010.
Sawin G, Shaughnessy AF. Glucose control in Hospitalized Patients. American Family Pysician. May 1, 2010.
Selvin E, Steffes MW, Gregg E, et al. Performance of A1C for the classification and prediction of diabetes. Diabetes Care. 2011 Jan;34(1):84-9.
Serlin D., et al. Diagnosis and Management of Gestational Diabetes Mellitus. Am Fam Physician. 2009; 80 (1):57-62.
Silverman RA, Thakker U, Ellman T, et al. Hemoglobin A1c as a screen for previously undiagnosed prediabetes and diabetes in an acute-care setting. Diabetes Care. 2011 Sep;34(9):1908-12.
Umpierez GE, How to manage type 2 diabetes in medical and surgical patients in the hospital. Cleveland Clinic Journal of Medicine 2011; 78(6):379-384; doi:10.3949/ccjm.78gr.11001.
Waugh N, Royle P, Clar C, et al. Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee. Health Technol Assess. 2010 Sep;14(45):1-183. The evidence base has improved since the last HTA review in 2002. There is now good evidence for treatment of oral drugs instead of insulin and it looks increasingly as if FPG could be the test of choice.
Wilson Jennifer F. In the Clinic: Diabetic Ketoacidosis. Ann Intern Med January 5, 2010 152:ITC1-1; doi:10.1059/0003-4819-152-1-201001050-01001.
Yu CH. "Safety" technology: a hidden cause of diabetic ketoacidosis. CMAJ. 2012 Mar 20;184(5):557-8.

Yuqian Bao, Xiaojing Ma, Huating Li et al. Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross sectional epidemiological survey; BMJ 2010;340.

Zhou X, Pang Z, Gao W, et al. Performance of an A1C and Fasting Capillary Blood Glucose Test for Screening Newly Diagnosed Diabetes and Pre-Diabetes Defined by an Oral Glucose Tolerance Test in Qingdao, China. Diabetes Care. 2010 Mar;33(3):545-50. Epub 2009 Dec 10.
Ziemer David C., Kolm Paul, Weintraub William S. et al. Glucose-Independent, Black–White Differences in Hemoglobin A1c Levels: A Cross-sectional Analysis of 2 Studies. Ann Intern Med June 15, 2010 152:770-777.

Glargine (Lantus) & Cancer: FDA evaluating possible association with increased cancer (July 2009). {based on data from 3 of 4 observational trials.} http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169722.htm;

Related links: http://www.medscape.com/viewarticle/705198?src=mp&spon=34&uac=93517FV ; http://www.nationalpost.com/life/health/story.html?id=4578946f-1f50-426e-b92a-bc0f7dd86eed ; http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_115-eng.php ;
http://www.endo-society.org/advocacy/policy/upload/Statement-for-Patients-on-Insulin-Glargine.pdf
Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009 Jul 2. [Epub ahead of print]
Giovannucci, Edward, Harlan, David M., Archer, Michael C., et al. Diabetes and Cancer: A Consensus Report. CA Cancer J Clin 2010 0: caac.20078.
Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia. 2009 Jun 30. [Epub ahead of print]
Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdóttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia. 2009 Jul 9. [Epub ahead of print]



www.RxFiles.ca

TOP

References
1) Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; 364 (9435): 685-96.
2) Collins R, Armitage J, Parish S, Sleigh P, Peto R. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005–2016.
3) Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with Type 2 Diabetes. Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm. (ASCOT-LLA) *Diabetes Care* 2005; 28: 1151-1157.
4) Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006;29:1478-85.
5) The ALLHAT Officers & Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; 288: 2998-3007.
6) Shepherd J, Cobbe SM, Ford I, et al. Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia. *NEJM* 1995; 333 (20): 1301-7.
7) Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279: 1615-22.
8) Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360: 1623-30.
9) Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomised controlled trial. *Lancet* 2006; 368: 1155-63.
10) Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008; 371: 117-125.
11) Vijan S, Hayward RA. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. *Ann Intern Med* 2004; 140: 650-658.
12) Dalhousie University - Academic Detailing Service. Statins and Cardiovascular Disease. April 2005. Available from: http://cme.medicine.dal.ca/files/statins.pdf. Accessed on: June 11, 2011.
13) Atorvastatin reduced major cardiovascular disease events in type 2 diabetes mellitus. *ACP Journal Club* 2005; 142(2): 29.
14) Hackam DG. Should a statin be routinely prescribed for primary prevention of cardiovascular disease in diabetes mellitus? *CMAJ* 2004; 171(8): 857.
15) Garg A. Statins for all patients with type 2 diabetes: not so soon. *Lancet* 2004; 364 (9435): 641-642.
16) Costa J, Borges M, David C, Carneiro AV. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006; doi: 10.1136/bmj.38793.468449.AE.
17) Koskinen P, Manttari M, Manninen V, et al. Coronary Heart Disease Incidence in NIDDM Patients in the Helsinki Heart Study. *Diabetes Care* 1992; 15(7): 820-825.
18) DeBerardis G, Sacco M, Strippoli GFM, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomized controlled trials. *BMJ* 2009; doi:10.1136/bmjb4531.
19) NHS. Regional Drug and Therapeutics Centre – Drug Update. Aspirin for primary prevention of cardiovascular disease. July 2010, No. 65. Available from: http://www.nyrdtc.nhs.uk/docs/dud/DU_65_Aspirin.pdf Accessed on: June 12, 2011.
20) Zhang C, Sun A, Zhang P, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. *Diabetes Research and Clinical Practice* 2010; 87: 211-218.
21) Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 375: 735-42.
22) Statin use increases risk for diabetes. ACP Journal Club 2010; 152(6): JC6-7.
23) Coleman CI, Reinhart K, Kluger J, White CM. The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomised controlled trials. *Curr Med Res Opin* 2008; 24: 1359-62.
24) Ogawa H, Nakayama M, Morimoto T, et al. Low dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes. *JAMA* 2008;300:2134-41.
25) Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ.* 2008; 337:a1840.
26) Fitchett D and Kraw M. Vascular Protection in People with Diabetes. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008; 32(Suppl 1):S102–S106.
27) Bell AD, Roussin A, Cartier R, et al. The Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society Guidelines. *Canadian Journal of Cardiology* 2011; 27: S1-S59.
28) ADA- American Diabetes Association. Standards of Medical Care in Diabetes—2011 Diabetes Care. January 2011 34:S11-S61; doi:10.2337/dc11-S011. http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html
29) Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes. A position statement of the American Diabetes Association, American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Circulation* 2010; 121: 2694-2701.
30) Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011 Jun 22;305(24):2556-64.
31) Mogensen CE, Neldam S, Tikkanen I, Oren S, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000;321:1440-4.
32) Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007 Sep 8;370(9590):829-40.
33) Weber MA, Bakris GL, Jamerson K, et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol* 2010; 56: 77-85.
34) Whelton PK, Barzilay J, Cushman WC, et al. ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia:Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005;165:1401-1409.
35) Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002; 324: 71-86.
36)Antithrombotic Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849-60.
37) Benazepril plus amlodipine reduced cardiovascular events more than benazepril plus hydrochlorothiazide with or without diabetes. *ACP Journal Club* 2010; 153(4).
38) ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med. 2010 Mar 14.
39) ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *N Engl J Med*. 2010 Mar 18. Supplement App: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1001282/suppl_file/nejm_accord_1563sa1.pdf
40) Allan GM, Ivers N, and McCormack J. Type 2 diabetes and ASA. Tools for Practice. *Canadian Family Physician.* 2010; 56: 664.
41) Vijan S and Hayward R. Treatment of Hypertension in Type 2 Diabetes Mellitus: Blood pressure goals, choice of agents and setting priorities in diabetes care. *Ann Intern Med.* 2003;138:593-602.
42) Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755-62.
43) UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.
44) UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713-20.
45) Cooper-DeHoff RM, Gong Y, Handberg EM et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary heart disease. JAMA. 2010; Jul 7; 304(1): 61-8.
46) Issues in Hypertension 2011, Dalhousie CME Academic Detailing Service, June 2011, http://cme.medicine.dal.ca/ad_resources.htm
47) Grossman E, Messerli FH, Goldbourt U. High blood pressure and DM: are all antihypertensives created equal? *Arch Intern Med.* 2000; 160(16): 2447-52.
48) Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med.* 2005; 165(12): 1410-9.
49) Balamuthusamy S, Molnar J, Adigopula S, Arora R. Comparative analysis of beta-blockers with other antihypertensive agents on cardiovascular outcomes in hypertensive patients with diabetes mellitus: a systematic review and meta-analysis. *Am J Ther.* 2009; 16(2): 133-142.
50) Yusuf S, Teo KK, Pogue J, et al for the ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008: 358:1547-155.
Mancia G, Schumacher H, Redon J, et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). Circulation. 2011;124:1727–1736.
51) Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009 Nov;27(11):2121-58.
52) Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006 Jun 20;144(12):884-93.
53) Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens. 2011 Jul;29(7):1253-69.
54) Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med. 2012;172 (10):761-769.

Other Resources
Aspirin and/or antioxidants did not prevent CV events in diabetes and peripheral arterial disease. *ACP Journal Club* 2009; 150(1).
Canadian Hypertension Education Program. 2011 CHEP recommendations for the management of hypertension. http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf. Accessed August 28, 2011.
Current evidence shows no overall benefit of aspirin for primary prevention of cardiovascular disease in diabetes. *ACP Journal Club* 2010; 152(4).
Do statins cause diabetes? *Pharmacist's Letter/Prescriber's Letter* 2009; 25(1):250110.
Hypertension treatment in patients with diabetes. In DynaMed [database online]. EBSCO Publishing.http://search.ebscohost.com/login.aspx?direct=true&site=dynamed&id=113862. Updated June 10, 2011. Accessed August 21, 2011.
Kerr E, Lucatorto MA, Holleman R, et al. Monitoring performance for blood pressure management among patients with diabetes mellitus. Arch Intern Med 2012.
Leiter L, Genest J, Harris SB, et al. Dyslipidemia. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008; 32(Suppl 1):S107–S114.
Nicolucci A. Aspirin for primary prevention of cardiovascular events in diabetes. Still an open question. *JAMA* 2008; 300: 2180-1.
Richie DM and McClendon KS. Role of statins for the primary prevention of cardiovascular disease in patients with Type 2 Diabetes Mellitus. *Am J Health-Syst Pharm*. 2007; 64: 1603-10.
Sampson UK, Linton MF, and Fazio S. Are statins diabetogenic? *Current Opinion in Cardiology*. 2011; 26: 342-347.
Snow V, Aronson MD, Hornbake R, et al. Lipid control in the management of Type 2 Diabetes Mellitus: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2004; 140: 644-649.

Extras

- ASCEND (A Study of Cardiovascular Events iN Diabetes) and ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes). These are large, ongoing studies that will enrol up to 15,000 participants with anticipated completion dates of 2011 and 2013, respectively.

ETDRS 5 yrs, n=3,711	T1DM & T2DM plus diabetic retinopathy; ~50% of pts with hx of CV disease <10% hx of MI or stroke	aspirin 2 x 325mg/day vs placebo	◆ 1°: all-cause mortality, 12.1 vs 14.9, RR 0.91 [99% CI, 0.75 to 1.11, p=0.24] ◆ 2°: cardiovascular mortality, 9.3 vs 11.2, RR 0.87 [99% CI, 0.7 to 1.1, p=0.12] ◆ 2°: fatal or non-fatal MI, 9.1 vs 12.3, RR 0.83 [99% CI, 0.66 to 1.04] ◆ 2°: fatal or non-fatal stroke, 4.5 vs 3.8, RR 1.17 [99% CI, 0.79 to 1.28] -no evidence of harmful effects of aspirin

ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study Report 14. *JAMA* 1992; 268(10); 1292-1300.

TOP

- From Circulation 2010: Intervention patients experienced a decreased risk of nonfatal or fatal MI (RR 0.85, 95% CI 0.73–1.00). In contrast, stroke occurred more frequently with aspirin, although the difference was not statistically significant (RR 1.18, 99% CI 0.88 –1.58). Men appeared to derive more benefit from aspirin than women for prevention of MI (RR for men 0.74, 99% CI 0.54 –1.00; RR for women 0.91, 99% CI 0.65–1.28), but this difference was not statistically significant and could represent a chance finding.
- From CCS 2011: For the predetermined secondary endpoint of fatal or nonfatal MI, the difference was significant at 5 years (RR 0.72, 99% CI 0.55-0.95) but not at 7 years (RR 0.83, 99% CI 0.66-1.04).

TOP

Extras

NNTs in T2DM - (Standardized for 5 yrs)

- ↓ Mortality: Metformin 2550mg/d in obese NNT=$7_{/5yrs}$ UKPDS-34
- ↑ Mortality: intensive blood glucose control $_{(A1C\ target=6)}$; NNH=$66_{/5yrs}$ ACCORD
- Blood pressure control: ?HOT trial??
- Major CHD Event: Atorvastatin 10mg daily; NNT=$26_{/5yrs}$ CARDS

Additional references:

Bodmer M, Becker C, Meier C et al. Use of Antidiabetic Agents and the Risk of Pancreatic Cancer: A Case-Control Analysis. Am J Gastroenterol. 2012 Jan 31. (metformin reduced risk in women)

Inzucchi SE, Bergenstal RM, Buse JB, et al. **Management of Hyperglycemia in Type 2 Diabetes**: A Patient-Centered Approach: Position Statement of the American Diabetes Association (**ADA**) and the European Association for the Study of Diabetes(**EASD**). Diabetes Care. 2012 Apr 19.

Qaseem A, Humphrey LL, Sweet DE, et al. for the Clinical Guidelines Committee of the American College of Physicians (**ACP**). Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-231.

References

[1] CADTH Reports. Second- and Third-Line Therapy for Patients with Diabetes. Accessed 10 Aug, 2011 at: http://www.cadth.ca/en/products/optimal-use/second-line-therapies

[2] Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.

[3] Canadian Optimal Medication Prescribing & Utilization Service (COMPUS), 2008; Current Topics, Diabetes: http://cadth.ca/index.php/en/compus/current-topics/-dm1 (www.cadth.ca)
{Long-acting IAs: Metaanalysis of Clinical Outcomes: http://cadth.ca/media/compus/reports/compus_Long-Acting-Insulin-Analogs-Report_Clinical-Outcomes.pdf }
{Rapid Acting IAs: Metaanalysis of Clinical Outcomes: http://cadth.ca/media/compus/reports/compus_Rapid-Acting-Insulin-Analogues-Report_Clinical=Outcomes.pdf }
{Optimal Therapy Recommendations for Prescribing and Use of Insulin Analogues: http://cadth.ca/media/pdf/compus_IA_OT_rec_report.pdf Final Report: January 2009}
{Grade Evidence Profiles of Long and Rapid Acting Insulin Analogues: http://cadth.ca/media/compus/reports/compus_GRADE-REPORT.pdf }

[4] Jin M, Regier L, Jensen B.RxFiles Insulin Tips and Pearls Chart. Accessed online Aug 10, 2011 at http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Diabetes-Insulin-ManagmentTool.pdf .

[5] Canadian 2008 Guidelines (Sept 2008): http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
(Bhattacharyya OK, Estey EA, Cheng AY; Canadian Diabetes Association 2008. Update on the Canadian Diabetes Association 2008 clinical practice guidelines. Can Fam Physician. 2009 Jan;55(1):39-43.)

[6] Lalau JD and Race JM. Metformin and lactic acidosis in diabetic humans. Diabetes, Obesity and Metabolism 2000;2:131-137.

[7] Breault R, Regier L, Jensen B. Metformin: Precautions with Renal Impairment, Hepatic Disease and Heart Failure. RxFiles Q&A, Oct 2008. Accessed online at http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Metformin-LacticAcidosis-QandA.pdf

[8] Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med. 2011 Apr 19;154(8):554-9.

[9] Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011 Jul 26;343:d4169. doi: 10.1136/bmj.d4169. Accessed online 15 Aug 2011 at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3144314/?tool=pubmed

[10] UKPDS Risk Engine (University of Oxford). Accessed online Aug 10, 2011at http://www.dtu.ox.ac.uk/riskengine/ .

[11] DeBerardis G, Sacco M, Strippoli GF, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009;339:doi:10.1136/bmj.b4531 (Published 6 November 2009).

[12] MDRD: (eGFR)= accurate, but need device with MedCalc to do the calculation. www.hdcn.com www.kidney.org

[13] PL Detail-Document, Treating Microalbuminuria. Pharmacist's Letter/Prescriber's Letter. April 2012.

[14] Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of **renal end points** in type 2 diabetes mellitus: systematic review & meta-analysis. Arch Intern Med. 2012;172 (10):761-769.

[15] J Genest, R McPherson, J Frohlich, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. Can J Cardiol 2009;25(10): 567-579.

[16] ADA. Executive Summary: Standards of medical care in diabetes – 2012. Diabetes Care 2012;35:S4-S10. http://care.diabetesjournals.org/content/35/Supplement_1/S4.full.

[17] Regier L. Bareham J. Jensen B. RxFiles Q&A: Glycemic Targets in the Frail Elderly Q&A. Accessed 06 Mar, 2012 online at http://www.rxfiles.ca/rxfiles/uploads/documents/members/Diabetes-Glucose-Targets-in-Elderly-LTC.pdf.

TOP

Lifestyle Activity Video
23 & ½ hrs 9 min (Link):
http://www.youtube.com/watch?v=aUaInS6HIGo&noredirect=1

References: Weight Loss Agents – COMPARISON CHART – www.RxFiles.ca

[1] Therapeutic Choices 4rd Edition, 2003 , (For Herbal warnings see Health Canada. http://www.hc-sc.gc.ca/dhp-mps/advisories-avis/index_e.html)

[2] Micromedex 2010

[3] Li Z, Maglione M, Tu W, Mojica W,et al. Meta-analysis: pharmacologic treatment of **obesity**. Ann Intern Med. 2005 Apr 5;142(7):532-46. CONCLUSIONS: Sibutramine, orlistat, phentermine, probably diethylpropion, bupropion, probably fluoxetine, and topiramate promote modest weight loss when given along with recommendations for diet. Sibutramine and orlistat are the 2 most-studied drugs. (InfoPOEMs: On the basis of flimsy evidence of benefit, The American College of Physicians recommends drug therapy for the treatment of obesity. They also recommend gastric bypass surgery, performed by an experienced surgeon, for patients with marked obesity and other risk factors for premature death. (LOE = 5))

[4] Jain A. Treating **obesity** in individuals and populations. BMJ. 2005 Dec 10;331(7529):1387-1390.

[5] Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. **Cochrane** Database Syst Rev. 2004;(3):CD004094. REVIEWERS' CONCLUSIONS: Studies evaluating the long-term efficacy of anti-obesity agents are limited to orlistat and sibutramine. Both drugs appear modestly effective in promoting weight loss; however, interpretation is limited by high attrition rates. Longer and more methodologically rigorous studies of anti- obesity drugs that are powered to examine endpoints such as mortality and cardiovascular morbidity are required to fully evaluate any potential benefit of such agents.

[6] Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (**XENDOS**) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004 Jan;27(1):155-61. Erratum in: Diabetes Care. 2004 Mar;27(3):856.

[7] Maahs D, de Serna DG, Kolotkin RL, Ralston S, Sandate J, Qualls C, Schade DS. Randomized, double-blind, placebo-controlled trial of orlistat for weight loss in adolescents.Endocr Pract. 2006 Jan-Feb;12(1):18-28.

[8] Norris SL, Zhang X, Avenell A, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. Arch Intern Med. 2004 Jul 12;164(13):1395-404.

[9] Chanoine JP, Hampl S, Jensen C, et al. Effect of **orlistat** on weight and body composition in obese adolescents. A randomized controlled trial. JAMA 2005;293:2873-83. n=539 54week (InfoPOEMs: Orlistat (Xenical), in combination with diet, exercise, & behavioral modification, improves weight management in obese adolescents. No major safety issues were identified after 1 year, but further follow-up for sustained weight management and safety is important. (LOE = 1b))
(Dunican KC, Desilets AR, Montalbano JK. Pharmacotherapeutic options for overweight adolescents. Ann Pharmacother. 2007 Sep;41(9):1445-55. Epub 2007 Jul 24.)
Rogovik, Alexander L., Goldman, Ran D. Pharmacologic **treatment of pediatric obesity**. Can Fam Physician 2011 57: 195-197.

[10] Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD004096.

[11] Toplak H, Hamann A, Moore R, Masson E, et al. Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind,placebo-controlled study. Int J Obes (Lond). 2006 May 16;epub ahead of print.

[12] Saenz A, Fernandez-Esteban I, Mataix A, et al. Metformin monotherapy for type 2 diabetes mellitus. **Cochrane** Database Syst Rev. 2005 Jul 20;(3):CD002966. CONCLUSIONS: Metformin may be the first therapeutic option in the diabetes mellitus type 2 with overweight or obesity, as it may prevent some vascular complications, and mortality. Metformin produces beneficial changes in glycaemia control, and moderated in weight, lipids, insulinaemia and diastolic blood pressure. Sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, insulin, and diet fail to show more benefit for glycaemia control, body weight, or lipids, than metformin.
Park MH, Kinra S, Ward KJ, et al. Metformin for obesity in children and adolescents: a systematic review. Diabetes Care. 2009 Sep;32(9):1743-5. Epub 2009 Jun 5.

[13] Pharmacist's Letter May 2006: Byetta (**Exenatide**) for **Weight Loss**.

[14] Despres, JP, Golay A, Sjostrom L. Effects of **rimonabant** on metabolic risk factors in overweight patients with dyslipidemia (**Rio-Lipids**). N Engl J Med 2005;353:2121-34. (Weight loss: 6.7kg at 1yr by repeated-measures method)
Pi-Sunyer FX, et al. RIO-North America Study Group. Effect of **rimonabant**, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: **RIO-North America**: a randomized controlled trial. JAMA. 2006 Feb 15;295(7):761-75. In this multicenter trial, treatment with 20 mg/d of rimonabant plus diet for **2 years** promoted modest but sustained reductions in weight and waist circumference and favorable changes in cardiometabolic risk factors. {InfoPOEMs: Rimonabant (Acomplia) is minimally effective for obese or overweight patients for achieving sustained weight loss. Less than half the subjects initially enrolled in this study completed the protocol at 1 year. Of those remaining in the study, only one fourth lost a clinically significant amount of weight (10% or more) and, as with other weight-loss drugs, the patients who stopped taking the medicine after 1 year regained the weight. (LOE = 1b-)
Van Gaal LF, Rissanen AM, Scheen AJ, et al. **RIO-Europe** Study Group. Effects of the cannabinoid-1 receptor blocker **rimonabant** on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet. 2005 Apr 16-22;365(9468):1389-97. Erratum in: Lancet. 2005 Jul 30-Aug 5;366(9483):370. (n=1507, weight loss at 1 year: placebo -1.8kg (±6.4), rimonabant 5mg/d -3.4kg (±5.7), rimonabant 20mg/d -6.6kg (±7.2) (p<0.001). {Medscape article on rimonabant in RIO-Diabetes: http://www.medscape.com/viewarticle/546739_print}
Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007 Nov 17;370(9600):1706-13. Our findings suggest that 20 mg per day rimonabant increases the risk of **psychiatric adverse events**--ie, depressed mood disorders and anxiety-despite depressed mood being an exclusion criterion in these trials. Taken together with the recent US Food and Drug Administration finding of increased risk of suicide during treatment with rimonabant, we recommend increased alertness by physicians to these potentially severe psychiatric adverse reactions. { InfoPOEMs Jan08: These authors searched several databases for double-blind randomized trials of rimonabant for weight loss in patients with a body mass index higher than 30 (27 if the patient also had an obesity-related comorbid condition such as diabetes). Two reviewers independently assessed the quality of the included studies using the Jadad score. The authors don't describe looking for unpublished studies. Four trials (4105 patients) were included in this analysis. After 1 year, patients taking rimonabant lost an average of 4.7 kg more than did those given placebo. Additionally, 25% of patients taking rimonabant lost at least 10% of their baseline weight compared with 7% of control patients (number needed to treat = 5.3; 95% CI, 4.8 - 6). However, patients taking rimonabant were more likely to have unspecified serious adverse events (4% vs 6%; number needed to treat to harm [NNTH] = 58; 95% CI, 33 - 295). Additionally, 3% of patients taking rimonabant developed depression compared with 1.4% of control patients (NNTH = 63; 95% CI, 41-150). Although it's not formally addressed in this study, the authors mention recent Food and Drug Administration reports of increased suicide risk in patients taking rimonabant.}
Topol E, Bousser MG, Fox KA, et al. Rimonabant for prevention of cardiovascular events (**CRESCENDO**): a randomised, multicenter, placebo-controlled trial. Lancet 2010: 376:517-23.

[15] Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial: **lifestyle modification & pharmacotherapy** for obesity. N Engl J Med 2005;353:2111-20. Combo of sibutramine & group lifestyle modifications resulted in more weight loss (**12.1 kg** at 1yr) then either alone.

[16] Berkowitz R., Fujioka K., Daniels SR., et al. Effects of Sibutramine treatment in obese adolescents: a randomized trial. Ann Intern Med 2006; 145(2): 81-90. n=498 1yr

[17] Berkowitz RI, Wadden TA, Tershakovec AM, et al. Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. JAMA. 2003 Apr 9;289(14):1805-12. n=82 RCT 6month, Open label 6month

[18] Wadden, T., Berkowitz, L., Womble, D. et al. Effects of Sibutramine Plus Orlistat in Obese Women Following 1 Year of Treatment by Sibutramine Alone: A Placebo-Controlled Trial. Obesity Research 2000; 8(6): 431-7.

[19] Sari, R., Balci, MK., Cakir, M., et al. Comparison of Efficacy of Sibutramine or Orlistat Versus Their Combination in Obese Women. Endocrine Research 2004; 30(2): 159-167.

[20] Kaya, A., Aydin, N., Topsever, P., et al. Efficacy of Sibutramine, orlistat and combination therapy on short-term weight management in obese patients. Biomedicine & Pharmacotherapy 2004; (58): 582-587.

[21] Coniff RF, Shapiro JA, Seaton TB. Long-term efficacy and safety of acarbose in the treatment of obese subjects with non-insulin-dependent diabetes mellitus. Arch Intern Med. 1994 Nov 14;154(21):2442-8.

[22] Chiasson JL, Josse RG, Gomis R, et al.; **STOP-NIDDM** Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003 Jul 23;290(4):486-94.

[23] Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized controlled trial. (**FINFAT** study) Ann Intern Med 1999;130:389-96.

[24] Jorenby DE, et al.; Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):56-63.

[25] Howard BV, Manson JE, Stefanick ML, Beresford SA, et al. **Low-fat dietary pattern** and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. JAMA. 2006 Jan 4;295(1):39-49.
(InfoPOEMs: Following the long-term recommendations to reduce dietary fat and increase consumption of fruits, vegetables, and whole grains does not cause weight gain among postmenopausal women. (LOE = 2b))

[26] Nordmann AJ, et al. Effects of **low-carbohydrate vs low-fat diets** on weight loss & cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Feb 13;166(3):285-93. (InfoPOEMs: People interested in weight loss can choose either a low-fat, reduced calorie diet or a low-carbohydrate, non-calorie-restricted diet to lose a small but sustained amount of weight. The effect on cardiovascular outcomes of either diet are not known, though each has different effects on lipid levels, which may or may not translate into an actual effect on patient-oriented outcomes that matter. (LOE = 1a))

[27] Strychar I. **Diet** in the management of weight loss. CMAJ. 2006 Jan 3;174(1):56-63.
Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med. 2003 May 22;348(21):2082-90.
Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med. 2004 May 18;140(10):778-85.
Dansinger ML, Gleason JA, et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA. 2005 Jan 5;293(1):43-53.

TOP

Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA. 2007 Mar 7;297(9):969-77. Erratum in: JAMA. 2007 Jul 11;298(2):178.

Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007 Jun;30(6):1374-83. Epub 2007 Mar 15.

Dietary Guidelines for Americans (DGA) 2010. Full Guideline: http://www.health.gov/dietaryguidelines/dga2010/DietaryGuidelines2010.pdf, Summary: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/ExecSumm.pdf

[28] Jakicic JM, Marcus BH, Gallagher KI, Napolitano M, Lang W. Effect of exercise duration and intensity on weight loss in overweight, sedentary women: a randomized trial. JAMA. 2003 Sep 10;290(10):1323-30.

[29] Knowler WC, Barrett-Connor E, Fowler SE et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403.

[30] Ni Mhurchu C, Dunshea-Mooij CAE, Bennett D, Rodgers A. Chitosan for overweight or obesity. *The Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD003892. DOI: 10.1002/14651858.CD003892.pub2

[31] Kleefstra N, et al. Chromium tx has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. Diabetes Care. 2006 Mar;29(3):521-5.

[32] Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. JAMA. 2003 Mar 26;289(12):1537-45. Epub 2003 Mar 10.

[33] Kovacs EM, Lejeune MP, Nijs I, Westerterp-Plantenga MS. Effects of green tea on weight maintenance after body-weight loss. Br J Nutr 2004;91:431-7.

[34] Chantre P, Lairon D. Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. Phytomedicine 2002;9:3-8.

[35] Kuriyama S, Shimazu T, Ohmori K, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 2006;296:1255-1265. InfoPOEMS Nov06: Green tea consumption is associated with reduced cardiovascular & all-cause mortality, but not cancer mortality. Women appear to benefit more than men: Men's mortality was significantly reduced only in those consuming more than 5 cups per day. Furthermore, there appears to be no benefit of green tea consumption in smokers. (LOE = 2b-)

[36] Pittler MH, Ernst E. **Complementary therapies** for reducing body weight: a systematic review. Int J Obes (Lond). 2005 Sep;29(9):1030-8.

[39] Sjostrom L, Narbro K, Sjostrom CD, et al.; Swedish Obese Subjects Study (**SOS**). Effects of **bariatric surgery** on mortality in Swedish obese subjects. N Engl J Med. 2007 Aug 23;357(8):741-52. Bariatric surgery for severe obesity is associated with long-term weight loss and decreased overall mortality.

Sjostrom L, et al.; Swedish Obese Subjects (**SOS**) Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004 Dec 23;351(26):2683-93. After two years, the weight had increased by 0.1 percent in the control group and had decreased by 23.4 percent in the surgery group (P<0.001). After 10 years, the weight had increased by 1.6 percent and decreased by 16.1 percent, respectively (P<0.001). Energy intake was lower and the proportion of physically active subjects higher in the surgery group than in the control group throughout the observation period. Two- and 10-year rates of recovery from diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hypertension, and hyperuricemia were more favorable in the surgery group than in the control group, whereas recovery from hypercholesterolemia did not differ between the groups. The surgery group had lower 2- and 10-year incidence rates of diabetes, hypertriglyceridemia, and hyperuricemia than the control group; differences between the groups in the incidence of hypercholesterolemia and hypertension were undetectable.

Sjöström L et al. Effects of bariatric surgery on **cancer incidence** in obese patients in Sweden (Swedish Obese Subjects Study-**SOS**): A prospective, controlled intervention trial. Lancet Oncol 2009 Jun 24; [e-pub ahead of print].

Sjostrom L, Narbro K, Sjostrom CD, et al. Eff ects of bariatric surgery on mortality in Swedish obese subjects (Swedish Obese Subjects Study-**SOS**). N Engl J Med 2007; 357: 741–52.

Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. (**SOS**) JAMA. 2012;307(1):56-65.

Adams TD, Gress RE, Smith SC, et al. Long-term mortality after **gastric bypass** surgery. N Engl J Med. 2007 Aug 23;357(8):753-61. Long-term total mortality after gastric bypass surgery was significantly reduced, particularly deaths from diabetes, heart disease, and cancer. However, the rate of death from causes other than disease was higher in the surgery group than in the control group.)

Dixon JB, O'Brien PE, Playfair J, et al. Adjustable **gastric banding** and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008 Jan 23;299(3):316-23.

Karmali, Shahzeer, Stoklossa, Carlene Johnson, Sharma, Arya, et al. **Bariatric surgery**: A primer. Can Fam Physician 2010 56: 873-879.

Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Guven S, Spitz AF, Apovian CM, Livingston EH, Brolin R, Sarwer DB, Anderson WA, Dixon J. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical guidelines for clinical practice for the **perioperative nutritional, metabolic, and nonsurgical support** [trunc]. Endocr Pract 2008 Jul-Aug;14 Suppl 1:1-83.

Heber David, Greenway Frank L ., Kaplan L ee M., et al. **Endocrine and Nutritional Management of the Post-Bariatric Surgery Patient**: An Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology & Metabolism, November 2010, 95 (11):4823–4843. http://www.endo-society.org/guidelines/final/upload/FINAL-Standalone-Post-Bariatric-Surgery-Guideline-Color.pdf

IDF: International Diabetes Federation. **Bariatric surgical** and procedural interventions in the treatment of obese patients with type 2 diabetes 2011 http://www.idf.org/webdata/docs/IDF-Position-Statement-Bariatric-Surgery.pdf

Søvik TT, Aasheim ET, Taha O, et al. Weight loss, cardiovascular risk factors, and quality of life after **gastric bypass and duodenal switch**: a randomized trial. Ann Intern Med. 2011 Sep 6;155(5):281-91.

Michalsky M, Kramer RE, Fullmer MA, et al. Developing criteria for **pediatric/adolescent bariatric surgery** programs. Pediatrics 2011;128:Suppl 2:S65-S70

Heneghan HM, Meron-Eldar S, Brethauer SA, et al.Effect of Bariatric Surgery on Cardiovascular Risk Profile. Am J Cardiol. 2011 Aug 29.

Romy S, Donadini A, Giusti V, et al. Gastric Bypass vs Gastric Banding for Morbid Obesity: A Case-Matched Study of 442 Patients. Arch Surg. 2012 Jan 16.

Schroeder R, Garrison JM Jr, Johnson MS. Treatment of adult obesity with bariatric surgery. Am Fam Physician. 2011 Oct 1;84(7):805-14.

Himpens J, Cadière GB, Bazi M, et al. Long-term outcomes of laparoscopic adjustable gastric banding. Arch Surg. 2011 Jul;146(7):802-7.

Mingrone G, Panunzi S, De Gaetano A, et al. **Bariatric surgery versus conventional medical therapy** for type 2 diabetes. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200111.

Schauer PR, Kashyap SR, Wolski K, et al. **Bariatric surgery versus intensive medical therapy** in obese patients with diabetes. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200225.

Leonetti F, et al. Obesity, type 2 diabetes mellitus, and other comorbidities: a prospective cohort study of **laparoscopic sleeve gastrectomy vs medical treatment** [online ahead of print April 16, 2012]. Arch Surg. 2012.

[40] de Gonzalez Amy Berrington, Hartge Patricia, Cerhan James R., et al. Body-Mass Index and Mortality among 1.46 Million White Adults. N Engl J Med 2010; 363:2211-2219.

Additional refs:

AAP: American Academy of Pediatrics: Policy Statement: Children, Adolescents, Obesity, and the **Media**. Council on Communications and Media. Pediatrics 2011; 128:1 201-208; doi:10.1542/peds.2011-1066

ACOG: Bariatric surgery and **pregnancy**. June,2009 http://mail.ny.acog.org/website/SMIPodcast/BariatricSurgery.pdf

Acosta AA et al. Prevalence of **Persistent Prehypertension** in Adolescents. J Pediatr. 2011 Dec 6.

Adams TD, Gress RE, Smith SC, Halverson RC, et al. Long-term mortality after **gastric bypass surgery**. N Engl J Med. 2007 Aug 23;357(8):753-61.

Allison DB, Gadde KM, Timothy W, et al. Controlled-release **phentermine/topiramate** in severely obese adults: A randomized controlled trial (**EQUIP**). Obesity 2011; DOI:10.1038/oby.2011.330.

Alley DE, Chang VW. The changing relationship of **obesity and disability**, 1988-2004. JAMA. 2007 Nov 7;298(17):2020-7. Recent cardiovascular improvements have not been accompanied by reduced disability within the obese older population. Rather, obese participants surveyed during 1999-2004 were more likely to report functional impairments than obese participants surveyed during 1988-1994, and reductions in ADL impairment observed for nonobese older individuals did not occur in those who were obese. Over time, declines in obesity-related mortality, along with a younger age at onset of obesity, could lead to an increased burden of disability within the obese older population.

Alvarez-Blasco F, et al. Prevalence and characteristics of the **polycystic ovary syndrome** in overweight and obese women. Arch Intern Med. 2006 Oct 23;166(19):2081-6.

Anderson JW, et al. **Low-dose orlistat** effects on body weight of mildly to moderately overweight individuals: a 16 week, double-blind, placebo-controlled trial. Ann Pharmacother. 2006 Oct;40(10):1717-23. Epub 2006 Aug 29.

Anderson SE, Gooze RA, Lemeshow S, et al. Quality of early **maternal-child relationship** and risk of adolescent obesity. Pediatrics. 2012 Jan;129(1):132-40.

Apovian CM, et al. Best practice guidelines in **pediatric**/adolescent **weight loss surgery**. Obes Res. 2005 Feb;13(2):274-82.

Apovian CM, Gokce N. **Obesity and cardiovascular** disease. Circulation. 2012 Mar 6;125(9):1178-82.

Appel LJ, Clark JM, Yeh H-C, et al. **Comparative effectiveness** of **weight-loss interventions** in clinical practice. (**POWER**) N Engl J Med 2011. DOI: 10.1056/NEJMoa1108660.

Arslan Alan A.; Helzlsouer Kathy J.; Kooperberg Charles; et al. Anthropometric Measures, Body Mass Index, and **Pancreatic Cancer**: A Pooled Analysis From the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med.

TOP

2010;170(9):791-802.
Bailey Clifford J. The challenge of managing **coexistent type 2 diabetes and obesity**. BMJ 2011;342:doi:10.1136/bmj.d1996 (Published 13 April 2011)
Bajos N et al. **Sexuality and obesity**, a gender perspective: Results from French national random probability survey of sexual behaviours. BMJ 2010 Jun 15; 340:c2573.
Baker JL, Olsen LW, Sørensen TI. **Childhood** body-mass index and the risk of **coronary heart disease** in adulthood. N Engl J Med. 2007 Dec 6;357(23):2329-37.
Bajos N, Wellings K, Laborde C, Moreau C; for the CSF Group. **Sexuality and obesity**, a gender perspective: results from French national random probability survey of sexual behaviours. BMJ 2010;340:c2573.
Baranowski T, Abdelsamad D, Baranowski J et al. Impact of an **Active Video Game** on Healthy Children's Physical Activity. Pediatrics. 2012 Mar;129(3):e636-42.
Barton Garry R, et al. **Lifestyle interventions** for knee pain in overweight and obese adults aged ≥45: economic evaluation of randomised controlled trial. BMJ 2009;339:b2273, doi: 10.1136/bmj.b2273 (Published 18 August 2009)
Bauditz J, Norman K, Biering H, Lochs H, Pirlich M. Severe weight loss caused by chewing gum (**sorbitol**). BMJ. 2008 Jan 12;336(7635):96-7.
Bech BH, Obel C, Henriksen TB, Olsen J. Effect of reducing **caffeine** intake on birth weight and length of gestation: randomised controlled trial. BMJ. 2007 Jan 26; [Epub ahead of print] A moderate reduction in caffeine intake in the second half of pregnancy has no effect on birth weight or length of gestation.
Beets, Michael W., Bornstein, Daniel, Dowda, Marsha, et al. Compliance With National Guidelines for **Physical Activity** in U.S. Preschoolers: Measurement and Interpretation. Pediatrics 2011 127: 658-664.
Beltrand J et al.**Post-Term Birth** is Associated with Greater Risk of Obesity in Adolescent Males. J Pediatr. 2011 Dec 6.
Ben-Menachem E. Weight issues for people with **epilepsy**-A review. Epilepsia. 2007;48 Suppl 9:42-5.
Ben Q, An W, Jiang Y et al. Body Mass Index Increases Risk for **Colorectal Adenomas** Based on Meta-Analysis. Gastroenterology. 2012 Jan 11.
Benedict C et al. **Acute sleep deprivation** enhances the brain's response to hedonic food stimuli: An fMRI study. J Clin Endocrinol Metab 2012 Jan 18.
Bennett WL, Gilson MM, Jamshidi R, et al. Impact of bariatric surgery on **hypertensive** disorders in pregnancy: retrospective analysis of insurance claims data. BMJ 2010;340:c1662, doi: 10.1136/bmj.c1662 (Published 13 April 2010)
Berz JP, Singer MR, Guo X et al. use of a **DASH food group** score to predict excess weight gain in adolescent girls in the National Growth and Health Study. Arch Pediatr Adolesc Med 2011; 165:540-546.
Beyerlein A, Schiessl B, Lack N, et al. Associations of **gestational weight loss** with birth-related outcome: a retrospective cohort study. *BJOG* 2011*;* **118***:* 55– 61.
Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. **Adolescent** overweight and future adult **coronary heart disease**. N Engl J Med. 2007 Dec 6;357(23):2371-9.
Biddiss E, Irwin J. Active **video games** to promote physical activity in children and youth: a systematic review. Arch Pediatr Adolesc Med. 2010;164(7):664-672.
Birkmeyer NJ, Dimick JB, Share D, et al. Michigan Bariatric Surgery Collaborative. Hospital **complication rates with bariatric surgery** in Michigan. JAMA. 2010 Jul 28;304(4):435-42.
Bliddal H, Leeds AR, Stigsgaard L, Astrup A, Christensen R. Weight loss as **treatment for knee osteoarthritis symptoms** in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis. 2011 Oct;70(10):1798-803.
Boggs DA, Rosenberg L, Cozier YC, et al. General and abdominal **obesity and risk of death among black women**. N Engl J Med. 2011 Sep 8;365(10):901-8.
Boone-Heinonen J, Gordon-Larsen P, Kiefe CI, et al. **Fast food restaurants and food stores**: longitudinal associations with diet in young to middle-aged adults: the CARDIA study. *Arch Intern Med*. 2011;171(13):1162-1170.
Bosomworth NJ. The **downside of weight loss**. Realistic intervention in bodyweight trajectory. Can Fam Physician 2012;58: 517-23.
Bouchard C, et al. The response to long-term **overfeeding** in **identical twins**. N Engl J Med. 1990 May 24;322(21):1477-82.
Boyland Emma J., Harrold Joanne A., Kirkham Tim C., et al. **Food Commercials** Increase Preference for Energy-Dense Foods, Particularly in Children Who Watch More Television. Pediatrics 2011; 128:1 e93-e100; ahead of print June 27, 2011.
Bravata DM, Smith-Spangler C, Sundaram V, et al. Using **pedometers** to increase physical activity and health. A systematic review. JAMA 2007; 298:2296-2304.
Bray GA, Smith SR, de Jonge L, et al. Effect of **dietary protein** content on weight gain, energy expenditure, and body composition during overeating: a randomized controlled trial. JAMA. 2012;307(1):47-55.
Bray GA, Ryan DH. **Medical therapy** for the patient with obesity. Circulation. 2012 Apr 3;125(13):1695-703.
Brotman LM, Dawson-McClure S, Huang KY et al. Early Childhood **Family Intervention** and Long-term Obesity Prevention Among High-risk Minority Youth. Pediatrics. 2012 Feb 6.
Burke GL, Bertoni AG, Shea S, et al. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. Arch Intern Med. 2008 May 12;168(9):928-35. These data confirm the epidemic of obesity in most but not all racial and ethnic groups. The observed **low prevalence of obesity in Chinese American** participants indicates that high rates of obesity should not be considered inevitable.
Campos GM, Rabl C, et al. Factors associated with weight loss after **gastric bypass**. Arch Surg. 2008 Sep;143(9):877-883; discussion 884. Gastric bypass results in substantial weight loss in most patients. Diabetes and larger pouch size are independently associated with poor weight loss after GBP.
Canadian Physical Activity Guidelines-Jan 2011. Clinical Practice Guideline Development Report. Canadian Society for Exercise Physiology. http://www.csep.ca/CMFiles/Guidelines/CPAGuideline_Report_JAN2011.pdf
Carter PJ, Taylor BJ, Williams SM, Taylor RW. Longitudinal analysis of **sleep in relation to BMI and body fat in children**: the **FLAME** study. BMJ 2011;342:d2712.
Chakravarty EF, Hubert HB, Lingala VB, Fries JF. **Reduced disability and mortality among aging runners**: a 21-year longitudinal study.Arch Intern Med. 2008 Aug 11;168(15):1638-46. Vigorous exercise (running) at middle and older ages is associated with reduced disability in later life and a notable survival advantage.
Chalasani N et al. The diagnosis and management of **non-alcoholic fatty liver disease (NAFLD):** Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012 Jun; 55:2005.
Chavez-Tapia NC, Tellez-Avila FI, Barrientos-Gutierrez T, Mendez-Sanchez N, Lizardi-Cervera J, Uribe M. **Bariatric surgery for non-alcoholic steatohepatitis** in obese patients. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007340.
Collins, Clare E., Okely, Anthony D., Morgan, Philip J., et al. **Parent Diet Modification, Child Activity**, or Both in Obese Children: An RCT. (at **24 months**) Pediatrics 2011 127: 619-627.
Colman E. **Food and Drug Administration's (FDA) Obesity Drug Guidance** Document: A Short History. Circulation. 2012 May 1;125(17):2156-64.
Colquitt JL, Picot J, Loveman E, Clegg AJ. **Surgery for obesity**. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD003641.
Cornier MA, Deprés JP, Davis N, et al. **Assessing adiposity**: a scientific statement from the American Heart Association (AHA). Circulation2011; DOI: 10.1161/CIR0b013e318233bc6a.
Crume TL, Ogden L, Maligie M, et al. Long-Term Impact of Neonatal **Breastfeeding** on Childhood Adiposity and Fat Distribution Among Children Exposed to Diabetes In Utero. Diabetes Care Mar 2011 34:641-645.
Crume TL, Ogden L, Daniels S, Hamman RF, Norris JM, Dabelea D. The Impact of **In Utero Exposure to Diabetes** on Childhood Body Mass Index Growth Trajectories: The EPOCH Study. J Pediatr. 2011 Jun;158(6):941-6.
Curioni C, Andre C. **Rimonabant** for overweight or obesity. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006162. Compared with placebo, rimonabant 20 mg produced a 4.9 kg greater reduction in body weight in trials with one-year results. The use of rimonabant after one year produces modest weight loss of approximately 5%. Even modest amounts of weight loss may be potentially beneficial. The observed results should be interpreted with some caution, though, since the evaluated studies presented some deficiencies in methodological quality. Studies with longer follow-ups after the end of treatment and of more rigorous quality should be done before definitive recommendations can be made regarding the role of this new medication in the management of overweight or obese patients.
Dansinger ML, Gleason JA, Griffith JL, Selker JP, Schaefer EJ. **Comparison of the Atkins, Ornish, Weight Watchers, and Zone** diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 2005;293:43-53.
Davies GA, Maxwell C, McLeod L, et al., Society of Obstetricians and Gynaecologists of Canada. **Obesity in pregnancy**. (**SOGC**) J Obstet Gynaecol Can 2010 Feb;32(2):165-73.
de Boer IH, Katz R, Fried LF, et al. Obesity and change in **estimated GFR** among older adults. Am J Kidney Dis. 2009 Dec;54(6):1043-51. Epub 2009 Sep 25.
De Jong A, Jung B, Chanques G, et al. **Obesity and mortality in critically ill patients**: another case of the simpson paradox? Chest. 2012 Jun;141(6):1637-8.
DeMaria EJ. **Bariatric surgery** for morbid obesity. N Engl J Med. 2007 May 24;356(21):2176-83.
Dennis EA, Dengo AL, Comber DL, et al. **Water consumption** increases weight loss during a hypocaloric diet intervention in middle-aged and older adults. Obesity (Silver Spring). 2010 Feb;18(2):300-7. Epub 2009 Aug 6.
Desilets A, Dhakal-Karki S, Dunican K. Role of metformin for weight management in patients without type 2 diabetes. Ann Pharmacother 2008;42:817-26.
Dhingra R, Sullivan L, Jacques PF, et al. **Soft drink consumption** & risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation 2007; DOI: 0.1161/circulationaha.107.689935.
Dietary Guidelines for Americans (DGA) 2010. Full Guideline: http://www.health.gov/dietaryguidelines/dga2010/DietaryGuidelines2010.pdf, Summary: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/ExecSumm.pdf
Dixon JB, O'Brien PE, Playfair J, et al. Adjustable **gastric banding** and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008 Jan 23;299(3):316-23. Participants randomized to surgical therapy were more likely to achieve remission of type 2 diabetes through greater weight loss.

TOP

Dixon JB, le Roux CW, Rubino F, Zimmet P. **Bariatric surgery** for **type 2 diabetes**. Lancet. 2012 Jun 8.

Dodd JM, Grivell RM, Crowther CA, Robinson JS. Antenatal interventions for **overweight or obese pregnant women**: a systematic review of randomised trials. BJOG. 2010 Oct;117(11):1316-26. This meta-analysis of randomized trials of antenatal dietary or exercise interventions for overweight or obese pregnant women identified no credible improvement in outcomes for the mothers or their newborns. (LOE = 1a-)

Drugs Associated with weight gain. Pharmacist's Letter Mar 2007.

Duffey Kiyah J.; Gordon-Larsen Penny; Shikany James M.; et al. **Food Price and Diet** and Health Outcomes: 20 Years of the CARDIA Study. Arch Intern Med. 2010;170(5):420-426.

Dumanovsky T, Huang CY, Nonas CA, et al. **Changes in energy content of lunchtime purchases from fast food** restaurants after introduction of **calorie labelling**: cross sectional customer surveys. BMJ 2011;343:d4464.

Dushay J, Gao C, Gopalakrishnan GS, et al. Short-term **exenatide** treatment leads to significant weight loss in a subset of obese women without diabetes. Diabetes Care. 2012 Jan;35(1):4-11.

Eckel RH. Clinical practice. **Nonsurgical management of obesity in adults**. N Engl J Med. 2008 May 1;358(18):1941-50.

Edelman S, et al. A double-blind, placebo-controlled trial assessing **pramlintide** treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care. 2006 Oct;29(10):2189-95.

Eisenberg MJ, Atallah R, Grandi SM, Windle SB, Berry EM. **Legislative approaches** to tackling the obesity epidemic. CMAJ. 2011 May 2.

Eliassen AH, et al. Adult weight change and risk of postmenopausal **breast cancer**. JAMA. 2006 Jul 12;296(2):193-201.

Emerging Risk Factors Collaboration. Separate and combined associations of **body-mass index and abdominal adiposity** with cardiovascular disease: collaborative analysis of 58 prospective studies.Lancet 2011;online Mar11/11.

Epstein LH, et al. A randomized trial of the effects of reducing **television viewing and computer use** on body mass index in young children. Arch Pediatr Adolesc Med. 2008 Mar;162(3):239-45. Reducing television viewing and computer use may have an important role in preventing obesity and in lowering BMI in young children, and these changes may be related more to changes in energy intake than to changes in physical activity.

Eriksson MK, Hagberg L, Lindholm L, et al. **Quality of Life and Cost-effectiveness** of a 3-Year Trial of **Lifestyle** Intervention in Primary Health Care. Arch Intern Med. 2010 Sep 13;170(16):1470-9.

Ersoy A, Baran B, Ersoy C, Kahvecioglu S, Akdag I. Calcineurin inhibitors and post-transplant weight gain. Nephrology (Carlton). 2008 Mar 5; [Epub ahead of print] Only pretransplant BMI, creatinine clearance, **cyclosporine A** usage, being hypertensive and dysplipidemic were independent predictors of weight gain at the 12th month. Our results suggested that the type of immunosuppression may affect post-transplant weight gain.

Ervin RS, Kit BK, Carroll MD, Ogden CL. **Consumption of added sugar** among US children and adolescents, 2005-2008. NCHS data brief, 87, March 2012.

Faith MS, Van Horn L, Appel LJ,et al. Evaluating **Parents and Adult Caregivers as "Agents of Change"** for Treating Obese Children: Evidence for Parent Behavior Change Strategies and Research Gaps: A Scientific Statement From the American Heart Association (AHA). Circulation. 2012 Mar 6;125(9):1186-1207.

Fariello RM, Pariz JR, Spaine DM, et al. Association between **obesity and alteration of sperm** DNA integrity and mitochondrial activity. BJU Int. 2012 Feb 2.

Faulkner G, Cohn TA. Pharmacologic and nonpharmacologic strategies for weight gain and metabolic disturbance in patients treated with **antipsychotic** medications. Can J Psychiatry. 2006 Jul;51(8):502-11. Review. Erratum in: Can J Psychiatry. 2006 Aug;51(9):620. Although difficult, the prevention of weight gain and the promotion of weight loss are possible for individuals treated with antipsychotic medications. Further research, including diabetes prevention studies, is required. We suggest a pathway for the management of weight gain and emerging metabolic disturbance.

FDA approves **Orlistat for OTC**, Pharmacist's Letter Mar 2007.

FDA Nov/08 Fashion Sanctuary announced a recall of **Zhen De Shou Fat Loss** Capsules because FDA analysis found the product to contain undeclared sibutramine, an FDA approved drug used as an appetite suppressant for weight loss.

FDA Jan/09 notified consumers not to take Venom **HYPERDRIVE 3.0**, a product sold as a dietary supplement but containing sibutramine.

FDA Mar/09 Herbal **Xenicol** (found to contain cetilistat, an obesity drug not approved in the U.S.) along with **Slimbionic** and **Xsvelten** (both containing sibutramine, a prescription-only weight loss drug) have been added to the list of tainted dietary supplements. There are now **72 products** on the list. http://www.fda.gov/bbs/topics/NEWS/2009/NEW01977.html

FDA Apr/09: **ABC Beauty Supply** & FDA notified consumers and healthcare professionals of a recall of 34 dietary supplement products. FDA lab analyses identified undeclared **sibutramine**, an FDA- approved drug, used as an appetite suppressant for weight loss. http://www.fda.gov/oc/po/firmrecalls/universalabc04_09.html **(34 products listed)**

FDA July/09 notified healthcare professionals that four weight loss dietary supplements sold and marketed by the firm (**Slimbionic, One Weight Loss Pill, SlimDemand Capsules, Botanical Weight Loss**) contain sibutramine.

FDA Aug/09 notified healthcare professionals and patients that it is reviewing new safety information regarding reports of liver-related adverse events in patients taking orlistat. **Orlistat** is marketed in the United States as a prescription product, Xenical, and as an over-the-counter (OTC) product, Alli. Between 1999 and October 2008, 32 reports of serious liver injury, including **6 cases of liver failure**, in patients using orlistat were submitted to FDA's Adverse Event Reporting System. The most commonly reported adverse events described in the 32 reports of serious liver injury were jaundice, weakness, and abdominal pain.

FDA Nov/09 & GMP Herbal Products notified consumers and healthcare professionals of a recall of **Pai You Guo**, a weight loss dietary supplement, due to the presence sibutramine & phenolphthalein **.**

FDA Jan/10 notified consumers and healthcare professionals about a counterfeit and potentially harmful version of **Alli 60 mg capsules** (120 count refill kit). The **counterfeit** version contained the controlled substance sibutramine and did not contain orlistat, the active ingredient.

FDA July/10 analysis of **Que She** found that it contains: fenfluramine – a stimulant drug withdrawn from the U.S. market in 1997 after studies demonstrated that it caused serious heart valve damage, propranolol – a prescription beta blocker drug that can pose a risk to people with bronchial asthma and certain heart conditions, sibutramine – a controlled substance and prescription weight loss drug, sibutramine was the subject of a recent study whose preliminary findings showed an association between sibutramine use and increased risk of heart attack and stroke in patients who have a history of heart disease, & ephedrine – a stimulant drug that is legally marketed over-the-counter for temporary relief of asthma but can pose a risk to people with certain cardiovascular conditions.

FDA Aug/10 lab analysis of **Solo Slim** was found to contain the undeclared drug ingredient Didesmethyl Sibutramine.

FDA July/10 lab analysis of **Slim-30** Herb Supplement distributed by the company was found to contain undeclared N-Desmethyl Sibutramine and traces of Sibutramine.

FDA July/10 lab analysis of this herb supplement, **Joyful Slim** Herb Supplement, was found to contain the undeclared drug, desmethyl sibutramine.

FDA Oct/10 notified consumers that **Slimming Beauty Bitter Orange Slimming Capsules** contain the active pharmaceutical ingredient sibutramine, a prescription-only drug which is a stimulant.

FDA Oct/10 Abbott Laboratories notified healthcare professionals and patients about the **voluntary withdrawal of Meridia (sibutramine)**, from the U.S. market because of clinical trial data indicating an increased risk of heart attack and stroke.

FDA Dec/10 has received multiple reports of adverse events associated with the use of **Fruta Planta**, including several cardiac events and one death. FDA laboratory analysis confirmed that Fruta Planta contains sibutramine.

FDA Jan/11 laboratory analysis confirmed that **Celerite Slimming Capsules** contain sibutramine

FDA Mar/11 lab analysis of **Svelte 30** orange & gray capsules determined that the product contains Sibutramine.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analyses of **Celerite Slimming Tea**: Recall - were found to contain undeclared Sibutramine.

FDA May/11 laboratory analysis confirmed that "**Slim Xtreme Herbal Slimming Capsule**" contains sibutramine.

FDA July/11 is advising consumers not to purchase or use "**Slim Forte Slimming Capsules**," "**Slim Forte Slimming Coffee**," and "**Botanical Slimming Soft Gel & Slim Forte Double Power Slimming Capsules**. FDA laboratory analysis confirmed that these products contain sibutramine.

FDA Dec/11 took joint action against several companies selling over-the-counter **hCG products** that falsely and illegally claim to promote weight loss. Labeled "homeopathic" by the seven companies who received the letters, the products contain human chorionic gonadotropin (hCG), a hormone produced during pregnancy by cells that form the placenta. 1. HCG Diet Direct LLC- HCG Diet Homeopathic Drops, 2. The hCG Drops LLC- Homeopathic HCG, 3. HCG Platinum LLC; RightWay Nutrition- HCG Platinum, HCG Platinum X-30, HCG Platinum X-14, 4. Nutri Fusion Systems LLC- HCG Fusion 30, HCG Fusion 43, 5. www.resetthebody.com; www.theoriginalhcgdrops.com-Homeopathic Original HCG, Homeopathic HCG, 6. Hcg-miracleweightloss.com- HCG Extra Weight Loss Homeopathic Drops, 7. Natural Medical Supply- Alcohol Free hCG Weight Loss Formula.

FDA Feb/12 **Healthy People Co.** notified the public of a recall of the company's dietary supplements sold under the brand names Healthy People Co. FDA lab analysis confirmed the presence of Sibutramine and Tadalafil, making these products unapproved new drugs. (**Mince Belle Dietary Supplement, PERFECT Men Dietary Supplement , EVERLAX Dietary Supplement, EVER Slim Dietary Supplement, Herbal Drink Acai-man Mangosteen Dietary Supplement, EVER SLIM Shake Mix Dietary Supplement**)

TOP

FDA Feb/12 is advising consumers not to purchase or use "**Japan Weight Loss Blue**," a product for weight loss sold on various websites, laboratory analysis confirmed that "Japan Weight Loss Blue" contains sibutramine, analogs of sibutramine, and ephedrine alkaloids.

FDA Apr/12 laboratory analysis confirmed that "**Japan Rapid Weight Loss Diet Pills Yellow**" contains sibutramine and phenolphthalein.

Finkelstein Eric A.; Zhen Chen; Nonnemaker James; et al. Impact of Targeted **Beverage Taxes** on Higher- and Lower-Income Households. Arch Intern Med. 2010;170(22):2028-2034.

Finucane MM, Stevens GA, Cowan MJ. **National, regional, and global trends in body-mass index since 1980**: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011; DOI: 10.1016/S0140-6736(10)62035-5.

Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and Trends in **Obesity Among US Adults, 1999-2008**. JAMA. 2010 Jan 13.

Flegal KM, Carroll MD, Kit BK, Ogden CL. **Prevalence of obesity and trends in the distribution of body mass index** among us adults, 1999-2010. JAMA 2012.

Ford AL, Bergh C, Södersten P, Sabin MA, Hollinghurst S, Hunt LP, Shield JP. Treatment of childhood obesity by **retraining eating behaviour (device)**: randomised controlled trial. BMJ. 2009 Jan 5;340:b5388. doi: 10.1136/bmj.b5388.

Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082-90.

Foster Gary D.; Borradaile Kelley E.; Sanders Mark H.; et al. for the Sleep AHEAD Research Group of the Look AHEAD Research Group. A Randomized Study on the Effect of Weight Loss on Obstructive **Sleep Apnea** Among Obese Patients With Type 2 Diabetes: The Sleep AHEAD Study. Arch Intern Med. 2009;169(17):1619-1626.

Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a **low-carbohydrate versus low-fat diet**: a randomized trial. Ann Intern Med. 2010 Aug 3;153(3):147-57.

Fournier A and Zureik M. Estimate of deaths due to valvular insufficiency attributable to the use of **benfluorex** in France.Pharmacoepidemiol Drug Saf 2012 Franks, Paul W., Hanson, Robert L., Knowler, William C., et al. **Childhood Obesity**, Other Cardiovascular Risk Factors, and Premature Death. N Engl J Med 2010 362: 485-493.

Friel S, Chopra M, Satcher D. Unequal weight: equity oriented **policy responses to the global obesity epidemic**. BMJ. 2007 Dec 15;335(7632):1241-3.

Fröhlich G, Pott W, Albayrak O, et al. Conditions of **Long-term Success in a Lifestyle** Intervention for Overweight and Obese Youths. Pediatrics. 2011 Oct;128(4):e779-85.

Gabbert, Charles, Donohue, Michael, Arnold, John, et al. **Adenovirus 36** and Obesity in Children and Adolescents. Pediatrics 2010 0: peds.2009-3362.

Gadde KM, Allison DB, Ryan DH. Et al. Effects of low-dose, controlled-release, **phentermine plus topiramate** combination on weight and associated comorbidities in overweight and obese adults (**CONQUER**): a randomised, placebo-controlled, phase 3 trial. www.thelancet.com Published online April 11, 2011 DOI:10.1016/S0140-6736(11)60205-5.

Gardner CD, Kiazand A, et al. Comparison of the **Atkins, Zone, Ornish, and LEARN** diets for change in weight and related risk factors among overweight premenopausal women. JAMA 2007;297:969-77. [Erratum, JAMA 2007;298:178.]

Garrel D. Is the treatment of **obesity futile?: NO**. Can Fam Physician. 2012 May;58(5):509-10.

Gesell SB, Tesdahl E, Ruchman E. The Distribution of **Physical Activity in an After-school Friendship Network**. Pediatrics. 2012 May 28.

Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal **gestational diabetes**, birth weight, and adolescent obesity. Pediatrics. 2003 Mar;111(3):e221-6.

Glaser Pediatric Research Network Obesity Study Group. **Metformin** Extended Release Treatment of Adolescent Obesity: A 48-Week Randomized, Double-Blind, Placebo-Controlled Trial With 48-Week Follow-up. Arch Pediatr Adolesc Med. 2010;164(2):116-123.

Gogebakan O, Kohl A, Osterhoff MA, et al. Effects of weight loss and long-term weight maintenance with **diets varying in protein and glycemic index** on cardiovascular risk factors: the Diet, Obesity, and Genes (**DiOGenes**) study, a randomized controlled trial. Circulation. 2011;124:2829 –2838.

Goldschmidt Andrea B., Stein Richard I., Saelens Brian E., et al. Importance of **Early Weight Change** in a Pediatric Weight Management Trial. Pediatrics 2011

Goodpaster Bret H.; DeLany James P.; Otto Amy D.; et al. Effects of **Diet and Physical Activity Interventions** on Weight Loss and Cardiometabolic Risk Factors in Severely Obese Adults: A Randomized Trial. *JAMA*. 2010;0(2010):jama.2010.1505.

Gortmaker SL, Swinburn BA, Levy D, et al. Changing the future of obesity: **science, policy, and action**. Lancet. 2011 Aug 27;378(9793):838-47.

Gould JC. **Bariatric surgery** as a highly effective intervention for diabetes Arch Surg 2012; DOI:10.1001/archsurg.2012.227.

Gray Linsay; Lee I-Min; et al. **Body Weight** in Early and Mid-Adulthood in Relation to Subsequent Coronary Heart Disease Mortality**: 80-Year Follow-up** in the Harvard Alumni Study. Arch Intern Med. 2011;171(19):1768-1770.

Grief SN, Miranda RLF. **Weight Loss Maintenance**. Am Fam Physician. 2010 Sep 15;82(6):630-634.

Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of **naltrexone plus bupropion** on weight loss in overweight and obese adults (**COR-I**): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010; DOI:10.1016/S0140-6736(10)60888-4.

Grøntved A, Hu FB. **Television viewing** and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. JAMA. 2011 Jun 15;305(23):2448-55.

Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs : effects on appetite expression and use for the treatment of obesity. Drugs. 2007;67(1):27-55.

Hankinson AL, Daviglus ML, Bouchard C, et al. Maintaining a high **physical activity level over 20 years** and weight gain. JAMA 2010; 304: 2603-2610.

Han JC, Lawlor DA, Kimm SY. **Childhood obesity**. Lancet. 2010 May 15;375(9727):1737-48. Epub 2010 May 5.

Harder T, Roepke K, Diller N, et al. **Birth weight, early weight gain**, and subsequent risk of type 1 **diabetes**: systematic review and meta-analysis. Am J Epidemiol. 2009 Jun 15;169(12):1428-36. Epub 2009 Apr 10. This meta-analysis indicates that high birth weight and increased early weight gain are risk factors for type 1 diabetes.

Harris KC, Kuramoto LK, Schulzer M, et al. Effect of **school-based physical activity interventions** on body mass index in children: a meta-analysis. CMAJ. 2009 Mar 31;180(7):719-26.

Havrankova J. Is the treatment of **obesity futile?: YES**. Can Fam Physician. 2012 May;58(5):508-10.

Hart Carole L, Morrison David S, Batty G David, et al. Effect of **body mass index and alcohol** consumption on **liver disease**: analysis of data from two prospective cohort studies. BMJ 2010

Healton CG, et al. **Smoking, obesity, and their co-occurrence** in the United States: cross sectional analysis. BMJ. 2006 May 12; [Epub ahead of print] 23.5% of adults were obese, 22.7% smoked, and 4.7% smoked and were obese.

Health Canada April 2007: The **Safe Use of Health Products** for Weight Loss. http://www.hc-sc.gc.ca/iyh-vsv/med/weight-amaigr_e.html

Health Canada Apr/07 is warning consumers about **Bitter orange** & cardiovascular reactions in the Canadian Adverse Reactions April 2007 Newsletter.

Health Canada Apr/07 is warning consumers from the Hong Kong Department of Health found **Lexscl Fat Rapid Loss capsules to be adulterated with sibutramine** and thyroid hormones.

Health Canada via July/07 Medsafe also advised the public not to use the product **Dai Dai Hua Jiao Nang** because it was found to contain sibutramine.

Health Canada Aug/07 is advising Canadians of a recall in the United States of one lot of **Metaboslim Apple Cider Vinegar**, which is marketed as a dietary supplement, because it has been found to contain sibutramine, a prescription medication that should only be taken under medical supervision.

Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang**, **J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.

Health Canada Jan/08 is warning Canadians not to use the unauthorized product **Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules** (batch number 28012007 / expiration date: Jan 2009). This product is promoted for weight loss and has been found to contain a derivative of the prescription drug sibutramine.

Health Canada April/08 is advising consumers not to use **Xian Zhi Wei II** was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.

Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Dan Bai Shou Shen Su** was found to contain undeclared thyroid hormones and sibutramine. **Karntien and Karntien Easy to Slim** were adulterated with sibutramine and a compound that is similar in structure to sibutramine (N-desmethylsibutramine). **More Slim** was found to contain the undeclared pharmaceutical ingredient sibutramine. **Soloslim** was found to contain an undeclared substance similar in structure to the prescription drug sibutramine. It also contains the prescription drug L-carnitine, as well as synephrine, which is not authorized for sale in weight loss products in Canada.

Health Canada Aug/08 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of Natural (Xin Yi Dai) and Lasmi because Natural (Xin Yi

TOP

Dai) was found to contain sibutramine and phenolphthalein, and Lasmi was found to contain sibutramine and spironolactone. The Hong Kong Department of Health warned against the use of AA Qu Feng Shu Jin Wan because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. Apisate contained fenfluramine and Energy ll contained sibutramine. Obat Asam Urat and Asam Urat both contained dexamethasone, phenylbutazone and piroxicam. The Hong Kong Department of Health warned against the use of Slim 3in1 (Xiao Nan zhi Bao) because it was found to contain the undeclared pharmaceutical ingredients sibutramine and phenolphthalein.

Health Canada Sep/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of **Hanguo shoushen yihao** (meiti xing) because it was found to contain the undeclared pharmaceutical ingredient sibutramine. The Hong Kong Department of Health warned against the use of **ARMA - Sin Gang San** and New ARMA - Sin Gang San because they were found to contain the undeclared pharmaceutical ingredients sibutramine and fenfluramine.

Health Canada Nov/08 is advising that the Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine.

Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains sibutramine.

Health Canada Mar/09 Foreign Product: **68 Weight Loss Products**; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien & Relacore. Plus Lami, Linglongquxian, Menergy M-Essence, Nyal Day & Night Cold & Flu Fighter (AUST L 146264), Nyal Cold & Flu Fighter (AUST L 146263), 999 Radix Notoginseng, Batch no. 0807021, Slim Pure, Carbohydrate, Kalomee, K Carbohydrate, K Tighten Slim, & K Slimming Pills. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php

Health Canada June/09 Foreign Product Alerts: **Jia Yi Jian** (undeclared sibutramine & tadalafil); **Shan Dian Qiang Xiao Shou** (undeclared sibutramine & phenolphthalein).

Health Canada June/09 is warning consumers not to use the unauthorized product **Slim Magic Herbal**, which is promoted as a weight-loss product, as it was found to contain an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning consumers not to use the unauthorized product **Nutural Slim**, which is promoted as a weight-loss product, as it was found to contain the undeclared pharmaceutical ingredient sibutramine and also an undeclared pharmaceutical ingredient similar to sibutramine.

Health Canada June/09 warns of foreign Product Alerts: ***Herbal Xenicol*** because it contains undeclared cetilistat. ***BioEmagrecim***, which the FDA had previously warned contained sibutramine, was also found to contain fluoxetine, furosemide and fenproporex. Products: ***Slimbionic***, ***Xsvelten***, ***999 Fitness Essence***, ***24" ince***, ***Light Some***, ***Paiyouji***, ***Pearl White Slimming***, & ***Reducing Weight Easily*** contain undeclared pharmaceutical ingredients (sibutramine and/or phenolphthalein) and/or excessive levels of lead, and may cause serious health effects..

Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is warning consumers not to use "**RevolutionDS Weight Loss**", an unauthorized health product promoted for weight loss, because it contains benzylpiperazine (BZP), and may pose serious health risks.

Health Canada Jan/10 informs that U.S. FDA: **Pai You Guo** contains sibutramine and phenolphthalein. Hong Kong Department of Health: **Ku Xiu Ba Xiang Jian Fei Wan** contains sibutramine and an unauthorized substance similar to sibutramine; **Super Slim (Yani)** contains sibutramine and phenolphthalein; **SHoufsy** contains sibutramine & **MIGAC (sic) FAT BURMING (sic) FACTOR** contains sibutramine.

Health Canada Jan/10 is warning consumers not to use the unauthorized product "**The Slimming Coffee**," which was previously sold as "**Lose Weight Coffee**," because it was found to contain sibutramine.

Health Canada Mar/10 is warning Canadians that an unauthorized health product, "**Herbal Diet Natural**" has been found on the Canadian market and contains an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning Canadians that an unauthorized health product, "**West Pharm Therma Lean Fat Burner Energizer**" was found on the Canadian market. West Pharm Therma Lean Fat Burner Energizer contains Ephedrine and caffeine, which combined together, may cause serious and possibly fatal adverse effects.

Health Canada Apr/10 is warning Canadians that an unauthorized health product, "Slim-30" distributed in Ontario and Quebec by Duxx Enterprises Inc., contains an undeclared pharmaceutical ingredient similar to the prescription drug, sibutramine.

Health Canada May/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Ba Bao Xiao Ke Dan** The Hong Kong Department of Health warned consumers not to buy or use Ba Bao Xiao Ke Dan after it was found to contain undeclared glibenclamide. 2. **Seven Slim 7 Seshou** (Qingchun Shaonüxing, Jieshixing, Guifurenxing, Songchixing), Shoushen Jiaoguan-Tinei Yundong Wan (Jian Xiabanshen, Jian Quanshen Feipang) The Hong Kong Department of Health warned consumers not to buy or use the six products listed above after they were found to contain undeclared sibutramine and phenolphthalein.

Health Canada May/10 is advising consumers not to use 1. **Botanical Slimming 100% Natural Soft Gel, also sold as Meizitang** The Australian Therapeutic Goods Administration warned consumers not to buy or use this product after it was found to contain undeclared sibutramine. 2. **Marsha Slim Plus** The Hong Kong Department of Health warned consumers not to buy or use Marsha Slim Plus after it was found to contain undeclared sibutramine, an unauthorized substance similar to sibutramine and phenolphthalein. 3**. S&S Super Slender** The Hong Kong Department of Health warned consumers not to buy or use S&S Super Slender after two samples were found to contain agent similar to sibutramine. One of the tested samples also contained undeclared sibutramine and phenolphthalein.

Health Canada June/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **COMECOO, ZHONGCAOYAO-JIANKANGJIANFEI** The Hong Kong Department of Health warned consumers not to buy or consume these two products after they were found to contain undeclared phenolphthalein, sibutramine and two unauthorized substances similar to sibutramine. 2. **Qingzhi Santian Shou** The Hong Kong Department of Health warned consumers not to buy or consume Qingzhi Santian Shou after it was found to contain undeclared sibutramine and an unauthorized substance similar to sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) 1.. **Po Chai Pills** (capsule form) The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain undeclared sibutramine and phenolphthalein. Sibutramine is a prescription drug and should only be used under the supervision of a health care practitioner while phenolphthalein is no longer authorized for sale in Canada because it may cause cancer. Po Chai Pills (capsule form) has been recalled by the manufacturer. 2. **LiPO-8 Cap and Glucomi 600 Cap** Hong Kong Department of Health warned consumers not to buy or use these products because they contain undeclared sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume *1 Body Beautiful* after it was found to contain undeclared phenolphthalein and sibutramine. 2. **USA Yaku Cell Slimming Capsules, Dong Gua Pai You Su, Qing Gua Pai You Su, and Mu Gua Pai You Su** The Hong Kong Department of Health warned consumers not to buy or consume these four products after they were found to contain undeclared phenolphthalein, sibutramine and an unauthorized substance similar to sibutramine.

Health Canada Aug/10 is advising consumers not to use the following foreign health product(s): **Que She** The U.S. FDA warned consumers not to buy or use Que She after it was found to contain undeclared fenfluramine, propranolol, sibutramine and ephedrine. **Sheng Yuan Fang** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use Sheng Yuan Fang after it was found to contain undeclared phenolphthalein and sibutramine.

Health Canada Sep/10 is advising consumers not to use : **Joyful Slim Herb** Supplement The U.S. FDA informed consumers of a recall of one lot (#101408) of Joyful Slim Herb Supplement after FDA tests found it to contain undeclared desmethyl sibutramine. The lot is being voluntarily recalled nationwide in the U.S. by the company J & H Besta Corp.

Health Canada Oct/10 is informing healthcare practitioners and Canadians that Abbott Laboratories is **voluntarily withdrawing the prescription weight-loss drug sibutramine**, which is marketed as Meridia®, from the Canadian market.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Goya–Bitter Melon - Miyura Fit'x Capsules** contained undeclared phenolphthalein and sibutramine **2. Solo Slim Extra Strength - Revivexxx Extra Strength** contained undeclared didesmethyl sibutramine.

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Slimming Beauty Bitter Orange Slimming Capsule (Slimming Beauty)** The U.S. Food and Drug Administration warned consumers not to buy or use Slimming Beauty after FDA lab tests revealed that this product contains undeclared sibutramine.

TOP

Health Canada Jan/11 The product **Synerate**, manufactured for Strive and distributed by Upper 49th, is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. Synerate, a product used for weight loss or body building, contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Feb/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Fruta Planta, Reduce Weight Fruta Planta** The U.S. FDA warned consumers not to buy or use Fruta Planta and Reduce Weight Fruta Planta after FDA lab tests revealed that this product contains undeclared sibutramine. **2. Slimming Factor** The Australian TGA warned consumers not to buy or use Slimming Factor after TGA lab tests confirmed the presence of the undeclared substances sibutramine, fenfluramine and phenolphthalein. According to the TGA release, the product is sold over the Internet.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Celerite Slimming Capsules**: The U.S. FDA informed consumers of a company recall of CeleriteTM Slimming Capsules after it was found to contain undeclared sibutramine. 2. **Herbal Flos Lonicerae** (Herbal Xenicol) Natural Weight Loss Formula: The product was found to contain undeclared sibutramine at more than twice the dose that was normally prescribed before sibutramine was removed from the UK market in 2010.

Health Canada May/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Dr. Health Series CM Factor** The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain an unauthorized substance similar to sibutramine that may pose similar health risks.

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Slim Xtreme Herbal Slimming Capsules** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *Slim Xtreme Herbal Slimming Capsules* was found to contain undeclared sibutramine.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Celerite Slimming Tea** The U.S. FDA informed consumers of a company recall of Celerite Slimming Tea after it was found to contain undeclared sibutramine. **2. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet. **3. Fifteen products promoted for weight loss** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use these 15 products after they were found to contain at least one of the following undeclared substances: phenolphthalein, sibutramine, and/or an unauthorized substance similar to sibutramine.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **Slim Forte Slimming Capsules**, **Slim Forte Double Power Slimming Capsules**, **Slim Forte Slimming Coffee** and **Meizitang Botanical Slimming Soft Gel**-The U.S. Food and Drug Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **OxyELITE Pro capsules and Pure Fat Three Days Reduce Weight capsules**-The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine), or a prescription drug (yohimbine).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. 1. **Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones). 2. **Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al,** and **Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine). 3. **Slimming Kapsul** The Hong Kong Department of Health warned that this weight-loss product contains an unauthorized drug (sibutramine) and a prescription drug (spironolactone). 4. **Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a prescription drug (glyburide).

Health Canada Jan/12 advises: 1)**17 weight loss products (see Alert for a complete list)** A-Slim 100% Natural Slimming Capsule, Acai Berry Soft Gel ABC, Advanced Slim 5 >DaiDaiHuaJiaoNang, Dream Body Slimming Capsule, Fruit Plant Lossing Fat Capsule, Health Slimming Coffee, Ja Dera 100% Natural Weight Loss Supplement, Leisure 18 Slimming Coffee, Lishou, Magic Slim Tea, Magic Slim Weight Reduction Capsule, P57 Hoodia, Pai You Guo Slim Tea, PhentraBurn Slimming Capsules, Slender Slim 11 Tengda. The U.S. Food and Drug Administration warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Slimina weightloss capsules, S-shape slim capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain prescription drugs (propranolol, nifedipine) and/or unauthorized drugs (sibutramine, fenfluramine, phenolphthalein). **3. Cardiotium, Paidusu, SlimEasy Herbs Capsule, Tianran Zuanshi Xianweisu** The Hong Kong Department of Health warned that these health products contain prescription drugs (losartan, atorvastatin, thyroxine) and/or unauthorized drugs (sibutramine, phenolphthalein).

Health Canada May/12 1. **CanSui; Lexscl Fat Rapid Loss Capsule; The Extreme-thin Fat Burning Bomb; Xiu Zhi Su L-Carnitine Slimming Capsule** The Hong Kong Department of Health warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). 2. **Lipro Diet Pills; Xiyouji Qingzhi** weight loss capsules The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine).

Health Canada June/12 **1. Japan Weight Loss Blue, Japan Rapid Weight Loss Diet Pills Green; Japan Rapid Weight Loss Diet Pills Yellow:** The U.S. Food and Drug Administration warned that these weight loss products contain prescription drugs (sibutramine, ephedrine alkaloids) and unauthorized drugs (phenolphthalein, and substances similar to sibutramine). **2. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil).

HEALTHY Study Group, A **School-Based Intervention** for Diabetes Risk Reduction. N Engl J Med 2010 0: NEJMoa1001933.

Heber David, Greenway Frank L ., Kaplan L ee M., et al. **Endocrine and Nutritional Management of the Post-Bariatric Surgery Patient**: An Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology & Metabolism, November 2010, 95 (11):4823–4843. http://www.endo-society.org/guidelines/final/upload/FINAL-Standalone-Post-Bariatric-Surgery-Guideline-Color.pdf

Henderson DC, et al. A double-blind, placebo-controlled trial of **sibutramine (n=21) for clozapine**-associated weight gain. Acta Psychiatr Scand. 2007 Feb;115(2):101-5. Sibutramine treatment did not show significant weight loss compared with placebo in clozapine-treated patients with schizophrenia or schizoaffective disorder.

Heneghan HM, Meron-Eldar S, Brethauer SA, et al.Effect of **Bariatric Surgery** on Cardiovascular Risk Profile. Am J Cardiol. 2011 Aug 29.

Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood Obesity and Metabolic Imprinting: The Ongoing Effects of Maternal Hyperglycemia. Diabetes Care. 2007 May 22; [Epub ahead of print] Our results in a multi-ethnic US population suggest that increasing **hyperglycemia in pregnancy is associated with an increased risk of childhood obesity**.

Himpens J, Cadière GB, Bazi M, et al. Long-term outcomes of **laparoscopic adjustable gastric banding**. Arch Surg 2011; DOI:10.1001/archsurg.2011.45.

Horvath K, Jeitler K, Siering U, et al. **Long-term effects of weight-reducing interventions in hypertensive patients**. Arch Intern Med 2008; 168:571-580.

Huh, Susanna Y., Rifas-Shiman, Sheryl L., Taveras, Elsie M., et al. Timing of **Solid Food Introduction** and Risk of Obesity in **Preschool-Aged Children**. Pediatrics 2011 0: peds.2010-0740.

IDF: International Diabetes Federation. **Bariatric surgical** and procedural interventions in the treatment of obese patients with type 2 diabetes 2011 http://www.idf.org/webdata/docs/IDF-Position-Statement-Bariatric-Surgery.pdf

Inge TH, Zeller MH, Lawson ML, Daniels SR. A critical appraisal of evidence supporting a **bariatric surgical** approach to weight management for **adolescents**. J Pediatr. 2005 Jul;147(1):10-9.

Institute of Medicine. Accelerating Progress in **Obesity Prevention:** Solving the Weight of the Nation. Washington, DC: National Academies Press, 2012.

Ioannides-Demos LL, Proietto J, McNeil JJ. **Pharmacotherapy** for obesity. Drugs. 2005;65(10):1391-418.

Ioannides-Demos LL, et al. Safety of **drug therapies** used for weight loss and treatment of obesity. Drug Saf. 2006;29(4):277-302.

Jacobs Eric J.; Newton Christina C.; Wang Yiting; et al. **Waist Circumference and All-Cause Mortality** in a Large US Cohort. Arch Intern Med. 2010;170(15):1293-1301.

Jacobson BC, et al. Body-mass index and symptoms of **gastroesophageal** reflux in women. N Engl J Med. 2006 Jun 1;354(22):2340-8.

Jago R, Davison KK, Thompson JL, Page AS, Brockman R, Fox KR. **Parental Sedentary Restriction**, Maternal Parenting Style, and Television Viewing Among 10- to 11-Year-Olds. Pediatrics. 2011 Aug 22.

Jakicic JM, Marcus BH, Lang W, Janney C. Effect of exercise on 24-month weight loss maintenance in overweight women. Arch Intern Med. 2008 Jul 28;168(14):1550-9; discussion 1559-60. The addition of **275 mins/wk of physical activity**, in combination with a reduction in energy intake, is important in allowing overweight women to sustain a weight loss of more than 10%. Interventions to facilitate this level of physical activity are needed.

James WPT, Caterson ID, Coutinho W, et al. Effect of **sibutramine on cardiovascular outcomes** in overweight and obese subjects (**Scout**) . N Engl J Med 2010;363:905-17.

Jebb SA, Ahern AL, Olson AD et al. Primary care referral to a **commercial provider (Weight Watchers) for weight loss treatment versus standard care**: a randomized controlled trial. Lancet 2011

Jenkins DJ, Wong JM, Kendall CW, et al. The effect of a plant-based low-carbohydrate (**"Eco-Atkins"**) diet on body weight and blood lipid concentrations in hyperlipidemic subjects. Arch Intern Med. 2009 Jun 8;169(11):1046-54.

Jia H, Lubetkin EI. Trends in **quality-adjusted life-years** lost contributed by smoking and obesity. Am J Prev Med 2010; DOI: 10.1016/j.amepre.2009.09.043.

Jick H, Vasilakis C, Weinrauch LA, et al. A population-based study of **appetite-suppressant drugs and the risk of cardiac-valve regurgitation**. N Engl J Med 1998; 339: 719–24.

Joffe G, Takala P, Tchoukhine E, et al.. Orlistat in **Clozapine- or Olanzapine**-Treated Patients With Overweight or Obesity: A 16-Week Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Psychiatry. 2008 Mar 11;:e1-e6

TOP

[Epub ahead of print] Without a hypocaloric diet, the effect of orlistat in overweight/obese clozapine-or olanzapine-treated patients is modest and may only be seen in men.
Johansson Kari, Neovius Martin, Lagerros Ylva Trolle, et al. Effect of a very low energy diet on moderate and severe obstructive **sleep apnoea** in obese men: a randomised controlled trial. BMJ 2009;339:b4609, doi: 10.1136/bmj.b4609 (3 Dec 2009)
Johansson Kari, Hemmingsson Erik, Harlid Richard, et al. Longer term effects of **very low energy diet on obstructive sleep apnoea** in cohort derived from randomised controlled trial: prospective observational follow-up study. BMJ 2011;342:doi:10.1136/bmj.d3017 (Published 1 June 2011)
Jolly K, Aveyard P. Provision of **commercial weight management programmes**. Lancet. 2011 Sep 7.
Jolly K, Lewis A, Beach J, et al. Comparison of range of **commercial or primary care led weight reduction programmes** with minimal intervention control for weight loss in obesity: Lighten Up randomised controlled trial. BMJ 2011;343:d6500.
Juonala M, Magnussen CG, Berenson GS, et al. **Childhood adiposity, adult adiposity, and cardiovascular risk factors**. N Engl J Med 2011;365:1876-85.
Kalarchian MA, Levine MD, Arslanian SA, et al. **Family-based treatment** of severe pediatric obesity: randomized, controlled trial. Pediatrics. 2009 Oct;124(4):1060-8. Epub 2009 Sep 28.
Kaltenbach T, Crockett S, Gerson LB. Are **lifestyle** measures effective in patients with **gastroesophageal reflux disease**? An evidence-based approach. Arch Intern Med. 2006 May 8;166(9):965-71. Weight loss and head of bed elevation are effective lifestyle interventions for GERD. There is no evidence supporting an improvement in GERD measures after cessation of tobacco, alcohol, or other dietary interventions.
Karmali, Shahzeer, Stoklossa, Carlene Johnson, Sharma, Arya, et al. **Bariatric surgery**: A primer. Can Fam Physician 2010 56: 873-879.
Kato PM, Cole SW, Bradlyn AS, Pollock BH. A **video game** improves behavioural outcomes in adolescents and young adults with cancer: a randomized trial. Pediatrics. 2008;122(2):e305-e317.
Kaulfers, Anne-Marie D., Bean, Judy A., Inge, Thomas H., Dolan, et al. **Bone Loss in Adolescents After Bariatric Surgery**. Pediatrics 2011 0: peds.2010-0785.
Kiel DW, Dodson EA, Artal R, Boehmer TK, Leet TL. **Gestational weight gain and pregnancy outcomes** in obese women: how much is enough? Obstet Gynecol. 2007 Oct;110(4):752-8. Limited or no weight gain in obese pregnant women has favorable pregnancy outcomes.
Kilpeläinen TO, Qi L, Brage S, et al. Physical Activity Attenuates the Influence of **FTO Variants on Obesity Risk**: A Meta-Analysis of 218,166 Adults and 19,268 Children. PLoS Med. 2011 Nov;8(11):e1001116.
King WC, Chen JY, Mitchell JE, et al. Prevalence of **Alcohol Use Disorders Before and After Bariatric Surgery**. JAMA. 2012 Jun18:1-10.
Kipping RR, Jago R, Lawlor DA. **Obesity in children. Part 1**: Epidemiology, measurement, risk factors, and screening. BMJ. 2008 Oct 15;337:a1824. doi: 10.1136/bmj.a1824.
Kipping RR, Jago R, Lawlor DA. **Obesity in children. Part 2**: Prevention and management. BMJ. 2008 Oct 22;337:a1848. doi: 10.1136/bmj.a1848.
Kirk S, Brehm B, Saelens BE et al. Role of **Carbohydrate Modification** in Weight Management among Obese Children: A Randomized Clinical Trial. J Pediatr. 2012 Feb 28.
Klein DJ, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of **Metformin** Treatment of Weight Gain Associated With Initiation of **Atypical Antipsychotic** Therapy in Children and Adolescents. Am J Psychiatry. 2006 Dec;163(12):2072-2079. (n=39 16weeks age 10-17) Metformin 850mg bid therapy is safe and effective in abrogating weight gain, decreased insulin sensitivity, and abnormal glucose metabolism resulting from treatment of children and adolescents with atypicals.
Kolt GS, Schofield GM, Kerse N, et al. Healthy steps trial: **pedometer-based** advice and physical activity for low-active older adults. Ann Fam Med. 2012 May;10(3):206-12.
Kokkinos P, Myers J, Kokkinos JP, et al. **Exercise Capacity and Mortality** in Black and White Men. Circulation. 2008 Jan 22; [Epub ahead of print] Exercise capacity is a strong predictor of all-cause mortality in blacks and whites. The relationship was inverse and graded, with a similar impact on mortality outcomes for both blacks and whites.
Kriemler Susi, Zahner Lukas, Schindler Christian, et al. Effect of **school based physical activity programme** (**KISS**) on fitness and adiposity in primary schoolchildren: cluster randomised controlled trial. BMJ 2010;340:c785, (23 Feb 2010).
Kumanyika SK, Obarzanek E, Stettler N, et al. **Population-Based Prevention of Obesity**. The Need for Comprehensive Promotion of Healthful Eating, Physical Activity, and Energy Balance. A Scientific Statement From American Heart Association Council on Epidemiology and Prevention, Interdisciplinary Committee for Prevention (Formerly the Expert Panel on Population and Prevention Science). Circulation. 2008 Jun 30. [Epub ahead of print]
Land SR, et al. Patient-Reported Symptoms and Quality of Life During Treatment With **Tamoxifen** or **Raloxifene** for Breast Cancer Prevention: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA. 2006 Jun 5; [Epub ahead of print] No significant differences existed between the tamoxifen and raloxifene groups in patient-reported outcomes for physical health, mental health, and depression, although the tamoxifen group reported better sexual function. Although mean symptom severity was low among these postmenopausal women, those in the tamoxifen group reported more gynecological problems, vasomotor symptoms, leg cramps, and bladder control problems, whereas women in the raloxifene group reported more musculoskeletal problems, dyspareunia, and weight gain.)
Larsen Thomas Meinert, Dalskov Stine-Mathilde, van Baak Marleen, et al. for the Diet, Obesity, and Genes (**Diogenes**) Project. **Diets with High or Low Protein Content and Glycemic Index** for Weight-Loss Maintenance. N Engl J Med 2010; 363:2102-2113. In this large European study, a modest increase in protein content and a modest reduction in the glycemic index led to an improvement in study completion and maintenance of weight loss.
Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E; Obesity Canada Clinical Practice Guidelines Expert Panel. **2006 Canadian clinical practice guidelines on the management & prevention of obesity in adults & children** Summary http://www.cmaj.ca/cgi/reprint/176/8/S1 Complete guidelines http://www.cmaj.ca/cgi/data/176/8/S1/DC1/1 CMAJ. 2007 Apr 10;176(8):S1-13.
Lawlor DA, Benfield L, Logue J, et al. Association between general and central adiposity in **childhood**, and change in these, with cardiovascular risk factors in **adolescence**: prospective cohort study. BMJ **341**:doi:10.1136/bmj.c6224 (25Nov10).
Lean M, Finer N. **ABC of obesity**. Management: part II--**drugs**. BMJ. 2006 Oct 14;333(7572):794-7. Available online at: http://bmj.bmjjournals.com/cgi/content/full/333/7572/794 (Oct 17, 2006).
(McMillan DC, et al. ABC of obesity. Obesity and **cancer**. BMJ. 2006 Nov 25;333(7578):1109-11. Lawlor DA, et al. ABC of obesity: obesity and **vascular disease**. BMJ. 2006 Nov 18;333(7577):1060-3. Wild SH, et al. ABC of obesity. Risk factors for **diabetes and coronary heart disease**. BMJ. 2006 Nov 11;333(7576):1009-11. Lean M, Lara J, Hill JO. ABC of obesity. Strategies for **preventing** obesity.BMJ. 2006 Nov 4;333(7575):959-62. Kral JG. ABC of obesity. Management: Part III--surgery. BMJ. 2006 Oct 28;333(7574):900-3.: Lean M, Finer N. ABC of obesity. **Management**: part II--drugs. BMJ. 2006 Oct 14;333(7572):794-7. Avenell A, Sattar N, Lean M. ABC of obesity. Management: Part I—**behaviour** change, diet, and activity. BMJ. 2006 Oct 7;333(7571):740-3. Han TS, Sattar N, Lean M. ABC of obesity. **Assessment** of obesity and its clinical implications. BMJ. 2006 Sep 30;333(7570):695-8. Haslam D, Sattar N, Lean M. ABC of obesity. Obesity--**time to wake up**. BMJ. 2006 Sep 23;333(7569):640-2. Ramsay JE. ABC of obesity. **Obesity and reproduction**. BMJ. 2006 Dec 2;333(7577):1159-62. Lean M, Gruer L, Alberti G, Sattar N. ABC of obesity. Obesity--**can we turn the tide**? BMJ. 2006 Dec 16;333(7581):1261-4. Reilly JJ, Wilson D. ABC of obesity. **Childhood obesity**. BMJ. 2006 Dec 9;333(7580):1207-10.
Leblanc ES, O'Connor E, Whitlock EP, et al. Effectiveness of **primary care-relevant treatments** for obesity in adults: a systematic evidence review for the US Preventive services task force. (USPSFT) Ann Intern Med. 2011Oct 4;155(7):434-47.
Lee I-Min; Djousse Luc; Sesso Howard D.; et al. **Physical Activity** and Weight Gain Prevention. JAMA. 2010;303(12):1173-1179. (Maintain weight if average **60mins** a day moderate-intensity activity)
Lee JM, Gebremariam A, Vijan S, Gurney JG. **Excess Body Mass Index-Years**, a Measure of Degree and Duration of Excess Weight, and Risk for Incident Diabetes. Arch Pediatr Adolesc Med. 2011 Sep 12
Leff DR, Heath D. **Surgery for obesity** in adulthood. BMJ. 2009 Sep 22;339:b3402. doi: 10.1136/bmj.b3402.
Leonetti F, et al. Obesity, type 2 diabetes mellitus, and other comorbidities: a prospective cohort study of **laparoscopic sleeve gastrectomy vs medical treatment** [online ahead of print April 16, 2012]. Arch Surg. 2012.
Li Donghui; Morris Jeffrey S.; et al. Body Mass Index and Risk, Age of Onset, and Survival in Patients With **Pancreatic Cancer**. JAMA. 2009;301(24):2553-2562.
Lin JS, O'Connor E, Whitlock EP, Beil TL. **Behavioral counseling to promote physical activity** and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the US Preventive services task force. (**USPSTF**) Ann Intern Med. 2010 Dec 7;153(11):736-50.
Lin, Wen-Yuan, Tsai, Shin-Li, Albu, Jeanine B., et al. **Body mass index and all-cause mortality in a large Chinese** cohort. CMAJ 2011 183: E329-336.
Liu Bette, Balkwill Angela, Reeves Gillian et al. on behalf of the Million Women Study Collaborators. Body mass index and risk of **liver cirrhosis** in middle aged UK women: prospective study. BMJ 2010
Livingston EH, Langert J. The impact of **age** and medicare status on **bariatric** surgical outcomes. Arch Surg. 2006 Nov;141(11):1115-20; discussion 1121. Limiting bariatric surgical procedures to those younger than 65 years is warranted because of the high morbidity and mortality associated with these operations in older patients.
Lombard C, Deeks A, Jolley D, et al. A **low intensity, community based lifestyle programme** to prevent weight gain in women with young children: cluster randomised controlled trial. BMJ. 2010 Jul 13;341:c3215. doi: 10.1136/bmj.c3215.
Lomenick JP, El-Sayyid M, Smith WJ. Effect of **levo-thyroxine treatment** on weight and body mass index in children with acquired hypothyroidism. J Pediatr. 2008 Jan;152(1):96-100. Epub 2007 Oct 24. Most children treated for acquired hypothyroidism exhibited little short-term or long-term change in weight or BMI despite near-normalization of TSH. Those children who lost weight tended to have severe hypothyroidism and to have only a small weight loss.
Longitudinal Assessment of Bariatric Surgery (**LABS**) Consortium, **Perioperative Safety in the Longitudinal Assessment of Bariatric Surgery.** N Engl J Med 2009 361: 445-454
Losina Elena, Walensky Rochelle P., Reichmann William M., et al. Impact of Obesity and **Knee Osteoarthritis** on Morbidity and Mortality in Older Americans. *Ann Intern Med* February 15, 2011 154:217-226.
Louzada ML, Campagnolo PD, Rauber F, Vitolo MR. Long-term Effectiveness of **Maternal Dietary Counseling** in a Low-Income Population: A Randomized Field Trial. Pediatrics. 2012 May 7.

TOP

Ludwig DS and Currie J. The association between **pregnancy weight gain and birthweight**: A within-family comparison. Lancet 2010 Aug 5;
Ludwig J, Sanbonmatsu L, Gennetian L, et al. **Neighborhoods**, obesity, and diabetes-a randomized social experiment. N Engl J Med2011; 365:1509-1519.
Ludwig DS. **Weight loss strategies for adolescents**: a 14-year-old struggling to lose weight. JAMA. 2012 Feb 1;307(5):498-508.
Lusk Anne C.; Mekary Rania A.; Feskanich Diane; et al. **Bicycle Riding, Walking, and Weight Gain** in Premenopausal Women. Arch Intern Med. 2010;170(12):1050-1056.
Macfarlane DJ, Taylor LH, Cuddihy TF. Very short **intermittent vs continuous bouts of activity** in sedentary adults. Prev Med. 2006 Oct;43(4):332-6. Epub 2006 Jul 27.
Maciejewski ML, Livingston EH, Smith VA, et al. **Survival** among high-risk patients **after bariatric surgery**. JAMA. 2011 Jun 15;305(23):2419-26.
Magarey, Anthea M., Perry, Rebecca A., Baur, Louise A., et al. **A Parent-Led Family-Focused Treatment Program** for Overweight Children Aged 5 to 9 Years: The PEACH RCT**.** Pediatrics 2011 127: 214-222.
Maggard MA, et al. Meta-analysis: **surgical treatment** of obesity. Ann Intern Med. 2005 Apr 5;142(7):547-59. Summary for patients in: Ann Intern Med. 2005 Apr 5;142(7):I55.
Makary MA, Clarke JM, Shore AD, et al. **Medication utilization** and annual health care costs in patients with type 2 diabetes mellitus **before and after bariatric surgery**. Arch Surg. 2010 Aug;145(8):726-31.
Maniccia Dayna M., Davison Kirsten K., Marshall Simon J., et al. A Meta-analysis of Interventions That Target Children's **Screen Time for Reduction**. Pediatrics 2011; 128:1 e193-e210; doi:10.1542/peds.2010-2353
Manini TM, et al. Daily activity **energy expenditure** and mortality among older adults. JAMA. 2006 Jul 12;296(2):171-9.
Marcus MD, Foster GD, El Ghormli L, et al. Shifts in **BMI Category and Associated Cardiometabolic Risk**: Prospective Results From HEALTHY Study. Pediatrics. 2012 Apr;129(4):e983-91.
Martino JL, Stapleton RD, Wang M, et al. **Extreme obesity and outcomes** in **critically ill patients**. Chest. 2011 Nov;140(5):1198-206.
Maruyama K, Sato S, Ohira T, et al. The joint impact on being overweight of self reported behaviours of **eating quickly and eating until full**: cross sectional survey. BMJ. 2008 Oct 21;337:a2002. doi: 10.1136/bmj.a2002.
Matlaga BR, Shore AD, Magnuson T, Clark JM, Johns R, Makary MA. Effect of **gastric bypass surgery** on **kidney stone disease**. J Urol. 2009 Jun;181(6):2573-7. Epub 2009 Apr 16.
Mayer-Davis EJ, et al. **Breast-Feeding** and Risk for Childhood Obesity: Does maternal diabetes or obesity status matter? Diabetes Care. 2006 Oct;29(10):2231-7. These data provide support for all mothers to breast-feed their infants to reduce the risk for childhood overweight.
McCallum Z, et al. Outcome data from the **LEAP** (Live, Eat and Play) trial: a randomized controlled trial of a primary care intervention for childhood overweight/mild obesity. Int J Obes (Lond). 2006 Dec 12; [Epub ahead of print]
McDonnell WM, Bhattacharya R, Halldorson JB. Fulminant Hepatic Failure After Use of the Herbal Weight-Loss Supplement **Exilis**. Ann Intern Med. 2009 Nov 3;151(9):673-674.
McCusker RR, Goldberger BA, Cone EJ. **Caffeine** content of energy drinks, carbonated sodas, and other beverages. J Anal Toxicol. 2006 Mar;30(2):112-4.
McDonald SD, Han Z, Mulla S, et al., on behalf of the Knowledge Synthesis Group. Overweight and **obesity in mothers** and **risk of preterm birth** and low birth weight infants: systematic review and meta-analyses. BMJ 2010;341:c3428
McMillan-Price J, et al. Comparison of **4 diets** of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: a randomized controlled trial. Arch Intern Med. 2006 Jul 24;166(14):1466-75.
McTigue K, et al. **Mortality and cardiac and vascular outcomes** in extremely obese women. JAMA. 2006 Jul 5;296(1):79-86.
Medical Letter: Treatment Guidelines –**Diet,Drugs and Surgery for Weight Loss**. April 2008. **Updated 2011.**
Mediterranean diet: [Mayo Clinic website] choose this heart-healthy diet option. Rochester, MN: Mayo Clinic; 2010. Available from: www.mayoclinic.com/health/mediterranean-diet/CL00011 . Accessed 2011 May 24.
Mehta S, Lopez ME, Chumpitazi BP et al. Clinical characteristics and risk factors for symptomatic pediatric **gallbladder disease**. Pediatrics. 2012 Jan;129(1):e82-8.
Meijer RI, van Wagensveld BA, Siegert CE, Eringa EC, Serné EH, Smulders YM. **Bariatric surgery** as a novel treatment for type 2 diabetes mellitus: a systematic review. Arch Surg 2011; 146: 744–50.
Mendoza JA, Watson K, Baranowski T, et al. The **Walking School Bus** and Children's Physical Activity: A Pilot Cluster Randomized Controlled Trial. Pediatrics. 2011 Aug 22.
Messier SP, et al. **Exercise and dietary** weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum. 2004 May;50(5):1501-10.
MHRA Feb/12 Herbal sliming products found to contain potentially dangerous undeclared pharmaceuticals: **Expelling Grease Slimming Abdomen, V12 Fruit Slimming, 100% Natural Weight Loss Coffee, Leisure 18 Slimming Orange Juice, Fashion Slimming Milk Shake, Langli, Ya Buk & Fruit and vegetables lose weight**. MHRA has received advice from the Danish Medicines Agency that these unlicensed products have been tested and found to contain the Prescription Only Medicine Sibutramine.
MHRA Feb/12 Following a safety alert issued in October 2010 about slimming products containing Paiyouji the Agency has received a further complaint about a product called **'Paiyouji Plus - Fast Acting Slimming Tea'**. This product has been tested by the Agency and, as in the case of other Paiyouji products, found to contain sibutramine.
Michalsky M, Kramer RE, Fullmer MA, et al. Developing **criteria for pediatric/adolescent bariatric surgery** programs. Pediatrics 2011;128:Suppl 2:S65-S70
Miller AD, Smith KM. Medication and nutrient administration considerations after **bariatric surgery**. Am J Health-Syst Pharm. 2006;63:1852-1857.
Mingrone G, Panunzi S, De Gaetano A, et al. **Bariatric surgery versus conventional medical therapy** for type 2 diabetes. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200111.
Mnatzaganian G, Ryan P, Norman PE, et al. Smoking, body **weight, physical exercise** and risk of **lower limb total joint replacement** in a population-based cohort of men. Arthritis Rheum. 2011 Jul 11.
Moleres A, Rendo-Urteaga T, Zulet MA, et al. EVASYON Study Group. **Obesity Susceptibility Loci** on Body Mass Index and Weight Loss in Spanish Adolescents after a Lifestyle Intervention. J Pediatr. 2012 May 18.
Mozaffarian Dariush, Hao Tao, Rimm Eric B., eft al. Changes in **Diet and Lifestyle and Long-Term Weight Gain** in Women and Men. N Engl J Med 2011; 364:2392-2404.
Murtagh L, Ludwig DS. **State intervention** in life-threatening childhood obesity. JAMA 2011;306:206-7
Must A, M Phillips S, Naumova EN. Occurance and **Timing of Childhood Overweight and Mortality**: Findings from the Third Harvard Growth Study. J Pediatr. 2011 Dec 17.
Nedeltcheva Arlet V., Kilkus Jennifer M., Imperial Jacqueline, et al. **Insufficient Sleep** Undermines Dietary Efforts to Reduce Adiposity. Ann Intern Med October 5, 2010 153:435-441; doi:10.1059/0003-4819-153-7-201010050-00006.
Nguyen NT et al. A prospective randomized trial of laparoscopic gastric **bypass versus laparoscopic adjustable gastric banding** for the treatment of morbid obesity: Outcomes, quality of life, and costs. Ann Surg 2009 Oct; 250:631.
Nissen SE, Nicholls SJ, Wolski K, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease. The **STRADIVARIUS** randomized controlled trial. JAMA 2008; 299: 1547-1560.
NICE Obesity Guidelines Dec 2006 http://www.nice.org.uk/guidance/CG43/?c=91500
Nicholls SJ, et al. Effects of obesity on lipid-lowering, anti-inflammatory, and antiatherosclerotic benefits of **atorvastatin** or **pravastatin** in patients with coronary artery disease (from the REVERSAL Study). Am J Cardiol. 2006 Jun 1;97(11): 1553-7. Epub 2006 Apr 6.
Nordestgaard BG, Palmer TM, Benn M, et al. The effect of elevated body mass index on **ischemic heart disease risk**: causal estimates from a mendelian randomisation approach. PLoS Med. 2012 May;9(5):e1001212.
O'Brien Paul E.; Sawyer Susan M.; Laurie Cheryl; et al. Laparoscopic Adjustable **Gastric Banding** in Severely Obese **Adolescents**: A Randomized Trial. *JAMA*. 2010;303 (6):519-526.
O'Connor GT et al. Prospective study of sleep-disordered breathing and **hypertension**: The Sleep Heart Health Study. Am J Respir Crit Care Med 2009 Jun 15; 179:1159.
Ogden CL, Carroll MD, Flegal KM. High body mass index for age among **US children and adolescents, 2003-2006**. JAMA. 2008 May 28;299(20):2401-5. The prevalence of high BMI for age among children and adolescents showed no significant changes between 2003-2004 and 2005-2006 and no significant trends between 1999 and 2006.
Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. **Prevalence** of overweight and obesity in the **United States, 1999-2004**. JAMA. 2006 Apr 5;295(13):1549-55. The prevalence of overweight among children and adolescents and obesity among men increased significantly during the 6-year period from 1999 to 2004; among women, no overall increases in the prevalence of obesity were observed. These estimates were based on a 6-year period and suggest that the increases in body weight are continuing in men and in children and adolescents while they may be leveling off in women.
Ogden Cynthia L.; Carroll Margaret D.; Curtin Lester R.; et al. Prevalence of High **Body Mass Index** in **US Children and Adolescents**, 2007-2008. JAMA. 2010;0(2010):2009.2012.
Ogden CL, Carroll MD, Kit BK, Flegal KM. **Prevalence of obesity and trends in body mass index** among us children and adolescents, 1999-2010. JAMA 2012.
Omalu BI, Ives DG, Buhari AM, Lindner JL, Schauer PR, Wecht CH, Kuller LH. Death rates & causes of death after **bariatric surgery** for Pennsylvania residents, 1995 to 2004. Arch Surg. 2007 Oct;142(10):923-8; discussion 929. There was a substantial excess of deaths owing to suicide and coronary heart disease. Careful monitoring of bariatric surgical procedures and more intense follow-up could likely reduce the long-term case fatality rate in this patient population.
Østergaard Pedersen J, Heitmann B L, Schnohr P, and Grønbæk M. The combined influence of leisure-time **physical activity and weekly alcohol** intake on fatal ischaemic heart disease and all-cause mortality. Eur Heart J 2008; DOI:10.1093/eurheartj/ehm574.

TOP

Otten Jennifer J.; Jones Katherine E.; et al. Effects of **Television Viewing** Reduction on Energy Intake and Expenditure in Overweight and Obese Adults: A Randomized Controlled Trial. Arch Intern Med. 2009;169(22):2109-2115.

Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, Summerbell CD. Interventions for treating **obesity in children. Cochrane** Database Syst Rev. 2009 Jan 21;(1):CD001872. While there is limited quality data to recommend one treatment program to be favoured over another, this review shows that combined behavioural lifestyle interventions compared to standard care or self-help can produce a significant and clinically meaningful reduction in overweight in children and adolescents. In obese adolescents, consideration should be given to the use of either orlistat or sibutramine, as an adjunct to lifestyle interventions, although this approach needs to be carefully weighed up against the potential for adverse effects.

Padwal RS, Majumdar SR. **Drug treatments for obesity**: orlistat, sibutramine, and rimonabant. Lancet. 2007 Jan 6;369(9555):71-7.

Padwal RS, Pajewski NM, Allison DB, Sharma AM. Using the **Edmonton obesity staging system to predict mortality** in a population-representative cohort of people with overweight and obesity. CMAJ. 2011 Aug 15.

Palamara KL, Mogul HR, Peterson SJ, Frishman WH. Obesity: new perspectives and pharmacotherapies. Cardiol Rev. 2006 Sep-Oct;14(5):238-58.

Parkin L, Sweetland S, Balkwill A, et al. the **Million Women Study Collaborators**. **Body Mass Index, Surgery, and Risk of Venous Thromboembolism** in Middle-Aged Women: A Cohort Study. Circulation. 2012 Apr 17;125(15):1897-1904.

Pedersen SD, Kang J, Kline GA. **Portion control plate** for weight loss in obese patients with type 2 diabetes mellitus: a controlled clinical trial. Arch Intern Med. 2007 Jun 25;167(12):1277-83.

Peng L, Wang J, Li F. Weight reduction for **non-alcoholic fatty liver disease** (NAFLD). Cochrane Database Syst Rev. 2011 Jun 15;6:CD003619. The sparse data and high risk of bias preclude us from drawing any definite conclusion on lifestyle programme or orlistat for treatment of NAFLD.

Pharmacist's Letter. **PolyGlycopleX (PGX)** for Weight Loss. April 2010.

Pharmacist's Letter. **Raspberry ketone** for Weight Loss. May 2012.

Plourde G. Preventing and **managing pediatric obesity. Recommendations for family physicians**. Can Fam Physician. 2006 Mar;52:322-8.

Poirier P, Cornier MA, Mazzone T. **Bariatric surgery and cardiovascular risk factors**: A scientific statement from the American Heart Association (**AHA**). Circulation. 2011; DOI: 10.1161/CIR.0b013e3182149099. http://circ.ahajournals.org/cgi/reprint/123/15/1683

Post RE, Mainous AG 3rd, Gregorie SH, et al. The influence of **physician acknowledgment** of patients' weight status on patient perceptions of overweight and obesity in the United States. Arch Intern Med 2011;171:316–21.

Prachand VN, Davee RT, Alverdy JC. Duodenal Switch Provides Superior Weight Loss in the Super-Obese (BMI >/=50kg/m2) Compared With Gastric Bypass. Ann Surg. 2006 Oct;244(4):611-9.

Preganancy: May/09 Obese women (BMI, 30 or higher) should gain only 11 to 20 pounds during a singleton pregnancy, according to new guidelines from the Institute of Medicine. The guidelines update the IOM's previous recommendations, issued in 1990. The group continues to recommend that: underweight women (BMI lower than 18.5) gain 28-40 pounds; normal-weight women (BMI, 18.5-24.9) gain 25-35 pounds; overweight women (BMI, 25.0-29.9) gain 15-25 pounds. Weight gain should be higher for multiple pregnancies. Excessive weight gain, the IOM notes, is associated with increased risk for gestational diabetes, pregnancy-associated hypertension, and delivery of large-for-gestational-age infants, among other outcomes. The group says that clinicians should supplement these guidelines with individualized counseling about diet and exercise. In addition, preconception counseling should stress the importance of conceiving at a normal BMI. http://www.iom.edu/Object.File/Master/68/110/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf

Puder JJ, Marques-Vidal P, Schindler C, et al. Effect of **multidimensional lifestyle intervention** on fitness and adiposity in predominantly migrant preschool children-Ballabeina: cluster randomised controlled trial. BMJ. 2011 Oct 13;343:d6195.

Puhl RM, Peterson JL, Luedicke J. **Parental Perceptions of Weight Terminology** That Providers Use With Youth. Pediatrics. 2011 Sep 26.

Rao G. **Office-based strategies** for the management of obesity. Am Fam Physician. 2010 Jun 15;81(12):1449-56 ; quiz 1429.

Rao G, Burke LE, Spring BJ, et al. on behalf of the American Heart Association Obesity Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Clinical Cardiology, Council on Cardiovascular Nursing, Council on the Kidney in Cardiovascular Disease, and Stroke Cou. **New and Emerging Weight Management Strategies** for Busy Ambulatory Settings: A Scientific Statement From the American Heart Association * Endorsed by the Society of Behavioral Medicine. Circulation. 2011 Sep 6;124(10):1182-1203.

Read J. Leighton, Shortell Stephen M.. **Interactive Games** to Promote Behavior Change in Prevention and Treatment. JAMA. 2011;305(16):1704-1705.

Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D; Million Women Study Collaboration. **Cancer incidence and mortality in relation to body mass index** in the Million Women Study: cohort study. BMJ. 2007 Dec 1;335(7630):1134. Epub 2007 Nov 6. Increasing body mass index is associated with a significant increase in the risk of cancer for 10 out of 17 specific types examined. Among postmenopausal women in the UK, 5% of all cancers (about 6000 annually) are attributable to being overweight or obese. For endometrial cancer and adenocarcinoma of the oesophagus, body mass index represents a major modifiable risk factor; about half of all cases in postmenopausal women are attributable to overweight or obesity.

Reicks M, Redden JP, Mann T, et al. **Photographs in lunch tray compartments** and vegetable consumption among children in elementary school cafeterias. JAMA 2012.

Reilly JJ, et al. **Physical activity** to prevent obesity in **young children**: cluster randomized controlled trial. BMJ. 2006 Oct 6; [Epub ahead of print] Physical activity can significantly improve motor skills but did not reduce body mass index in young children in this trial.

Renehan AG, et al. **Body-mass index and incidence of cancer**: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008 Feb 16;371(9612):569-78. Increased BMI is associated with increased risk of common and less common malignancies. For some cancer types, associations differ between sexes and populations of different ethnic origins.

Rejeski W. Jack; Brubaker Peter H.; Goff David C., et al. Translating **Weight Loss and Physical Activity Programs** Into the Community to Preserve Mobility in Older, Obese Adults in Poor Cardiovascular Health. Arch Intern Med. 2011;171(10):880-886.

Rejeski WJ, Ip EH, Bertoni AG, et al. **Lifestyle change and mobility** in obese adults with type 2 diabetes. N Engl J Med. 2012 Mar 29;366(13):1209-17.

Rich S, Rubin L, Walker AM, et al. **Anorexigens and pulmonary hypertension** in the United States: results from the surveillance of North American Pulmonary Hypertension. Chest 2000; 117: 870–74.

Richardson CR, Newton TL, Abraham JJ, Sen A, Jimbo M, Swartz AM. A meta-analysis of **pedometer**-based walking interventions and weight loss. Ann Fam Med. 2008 Jan-Feb;6(1):69-77. Using pedometers to guide physical activity, even when not accompanied by dietary interventions, promotes modest weight loss among sedentary and obese or overweight individuals. (LOE = 2a)

Richelsen B, et al. Effect of Orlistat on Weight Regain and Cardiovascular Risk Factors Following a Very-Low-Energy Diet in Abdominally Obese Patients: A 3-year randomized, placebo-controlled study. Diabetes Care. 2007 Jan;30(1):27-32. The addition of orlistat to lifestyle intervention was associated with maintenance of an extra 2.4 kg weight loss after VLED for up to 3 years in obese subjects. The combination of orlistat and lifestyle intervention was associated with a reduced occurrence of type 2 diabetes.

Riddoch CJ, Leary SD, Ness AR, et al. Prospective associations between objective measures of **physical activity** and fat mass in 12-14 year old children: the Avon Longitudinal Study of Parents and Children (ALSPAC). BMJ. 2009 Nov 26;339:b4544. doi: 10.1136/bmj.b4544.

Robinson TN, Matheson DM, Kraemer HC, et al. A randomized controlled trial of **culturally tailored dance and reducing screen time** to prevent weight gain in low-income African American girls: Stanford GEMS. Arch Pediatr Adolesc Med. 2010 Nov;164(11):995-1004.

Rock Cheryl L.; Flatt Shirley W.; Sherwood Nancy E.; et al. Effect of a **Free Prepared Meal and Incentivized Weight Loss Program** on Weight Loss and Weight Loss Maintenance in Obese and Overweight Women: A Randomized Controlled Trial. *JAMA*. 2010;0(2010):jama.2010.1503.

Rogovik AL, Chanoine JP, Goldman RD. Pharmacotherapy and weight-loss supplements for treatment of **paediatric obesity**. Drugs. 2010 Feb 12;70(3):335-46.

Rogovik, Alexander L., Goldman, Ran D. Pharmacologic **treatment of pediatric obesity**. Can Fam Physician 2011 57: 195-197.

Rosenstock J, Hollander P, Gadde KM, et al.; OBD-202 Study Group. A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. Diabetes Care. 2007 Jun;30(6):1480-6. Epub 2007 Mar 15.

Ross R, Lam M, Blair SN, et al. Trial of Prevention and Reduction of Obesity Through **Active Living** in Clinical Settings: A Randomized Controlled Trial. Arch Intern Med. 2012 Feb 27. (over 2yrs)

Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term **pharmacotherapy** for obesity and overweight: **updated meta-analysis**. BMJ. 2007 Nov 15; [Epub ahead of print] Attrition rates averaged 30-40%. Compared with placebo, orlistat reduced weight by 2.9 kg (95% confidence interval 2.5 kg to 3.2 kg), sibutramine by 4.2 kg (3.6 kg to 4.7 kg), and rimonabant by 4.7 kg (4.1 kg to 5.3 kg). Patients receiving active drug treatment were significantly more likely to achieve 5% and 10% weight loss thresholds. Orlistat reduced the incidence of diabetes and improved concentrations of total cholesterol and low density lipoprotein cholesterol, blood pressure, and glycaemic control in patients with diabetes but increased rates of gastrointestinal side effects and slightly lowered concentrations of high density lipoprotein. Sibutramine lowered concentrations of high density lipoprotein cholesterol and triglycerides but raised blood pressure and pulse rate. Rimonabant improved concentrations of high density lipoprotein cholesterol and triglycerides, blood pressure, and glycaemic control in patients with diabetes but increased the risk of mood disorders. Orlistat, sibutramine, and rimonabant modestly reduce weight, have differing effects on cardiovascular risk profiles, and have specific adverse effects.

TOP

Ryan Donna H.; Johnson William D.; Myers Valerie H.; et al. **Nonsurgical** Weight Loss for Extreme Obesity in Primary Care Settings: Results of the Louisiana Obese Subjects Study (**LOSS**). Arch Intern Med. 2010;170(2):146-154.
Ryckman KK, Feenstra B, Shaffer JR, Bream EN, Geller F, Feingold E, et al. Replication of a **genome-wide association** study of birth weight in preterm neonates. J Pediatr 2011.
Sacks FM, Bray GA, Carey VJ, Smith SR, et al. Comparison of **weight-loss diets** with different compositions of fat, protein, and carbohydrates. N Engl J Med. 2009 Feb 26;360(9):859-73. Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize.
Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003; 348:2074-81.
Savoye, Mary, Nowicka, Paulina, Shaw, Melissa, et al. **Long-term Results of an Obesity Program** in an Ethnically Diverse **Pediatric** Population. Pediatrics 2011 0: peds.2010-0697.
Sawyer MG, Harchak T, Wake M, Lynch J. **Four-Year** Prospective Study of BMI and Mental Health Problems in Young **Children**. Pediatrics. 2011 Oct;128(4):677-84.
Schauer PR, Kashyap SR, Wolski K, et al. **Bariatric surgery versus intensive medical therapy** in obese patients with diabetes. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200225.
Scheen AJ, Finet al. **RIO-Diabetes Study Group**. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet. 2006 Nov 11;368(9548):1660-72.
Schroeder R, Garrison JM Jr, Johnson MS. Treatment of adult obesity with **bariatric surgery**. Am Fam Physician. 2011 Oct 1;84(7):805-14.
Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on **C-reactive protein**: a systematic review.Arch Intern Med. 2007 Jan 8;167(1):31-9.
Shah N, Braverman E. Measuring Adiposity in Patients: The Utility of **Body Mass Index (BMI), Percent Body Fat, and Leptin.** PLoS ONE 7(4): e33308.
Shai I, Schwarzfuchs D, Henkin Y, et al. Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008 Jul 17;359(3):229-41. **Mediterranean** and **low-carbohydrate diets** may be effective alternatives to low-fat diets. The more favorable effects on lipids (with the low-carbohydrate diet) and on glycemic control (with the Mediterranean diet) suggest that personal preferences and metabolic considerations might inform individualized tailoring of dietary interventions.
Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a **low-carbohydrate, Mediterranean, or low-fat diet**. N Engl J Med 2008;359:229-41.
Shankar P, Boylan M, Sriram K. **Micronutrient deficiencies** (vitamins) after bariatric surgery. Nutrition. 2010 Nov-Dec;26(11-12):1031-7.
Siavash Dastjerdi M, et al. An open-label pilot study of the combination therapy of **metformin and fluoxetine** for weight reduction. Int J Obes (Lond). 2006 Sep 12; [Epub ahead of print]
Siddiqui SA, et al. Obesity and survival after radical **prostatectomy**: A 10-year prospective cohort study. Cancer. 2006 Aug 1;107(3):521-9. (InfoPOEMs: In spite of worse baseline disease status, obesity does not affect survival or other outcomes in men undergoing radical prostatectomy for prostate cancer. (LOE = 1b))
Sievenpiper JL, de Souza RJ, Mirrahimi A, et al. Effect of **Fructose** on Body Weight in Controlled Feeding Trials: A Systematic Review and Meta-analysis. Ann Intern Med. 2012 Feb 21;156(4):291-304.
SIGN: Scottish Intercollegiate Guidelines Network (**SIGN**). **Management of obesity**. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2010 Feb.
Simpson SA, Shaw C, McNamara R. What is the most effective way to **maintain weight loss** in adults? BMJ. 2011 Dec 28;343:d8042.
Sinha R, et al. Prevalence of **impaired glucose tolerance** among children and adolescents with marked obesity. N Engl J Med. 2002 Mar 14;346(11):802-10. Erratum in: N Engl J Med 2002 May 30;346(22):1756.
Sjostrom L, et al.; Swedish Obese Subjects (**SOS**) Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004 Dec 23;351(26):2683-93. After two years, the weight had increased by 0.1 percent in the control group and had decreased by 23.4 percent in the surgery group (P<0.001). After 10 years, the weight had increased by 1.6 percent and decreased by 16.1 percent, respectively (P<0.001). Energy intake was lower and the proportion of physically active subjects higher in the surgery group than in the control group throughout the observation period. Two- and 10-year rates of recovery from diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hypertension, and hyperuricemia were more favorable in the surgery group than in the control group, whereas recovery from hypercholesterolemia did not differ between the groups. The surgery group had lower 2- and 10-year incidence rates of diabetes, hypertriglyceridemia, and hyperuricemia than the control group; differences between the groups in the incidence of hypercholesterolemia and hypertension were undetectable.
Sjöström L et al. Effects of bariatric surgery on **cancer incidence** in obese patients in Sweden (Swedish Obese Subjects Study-**SOS**): A prospective, controlled intervention trial. Lancet Oncol 2009 Jun 24; [e-pub ahead of print].
Sjostrom L, Narbro K, Sjostrom CD, et al. Eff ects of bariatric surgery on mortality in Swedish obese subjects (Swedish Obese Subjects Study-**SOS**). N Engl J Med 2007; 357: 741–52.
Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. (**SOS**) JAMA. 2012;307(1):56-65. During a median 15 years' follow-up, significantly fewer surgery patients than controls experienced a first cardiovascular event (199 vs. 234 patients; adjusted hazard ratio, 0.67). Cardiovascular mortality was similarly reduced with bariatric surgery (HR, 0.47).
Smith GD, Sterne JA, Abigail F, et al. The association between **BMI and mortality** using offspring BMI as an indicator of own BMI: large intergenerational mortality study. BMJ 2009;339:b5043, doi: 10.1136/bmj.b5043 (22 Dec 2009)
Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of **lorcaserin** for weight management (**Bloom**). N Engl J Med 2010;363:245-56.
Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Ad herence to **Mediterranean diet** and health status: meta-analysis. BMJ 2008;337:a1344.
Soltani-Arabshahi Razieh, Wong Bob, Feng Bing-Jian, et al. Obesity in Early Adulthood as a Risk Factor for **Psoriatic Arthritis**. *Arch Dermatol*. 2010;146(7):721-726.
Søvik TT, Aasheim ET, Taha O, Engstro¨m M, et al. Weight loss, cardiovascular risk factors, and quality of life **after gastric bypass and duodenal switch**. A randomized trial. Ann Intern Med. 2011;155: 281-91.
Spring B, Schneider K, McFadden HG, et al. Multiple behavior changes in diet and activity: A randomized controlled trial using **mobile technology**. Arch Intern Med 2012; 172:789-796.
Spyropoulos C, Kehagias I, Panagiotopoulos S, Mead N, Kalfarentzos F. **Revisional bariatric surgery**: 13-year experience from a tertiary institution. Arch Surg. 2010 Feb;145(2):173-7.
Stessman J, Jacobs JM, Ein-Mor E, Bursztyn M. Normal body mass index **rather than obesity** predicts greater mortality in **elderly people**: the Jerusalem longitudinal study. J Am Geriatr Soc. 2009 Dec;57(12):2232-8. Epub 2009 Nov 17.
Stewart ST, Cutler DM, Rosen AB. Forecasting the effects of obesity and smoking on U.S. **life expectancy**. N Engl J Med. 2009 Dec 3;361(23):2252-60. PubMed
Stevens VJ, Brantley PJ, et al. Weight Loss Maintenance (WLM) Collaborative Research Group. Comparison of strategies for sustaining weight loss: the weight loss maintenance randomized controlled trial. JAMA. 2008 Mar 12;299(10):1139-48. The majority of individuals who successfully completed an initial behavioral weight loss program maintained a weight below their initial level. Monthly brief **personal contact** provided modest benefit in sustaining weight loss, whereas an interactive technology-based intervention provided early but transient benefit. N=1032, 30months
Stotland NE. **Obesity and pregnancy**. BMJ. 2008 Dec 15;337:a2450. doi: 10.1136/bmj.a2450.
Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of **congenital anomalies**: a systematic review and meta-analysis. JAMA. 2009 Feb 11;301(6):636-50. Maternal obesity is associated with an increased risk of a range of structural anomalies, although the absolute increase is likely to be small.
Suglia SF, Chambers EC, Rosario A, Duarte CS. **Asthma and obesity in three-year-old urban children**: role of sex and home environment. J Pediatr. 2011 Jul;159(1):14-20.e1.
Sui X, LaMonte MJ, Laditka JN, et al. Cardiorespiratory **fitness** and adiposity as mortality predictors in older adults. JAMA. 2007 Dec 5;298(21):2507-16. In this study population, fitness was a significant mortality predictor in older adults, independent of overall or abdominal adiposity. Clinicians should consider the importance of preserving functional capacity by recommending regular physical activity for older individuals, normal-weight and overweight alike.
Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of **hormonal adaptations** to weight loss. N Engl J Med. 2011 Oct 27;365(17):1597-604.
Sun Qi, Townsend Mary K, Okereke Olivia I, et al. Adiposity and weight change in mid-life in relation to healthy **survival after age 70** in women: prospective cohort study**.** BMJ 2009;339:b3796, doi: 10.1136/bmj.b3796 Tabák AG, Svetkey LP,
Swinburn BA, Sacks G, Hall KD, et al. The **global obesity pandemic**: shaped by global drivers and local environments. Lancet. 2011 Aug 27;378(9793):804-14.
Tate DF, et al. A randomized trial comparing human e-mail counseling, computer-automated tailored counseling, and no counseling in an Internet weight loss program. Arch Intern Med. 2006 Aug 14-28;166(15):1620-5.
Taveras EM, Rifas-Shiman SL, Oken E, Gunderson EP, Gillman MW. **Short sleep duration** in infancy and risk of childhood overweight. Arch Pediatr Adolesc Med. 2008 Apr;162(4):305-11. Daily sleep duration of less than 12 hours during infancy appears to be a risk factor for overweight and adiposity in preschool-aged children.
Tchoukhine E, Takala P, et al. Orlistat in **clozapine- or olanzapine**-treated patients with overweight or obesity: a 16-week open-label extension phase and both phases of a randomized controlled trial. J Clin Psychiatry. 2010 Aug 24.
ter Bogt Nancy C. W.; Bemelmans Wanda J. E.; Beltman FW.; et al. Preventing Weight Gain by **Lifestyle Intervention in a General Practice Setting**: Three-Year Results of a Randomized Controlled Trial. Arch Intern Med. 2011;171(4):306-313.
The Natalie S.; Suchindran Chirayath; North Kari E.; et al. Association of **Adolescent Obesity With Risk of Severe Obesity in Adulthood**. JAMA. 2010;304(18):2042-2047
Thompson DR, Obarzanek E, Franko DL, et al. **Childhood** overweight and cardiovascular disease risk factors: The National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr 2007; 150: 18-25.
Tindle HA et al. Risk of **suicide after long-term follow-up from bariatric surgery**. Am J Med 2010 Nov; 123:1036.
Tirosh A et al. Adolescent **BMI trajectory and risk of diabetes versus coronary disease**. N Engl J Med 2011 Apr 7; 364:1315.
Topol E, Bousser MG, Fox KA, et al. **Rimonabant** for prevention of cardiovascular events (**CRESCENDO**): a randomised, multicenter, placebo-controlled trial. Lancet 2010: 376:517-23.
Torp-Pedersen C, Caterson I, et al,on the behalf of the **SCOUT** Investigators. Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial. Eur Heart J. 2007 Jun 26; [Epub ahead of print] Six-week treatment with sibutramine appears to be efficacious, tolerable and safe in this high-risk population for whom sibutramine is usually contraindicated.

TOP

Towbin A, et al. **Beriberi** after gastric bypass surgery in adolescence. J Pediatr. 2004 Aug;145(2):263-7.
Tsai WS, Inge TH, Burd RS. **Bariatric surgery** in adolescents: recent national trends in use and in-hospital outcome. Arch Pediatr Adolesc Med. 2007 Mar;161(3):217-21.
Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of **Mediterranean diet**: Greek EPIC prospective cohort study. BMJ. 2009 Jun 23;338:b2337. doi: 10.1136/bmj.b2337. Some food groups in the Mediterranean diet are more important than others in promoting health and longer life, according to this prospective cohort study from the Greek segment of the European Prospective Investigation into Cancer and nutrition (EPIC). The researchers investigated the importance of individual components of the diet and found that eating more vegetables, fruits, nuts, pulses, and olive oil, and drinking moderate amounts of alcohol is linked to people living longer, whereas following a Mediterranean diet high in seafood and cereals and low in dairy products was not an indicator of longevity.
Truby H, et al. Randomised controlled trial of **four commercial weight loss programmes** in the UK: initial findings from the BBC "diet trials". BMJ. 2006 Jun 3;332(7553):1309-14. Epub 2006 May 23. Erratum in: BMJ. 2006 Jun 17;332(7555):1418.
Tuah NAA, Amiel C, Qureshi S, Car J, Kaur B, Majeed A. **Transtheoretical model** for dietary and physical exercise modification in weight loss management for overweight and obese adults. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD008066. DOI: 10.1002/14651858.CD008066.pub2. TTM SOC and a combination of physical activity, diet and other interventions resulted in minimal weight loss, and there was no conclusive evidence for sustainable weight loss.
Tuomilehto HP, Seppa JM, Partinen MM, Peltonen M, Gylling H, Tuomilehto JO, et al. Lifestyle Intervention with Weight Reduction-First Line Treatment in Mild Obstructive **Sleep Apnea**. Am J Respir Crit Care Med. 2008 Nov 14. [Epub ahead of print]
Urban LE, McCrory MA, Dallal GE, et al. Accuracy of **stated energy contents of restaurant foods**. JAMA. 2011 Jul 20;306(3):287-93.
Vanherweghem JL, et al. Rapidly progressive **interstitial renal fibrosis** in young women: association with **slimming regimen** including **Chinese herbs**. Lancet. 1993 Feb 13;341(8842):387-91.
Vemmos K, Ntaios G, Spengos K, et al. Association between obesity and **mortality after acute first-ever stroke**: the obesity-stroke paradox. Stroke. 2011 Jan;42(1):30-6.
Vetter ML, Cardillo S, Rickels MR, Iqbal N. Narrative review: effect of bariatric surgery on **type 2 diabetes** mellitus. Ann Intern Med. 2009 Jan 20;150(2):94-103.
Villamor E, Cnattingius S. **Interpregnancy** weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet. 2006 Sep 30;368(9542):1164-70.
Villareal DT, et al. **Bone mineral density** response to caloric restriction-induced weight loss or exercise-induced weight loss: A randomized controlled trial. Arch Intern Med. 2006 Dec 11-25;166(22):2502-10. CR-induced weight loss, but not EX-induced weight loss, is associated with reductions in BMD at clinically important sites of fracture. These data suggest that EX should be an important component of a weight loss program to offset adverse effects of CR on bone.
Villareal DT, Chode S, Parimi N, et al. **Weight loss, exercise, or both** and physical function in obese older adults. N Engl J Med 2011; 364: 1218-29.
Virji A, Murr MM. Caring for patients after **bariatric surgery**. Am Fam Physician. 2006;73:1403-1408.
Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. **Financial incentive-based** approaches for weight loss: a randomized trial. JAMA. 2008 Dec 10;300(22):2631-7.
Wadden TA, Volger S, Sarwer DB, et al. A two-year randomized trial of obesity **treatment in primary care** practice. (**POWER-UP**) N Engl J Med 2011. DOI: 10.1056/NEJMoa1109220.
Wahi G, Parkin PC, Beyene J, et al. Effectiveness of interventions aimed at **reducing screen time** in children: a systematic review and meta-analysis of randomized controlled trials. Arch Pediatr Adolesc Med. 2011 Nov;165(11):979-86.
Wake Melissa, Baur Louise A, Gerner Bibi, et al. Outcomes and costs of **primary care surveillance** and intervention for overweight or obese children: the LEAP 2 randomised controlled trial. BMJ 2009;339:b3308, doi: 10.1136/bmj.b3308
Wang Lu; Lee I-Min; Manson JoAnn E.; et al. **Alcohol** Consumption, Weight Gain, and Risk of Becoming Overweight in Middle-aged and Older Women. Arch Intern Med. 2010;170(5):453-461.
Wang YC, McPherson K, Marsh T, et al. Health and economic burden of the projected obesity **trends in the USA and the UK**. Lancet. 2011 Aug 27;378(9793):815-25.
Waters E, de Silva-Sanigorski A, Hall BJ, et al. **Interventions for preventing obesity in children**. Cochrane Database Syst Rev 2011; 12:CD001871. Obesity-prevention programs targeted to children that emphasize improving nutrition and physical-activity levels are generally effective and worth the investment, according to a review of evidence on obesity-intervention strategies around the world.
Wee Christina C. A 52-Year-Old Woman With Obesity: Review of **Bariatric Surgery**. *JAMA*. 2009;302(10):1097-1104.
Weiss R, et al. Obesity and the **metabolic syndrome** in children and adolescents. N Engl J Med. 2004 Jun 3;350(23):2362-74.
Welsh JA, Sharma A, Abramson JL, et al. **Caloric sweetener consumption** and dyslipidemia among us adults. JAMA 2010; 303:1490-1497.
Weir Matthew A.; Beyea Michael M.; Gomes Tara; et al. **Orlistat and Acute Kidney Injury**: An Analysis of 953 Patients. *Arch Intern Med*. 2011;171(7):703-704.
WGO Practice Guidelines Obesity - August 2009 http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/22_obesity.pdf
Williams DE, et al. Prevalence of impaired **fasting glucose** and its relationship with cardiovascular disease risk factors in US adolescents, 1999-2000. Pediatrics. 2005 Nov;116(5):1122-6.
Wilson DM, Abrams SH, Aye T, Lee PD, Lenders C, Lustig RH, Osganian SV, Feldman HA; Glaser Pediatric Research Network Obesity Study Group. **Metformin** extended release treatment of adolescent obesity: a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. Arch Pediatr Adolesc Med. 2010 Feb;164(2):116-23.
Wing RR, et al. A **self-regulation program** for maintenance of weight loss. (STOP Regain)N Engl J Med. 2006 Oct 12;355(15):1563-71. As compared with receiving quarterly newsletters, a self-regulation program based on daily weighing improved maintenance of weight loss, particularly when delivered face to face.
Woodard GA, Encarnacion B, PerazaJ, et al. **Halo effect for bariatric surgery**. Arch Surg 2011; 10:1185-1190.
Wu RR, Zhao JP, Jin H, et al. Lifestyle intervention and **metformin for treatment of antipsychotic-induced** weight gain: a randomized controlled trial. JAMA. 2008 Jan 9;299(2):185-93.Lifestyle intervention and metformin alone and in combination demonstrated efficacy for antipsychotic-induced weight gain. Lifestyle intervention plus metformin showed the best effect on weight loss. Metformin alone was more effective in weight loss and improving insulin sensitivity than lifestyle intervention alone.
USPSTF- US Preventive Services Task Force, **Screening** for Obesity in **Children and Adolescents**: US Preventive Services Task Force Recommendation Statement Pediatrics 2010 0: peds.2009-2037
The USPSTF recommends that clinicians screen children aged 6 years and older for obesity and offer them or refer them to intensive counseling and behavioral interventions to promote improvements in weight status (grade B recommendation).
USPSTF- U.S. Preventive Services Task Force. **Screening** for obesity in **adults**: recommendations and rationale. Ann Intern Med. 2003 Dec 2;139(11):930-2.
Urban LE, McCrory MA, Dallal GE, et al. Accuracy of **stated energy contents of restaurant foods**. JAMA. 2011;306(3):287-293.
Van Cleave J, Gortmaker SL, Perrin JM. **Dynamics of obesity and chronic health conditions among children** and youth. JAMA. 2010 Feb 17;303(7):623-30.
Vilsbøll T, Christensen M, Junker AE, et al. Effects of **glucagon-like peptide-1 receptor agonists** (exenatide, liraglutide) on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2011;343:d7771.
Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. **Effectiveness of Weight Management Interventions** in **Children**: A Targeted Systematic Review for the USPSTF. Pediatrics. 2010 Jan 18.
Yancy William S Jr; Westman Eric C.; McDuffie Jennifer R.; et al. A Randomized Trial of a **Low-Carbohydrate** Diet vs **Orlistat Plus a Low-Fat** Diet for Weight Loss. Arch Intern Med. 2010;170(2):136-145.
Yanovski JA, Parikh SJ. Effects of **Calcium Supplementation** on Body Weight and Adiposity in Overweight and Obese Adults: A Randomized Trial. Ann Intern Med 2009; 821-829. (No effect)
Zheng W, McLerran DF, and Rolland B. Association between BMI and **risk of death** in more than one million Asians. New Engl J Med 2011; 364:719-729.

Useful websites:

American Heart Association: Healthy Lifestyle www.americanheart.org/presenter.jhtml?identifier=1200009
Centers for Disease Control and Prevention: Overweight and Obesity www.cdc.gov/nccdphp/dnpa/obesity/index.htm
Cochrane reviews www.cochrane.org
Lifestyle changes week by week plan for patients taking sibutramine www.changeforlifeonline.com
Heart Healthy Diet(s): http://www.**mayoclinic**.com/health/**mediterranean**-diet/CL00011 ; http://www.**cfp**.ca/content/57/8/894.full#ref-20
National Heart, Lung, and Blood Institute: Aim for a Healthy Weight! www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/index.htm
Obesity drug news www.obesity-news.com

TOP

Surgeon General: Physical activity and health: A report of the Surgeon General www.cdc.gov/nccdphp/sgr/sgr.htm
Rimonabant support site www.itswhatyougain.co.uk
UK multicentre obesity management project www.counterweight.org

TOP

Extras (RxFiles Herbal Weight Loss

Energy Drinks	**Health Canada: Safe Use of Energy Drinks.** Accessed online at http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/food-aliment/boissons-energ-drinks-eng.php. {Excessive drinking of energy drinks or mixing them with alcohol can have serious health effects. Energy drinks are meant to supply mental and physical stimulation for a short period of time. They usually contain caffeine, taurine (an amino acid, one of the building blocks of protein), vitamins and glucuronolactone, a carbohydrate. Energy drinks should not be confused with sports drinks such as Gatorade® or Powerade®. Sports drinks re-hydrate the body and provide sugars, which the body burns to create energy and replenish electrolytes.}
Glucomannan (in PGX PolyGlycopleX)	Plant fibre water-soluble: unabsorbable polysaccharide (glucose + mannose). May ↓LDL, ↓gastric emptying & improve BG control. Conflicting evidence. SE: gas, bloating, etc.

WEIGHT LOSS – "HERBAL / NATURAL" PRODUCTS

1 Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut. Ann Intern Med. 2005 Mar 15;142(6):477-8 .

2 Walsh DE, Yaghoubian V, Behforooz A. Effect of glucomannan on obese patients: a clinical study. Int J Obes. 1984;8(4):289-93.

3 Copeland P. How Successful are commercial weight-loss programs? Nat Clin Pract Endocrinol Metab. 2006;2:658-659.

4 Bui L, Nguyen D, Ambrose P. Blood pressure and heart rate effects following a single dose of bitter orange. Ann Pharmacother 2006;40:53-7.

5 Nykamp D, Fackih M, Compton A. Possible association of acute lateral-wall myocardial infarction and bitter orange supplement. Ann Pharmacother 2004;38:812-6.

6 Heymsfield S, Allison D, Vasselli J, et al. Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. JAMA 1988;280:1596-1600.

7 Natural Medicines Comprehensive Database 2006.

8 Pharmacists Letter. Problems with Weight Loss Products. Jan 2006

9 Robinson R., Griffith J., Nahata M., et al. Herbal Weight-loss supplement misadventures per a regiona poison centre. Ann Pharmacother 2004;38:787-90.

10 Pittler M, Ernst E. Dietary supplements for body weight reduction: a systematic review. Am J Clin Nutr 2004;79:529-36. {InfoPOEMS July 14, 2004. Evidence weak that any commonly used alternative products are effective for reducing weight in moderately overweight individuals. None of the products have been studied for longer than 3 months.}

11 Dwyer J, Allison D, Coates P. Dietary Supplements in Weight Reduction. J Am Diet Assoc 2005;105:S80-S86.

12 Micromedex 2010

Additional references:

Berz JP, Singer MR, Guo X et al. use of a **DASH food group** score to predict excess weight gain in adolescent girls in the National Growth and Health Study. Arch Pediatr Adolesc Med 2011; 165:540-546.

Bliddal H, Leeds AR, Stigsgaard L, Astrup A, Christensen R. Weight loss as **treatment for knee osteoarthritis** symptoms in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis. 2011 Oct;70(10):1798-803.

Canadian Physical Activity Guidelines-Jan 2011. Clinical Practice Guideline Development Report. Canadian Society for Exercise Physiology. http://www.csep.ca/CMFiles/Guidelines/CPAGuideline_Report_JAN2011.pdf

CARE Study Group. Maternal **caffeine intake during pregnancy** and risk of fetal growth restriction: a large prospective observational study. BMJ. 2008 Nov 3;337:a2332. doi: 10.1136/bmj.a2332. Caffeine consumption during pregnancy was associated with an increased risk of fetal growth restriction and this association continued throughout pregnancy. Sensible advice would be to reduce caffeine intake before conception and throughout pregnancy.

Carter PJ, Taylor BJ, Williams SM, et al. Longitudinal analysis of **sleep in relation to BMI and body fat in children**: the **FLAME** study. BMJ 2011;342:d2712.

Davies GA, Maxwell C, McLeod L, et al., Society of Obstetricians and Gynaecologists of Canada. **Obesity in pregnancy**. (**SOGC**) J Obstet Gynaecol Can 2010 Feb;32(2):165-73.

Dietary Guidelines for Americans (DGA) 2010. Full Guideline: http://www.health.gov/dietaryguidelines/dga2010/DietaryGuidelines2010.pdf , Executive summary: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/ExecSumm.pdf

Eisenberg MJ, Atallah R, Grandi SM, Windle SB, Berry EM. **Legislative approaches** to tackling the obesity epidemic. CMAJ. 2011 May 2.

FDA Dec/08 alerted consumers nationwide not to purchase or consume more than **25 different products** marketed for weight loss because they contain undeclared, active pharmaceutical ingredients that may put consumers' health at risk. The undeclared active pharmaceutical ingredients in some of these products include sibutramine (a controlled substance), rimonabant (a drug not approved for marketing in the United States), phenytoin (an anti-seizure medication), and phenolphthalein (a solution used in chemical experiments and a suspected cancer causing agent). The weight loss products, some of which are marked as "dietary supplements," are promoted and sold on various web sites and in some retail stores. FDA advises consumers who use the products to stop taking them and consult their healthcare professional immediately as the health risks posed by these products can be serious (for

TOP

example, high blood pressure, seizures, tachycardia, palpitations, heart attack or stroke). FDA also encourages consumers to seek guidance from healthcare professional before purchasing weight loss products. See the FDA News Release for a listing of the names of the 25 referenced products. Read the MedWatch 2008 safety summary, including links to http://www.fda.gov/medwatch/safety/2008/safety08.htm#Weight

FDA May/09 warned consumers to immediately stop using **Hydroxycut products by Iovate Health Sciences**, Inc. Hydroxycut products are associated with a number of **serious liver injuries**. Hydroxycut products are dietary supplements that are marketed for weight-loss, as fat burners, as energy-enhancers, as low carb diet aids, and for water loss under the Iovate and MuscleTech brand names. FDA has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, an indicator of potential liver injury, to liver damage requiring liver transplant. One death due to liver failure has been reported to FDA. Other health problems reported include seizures; cardiovascular disorders; and rhabdomyolysis, a type of muscle damage that can lead to other serious health problems such as kidney failure.

FDA Jan/10 notified consumers and healthcare professionals about a counterfeit and potentially harmful version of **Alli 60 mg capsules** (120 count refill kit). The **counterfeit version** contained the controlled substance sibutramine and did not contain orlistat, the active ingredient.

FDA July/10 analysis of **Que She** found that it contains: fenfluramine – a stimulant drug withdrawn from the U.S. market in 1997 after studies demonstrated that it caused serious heart valve damage, propranolol – a prescription beta blocker drug that can pose a risk to people with bronchial asthma and certain heart conditions, sibutramine – a controlled substance and prescription weight loss drug, sibutramine was the subject of a recent study whose preliminary findings showed an association between sibutramine use and increased risk of heart attack and stroke in patients who have a history of heart disease, & ephedrine –a stimulant drug that is legally marketed over-the-counter for temporary asthma relief but can pose a risk to people with cardiovascular disease.

FDA Aug/10 lab analysis of **Solo Slim** was found to contain the undeclared drug ingredient Didesmethyl Sibutramine.

FDA July/10 lab analysis of **Slim-30** Herb Supplement distributed by the company was found to contain undeclared N-Desmethyl Sibutramine & Sibutramine.

FDA July/10 lab analysis of this herb supplement, **Joyful Slim** Herb Supplement, was found to contain the undeclared drug, desmethyl sibutramine.

FDA Oct/10 notified consumers that **Slimming Beauty Bitter Orange Slimming Capsules** contain sibutramine, a prescription-only drug which is a stimulant.

FDA Dec/10 has received multiple reports of adverse events associated with the use of **Fruta Planta**, including several cardiac events and one death. FDA lab analysis confirmed that Fruta Planta contains sibutramine.

FDA Jan/11 laboratory analysis confirmed that **Celerite Slimming Capsules** contain sibutramine

FDA Mar/11 lab analysis of **Svelte 30** orange & gray capsules determined that the product contains Sibutramine.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analyses of **Celerite Slimming Tea**: Recall - were found to contain undeclared Sibutramine.

FDA May/11 laboratory analysis confirmed that "**Slim Xtreme Herbal Slimming Capsule**" contains sibutramine.

FDA July/11 is advising consumers not to purchase or use "**Slim Forte Slimming Capsules**," "**Slim Forte Slimming Coffee**," and "**Botanical Slimming Soft Gel & Slim Forte Double Power Slimming Capsules**. FDA laboratory analysis confirmed that these products contain sibutramine.

FDA Dec/11 took joint action against several companies selling over-the-counter **hCG products** that falsely and illegally claim to promote weight loss. Labeled "homeopathic" by the seven companies who received the letters, the products contain human chorionic gonadotropin (hCG), a hormone produced during pregnancy by cells that form the placenta. 1. HCG Diet Direct LLC- HCG Diet Homeopathic Drops, 2. The hCG Drops LLC- Homeopathic HCG, 3. HCG Platinum LLC; RightWay Nutrition- HCG Platinum, HCG Platinum X-30, HCG Platinum X-14, 4. Nutri Fusion Systems LLC- HCG Fusion 30, HCG Fusion 43, 5. www.resetthebody.com; www.theoriginalhcgdrops.com-Homeopathic Original HCG, Homeopathic HCG, 6. Hcg-miracleweightloss.com- HCG Extra Weight Loss Homeopathic Drops, 7. Natural Medical Supply- Alcohol Free hCG Weight Loss Formula.

FDA Feb/12 is advising consumers not to purchase or use "**Japan Weight Loss Blue**," a product for weight loss sold on various websites, laboratory analysis confirmed that "Japan Weight Loss Blue" contains sibutramine, analogs of sibutramine, and ephedrine alkaloids.

FDA Apr/12 laboratory analysis confirmed that "**Japan Rapid Weight Loss Diet Pills Yellow**" contains sibutramine and phenolphthalein.

Finucane MM, Stevens GA, Cowan MJ. **National, regional, and global trends in body-mass index since 1980**: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011; DOI: 10.1016/S0140-6736(10)62035-5.

Health Canada April 2007: The **Safe Use of Health Products** for Weight Loss. http://www.hc-sc.gc.ca/iyh-vsv/med/weight-amaigr_e.html

Health Canada Apr/07 is warning consumers about **Bitter orange** & cardiovascular reactions in the Canadian Adverse Reactions April 2007 Newsletter.

Health Canada Apr/07 is warning consumers from the Hong Kong Department of Health found **Lexscl Fat Rapid Loss capsules to be adulterated with sibutramine** and thyroid hormones.

Health Canada via July/07 Medsafe also advised the public not to use the product **Dai Dai Hua Jiao Nang** because it was found to contain sibutramine.

Health Canada Aug/07 is advising Canadians of a recall in the United States of one lot of **Metaboslim Apple Cider Vinegar**, which is marketed as a dietary supplement, because it has been found to contain sibutramine, a prescription medication that should only be taken under medical supervision.

Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da**

TOP

Dai Dai Hua Jiao Nang, **J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.

Health Canada Jan/08 is warning Canadians not to use the unauthorized product **Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules** (batch number 28012007 / expiration date: Jan 2009). This product is promoted for weight loss and has been found to contain a derivative of the prescription drug sibutramine.

Health Canada April/08 is advising consumers not to use **Xian Zhi Wei II** was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.

Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Dan Bai Shou Shen Su** was found to contain undeclared thyroid hormones and sibutramine. **Karntien and Karntien Easy to Slim** were adulterated with sibutramine and a compound that is similar in structure to sibutramine (N-desmethylsibutramine). **More Slim** was found to contain the undeclared pharmaceutical ingredient sibutramine. **Soloslim** was found to contain an undeclared substance similar in structure to the prescription drug sibutramine. It also contains the prescription drug L-carnitine, as well as synephrine, which is not authorized for sale in weight loss products in Canada.

Health Canada Aug/08 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of Natural (Xin Yi Dai) and Lasmi because Natural (Xin Yi Dai) was found to contain sibutramine and phenolphthalein, and Lasmi was found to contain sibutramine and spironolactone. The Hong Kong Department of Health warned against the use of AA Qu Feng Shu Jin Wan because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. Apisate contained fenfluramine and Energy ll contained sibutramine. Obat Asam Urat and Asam Urat both contained dexamethasone, phenylbutazone and piroxicam. The Hong Kong Department of Health warned against the use of Slim 3in1 (Xiao Nan zhi Bao) because it was found to contain the undeclared pharmaceutical ingredients sibutramine and phenolphthalein.

Health Canada Sep/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of **Hanguo shoushen yihao** (meiti xing) because it was found to contain the undeclared pharmaceutical ingredient sibutramine. The Hong Kong Department of Health warned against the use of **ARMA - Sin Gang San** and New ARMA - Sin Gang San because they were found to contain the undeclared pharmaceutical ingredients sibutramine and fenfluramine.

Health Canada Nov/08 is advising that the Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine.

Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains sibutramine.

Health Canada Mar/09 Foreign Product: **68 Weight Loss Products**; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien & Relacore. Plus Lami, Linglongquxian, Menergy M-Essence, Nyal Day & Night Cold & Flu Fighter (AUST L 146264), Nyal Cold & Flu Fighter (AUST L 146263), 999 Radix Notoginseng, Batch no. 0807021, Slim Pure, Carbohydrate, Kalomee, K Carbohydrate, K Tighten Slim, & K Slimming Pills. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php

Health Canada June/09 Foreign Product Alerts: **Jia Yi Jian** (undeclared sibutramine & tadalafil); **Shan Dian Qiang Xiao Shou** (undeclared sibutramine & phenolphthalein).

Health Canada June/09 is warning consumers not to use the unauthorized product **Slim Magic Herbal**, which is promoted as a weight-loss product, as it was found to contain an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning consumers not to use the unauthorized product **Nutural Slim**, which is promoted as a weight-loss product, as it was found to contain the undeclared pharmaceutical ingredient sibutramine and also an undeclared pharmaceutical ingredient similar to sibutramine.

Health Canada June/09 warns of foreign Product Alerts: ***Herbal Xenicol*** because it contains undeclared cetilistat. ***BioEmagrecim***, which the FDA had previously warned contained sibutramine, was also found to contain fluoxetine, furosemide and fenproporex. Products: ***Slimbionic***, ***Xsvelten***, ***999 Fitness Essence***, ***24" ince***, ***Light Some***, ***Paiyouji***, ***Pearl White Slimming***, & ***Reducing Weight Easily*** contain undeclared pharmaceutical ingredients (sibutramine and/or phenolphthalein) and/or excessive levels of lead, and may cause serious health effects..

Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the

TOP

border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is warning consumers not to use "**RevolutionDS Weight Loss**", an unauthorized health product promoted for weight loss, because it contains benzylpiperazine (BZP), and may pose serious health risks.

Health Canada Dec/09 is advising consumers not to use **Show Party**: Hong Kong Department of Health warned consumers not to buy or consume [shou-shen pai] after it was found to contain undeclared sibutramine and phenolphthalein.

Health Canada Jan/10 informs that U.S. FDA: **Pai You Guo** contains sibutramine and phenolphthalein. Hong Kong Department of Health: **Ku Xiu Ba Xiang Jian Fei Wan** contains sibutramine and an unauthorized substance similar to sibutramine; **Super Slim (Yani)** contains sibutramine and phenolphthalein; **SHoufsy** contains sibutramine & **MIGAC (sic) FAT BURMING (sic) FACTOR** contains sibutramine.

Health Canada Jan/10 is warning consumers not to use the unauthorized product "**The Slimming Coffee**," which was previously sold as "**Lose Weight Coffee**," because it was found to contain sibutramine.

Health Canada Mar/10 is warning Canadians that an unauthorized health product, "**Herbal Diet Natural**" has been found on the Canadian market and contains an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning Canadians that an unauthorized health product, "**West Pharm Therma Lean Fat Burner Energizer**" was found on the Canadian market. West Pharm Therma Lean Fat Burner Energizer contains Ephedrine and caffeine, which combined together, may cause serious and possibly fatal adverse effects.

Health Canada Apr/10 is warning Canadians that an unauthorized health product, "**Slim-30**" distributed in Ontario and Quebec by Duxx Enterprises Inc., contains an undeclared pharmaceutical ingredient similar to the prescription drug, sibutramine.

Health Canada May/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Ba Bao Xiao Ke Da**n The Hong Kong Department of Health warned consumers not to buy or use Ba Bao Xiao Ke Dan after it was found to contain undeclared glibenclamide. 2. **Seven Slim 7 Seshou** (Qingchun Shaonüxing, Jieshixing, Guifurenxing, Songchixing), Shoushen Jiaoguan-Tinei Yundong Wan (Jian Xiabanshen, Jian Quanshen Feipang) The Hong Kong Department of Health warned consumers not to buy or use the six products listed above after they were found to contain undeclared sibutramine and phenolphthalein.

Health Canada May/10 is advising consumers not to use 1. **Botanical Slimming 100% Natural Soft Gel, also sold as Meizitang** Australian Therapeutic Goods Administration warned consumers not to buy or use this product after it was found to contain undeclared sibutramine. 2. **Marsha Slim Plus** Hong Kong Department of Health warned consumers not to buy or use Marsha Slim Plus after it was found to contain undeclared sibutramine, an unauthorized substance similar to sibutramine and phenolphthalein. 3. **S&S Super Slender** The Hong Kong Department of Health warned consumers not to buy or use S&S Super Slender after two samples were found to contain agent similar to sibutramine. One of the tested samples also contained undeclared sibutramine and phenolphthalein.

Health Canada June/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **COMECOO**, **ZHONGCAOYAO-JIANKANGJIANFEI** The Hong Kong Department of Health warned consumers not to buy or consume these two products after they were found to contain undeclared phenolphthalein, sibutramine and two unauthorized substances similar to sibutramine. 2. **Qingzhi Santian Shou** The Hong Kong Department of Health warned consumers not to buy or consume Qingzhi Santian Shou after it was found to contain undeclared sibutramine and an unauthorized substance similar to sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) 1. **Po Chai Pills** (capsule form) The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain undeclared sibutramine and phenolphthalein. Sibutramine is a prescription drug and should only be used under the supervision of a health care practitioner while phenolphthalein is no longer authorized for sale in Canada because it may cause cancer. Po Chai Pills (capsule form) has been recalled by the manufacturer. 2. **LiPO-8 Cap and Glucomi 600 Cap** The Hong Kong Department of Health warned consumers not to buy or use these products because they contain undeclared sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume *1 Body Beautiful* after it was found to contain undeclared phenolphthalein and sibutramine. 2. **USA Yaku Cell Slimming Capsules, Dong Gua Pai You Su, Qing Gua Pai You Su, and Mu Gua Pai You Su** The Hong Kong Department of Health warned consumers not to buy or consume these four products after they were found to contain undeclared phenolphthalein, sibutramine and an unauthorized substance similar to sibutramine.

Health Canada Aug/10 is advising consumers not to use the following foreign health product(s): **Que She** The U.S. FDA warned consumers not to buy or use Que She after it was found to contain undeclared fenfluramine, propranolol, sibutramine and ephedrine. **Sheng Yuan Fang** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use Sheng Yuan Fang after it was found to contain undeclared phenolphthalein and sibutramine.

Health Canada Sep/10 is advising consumers not to use : **Joyful Slim** Herb Supplement The U.S. FDA informed consumers of a recall of one lot (#101408) of

TOP

Joyful Slim Herb Supplement after FDA tests found it to contain undeclared desmethyl sibutramine. The lot is being voluntarily recalled nationwide in the U.S. by the company J & H Besta Corp.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Goya–Bitter Melon - Miyura Fit'x Capsules** contained undeclared phenolphthalein and sibutramine **2. Solo Slim Extra Strength - Revivexxx Extra Strength** contained undeclared didesmethyl sibutramine

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Slimming Beauty Bitter Orange Slimming Capsule (Slimming Beauty)** The U.S. Food and Drug Administration warned consumers not to buy or use Slimming Beauty after FDA lab tests revealed that this product contains undeclared sibutramine.

Health Canada Jan/11 The product **Synerate**, manufactured for Strive and distributed by Upper 49th, is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. Synerate, a product used for weight loss or body building, contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Feb/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Fruta Planta, Reduce Weight Fruta Planta** The U.S. FDA warned consumers not to buy or use Fruta Planta and Reduce Weight Fruta Planta after FDA lab tests revealed that this product contains undeclared sibutramine. **2. Slimming Factor** The Australian TGA warned consumers not to buy or use Slimming Factor after TGA lab tests confirmed the presence of the undeclared substances sibutramine, fenfluramine and phenolphthalein. According to the TGA release, the product is sold over the Internet.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Celerite Slimming Capsules**: The U.S. FDA informed consumers of a company recall of CeleriteTM Slimming Capsules after it was found to contain undeclared sibutramine. 2. **Herbal Flos Lonicerae** (Herbal Xenicol) Natural Weight Loss Formula: The product was found to contain undeclared sibutramine at more than twice the dose that was normally prescribed before sibutramine was removed from the UK market in 2010.

Health Canada May/11 is advising consumers not to use: 1. **Dr. Health Series CM Factor** The Hong Kong Department of Health warned consumers not to buy or use this product after found to contain substance similar to sibutramine.

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Slim Xtreme Herbal Slimming Capsules** The U.S. Food and Drug Administration informed consumers of a voluntary recall after Slim Xtreme Herbal Slimming Capsules was found to contain undeclared sibutramine.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Celerite Slimming Tea** The U.S. FDA informed consumers of a company recall of Celerite Slimming Tea after it was found to contain undeclared sibutramine. **2. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet. **3. Fifteen products promoted for weight loss** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use these 15 products after they were found to contain at least one of the following undeclared substances: phenolphthalein, sibutramine, and/or an unauthorized substance similar to sibutramine.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **Slim Forte Slimming Capsules**, **Slim Forte Double Power Slimming Capsules**, **Slim Forte Slimming Coffee** and **Meizitang Botanical Slimming Soft Gel**-The U.S. Food and Drug Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **OxyELITE Pro capsules and Pure Fat Three Days Reduce Weight capsules**- The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine), or a prescription drug (yohimbine).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. 1. **Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones). 2. **Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al,** and **Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine). 3. **Slimming Kapsul** The Hong Kong Department of Health warned that this weight-loss product contains an unauthorized drug (sibutramine) and a prescription drug (spironolactone). 4. **Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a

TOP

prescription drug (glyburide).
Health Canada Jan/12 advises: 1)**17 weight loss products (see Alert for a complete list)** A-Slim 100% Natural Slimming Capsule, Acai Berry Soft Gel ABC, Advanced Slim 5 >DaiDaiHuaJiaoNang, Dream Body Slimming Capsule, Fruit Plant Lossing Fat Capsule, Health Slimming Coffee, Ja Dera 100% Natural Weight Loss Supplement, Leisure 18 Slimming Coffee, Lishou, Magic Slim Tea, Magic Slim Weight Reduction Capsule, P57 Hoodia, Pai You Guo Slim Tea, PhentraBurn Slimming Capsules, Slender Slim 11 Tengda. The U.S. Food and Drug Administration warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Slimina weightloss capsules, S-shape slim capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain prescription drugs (propranolol, nifedipine) and/or unauthorized drugs (sibutramine, fenfluramine, phenolphthalein). **3. Cardiotium, Paidusu, SlimEasy Herbs Capsule, Tianran Zuanshi Xianweisu** The Hong Kong Department of Health warned that these health products contain prescription drugs (losartan, atorvastatin, thyroxine) and/or unauthorized drugs (sibutramine, phenolphthalein).
Health Canada May/12 1. **CanSui; Lexscl Fat Rapid Loss Capsule; The Extreme-thin Fat Burning Bomb; Xiu Zhi Su L-Carnitine Slimming Capsule** The Hong Kong Department of Health warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). 2. **Lipro Diet Pills; Xiyouji Qingzhi** weight loss capsules The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine).
Health Canada June/12 **1. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil). **2. Japan Weight Loss Blue, Japan Rapid Weight Loss Diet Pills Green; Japan Rapid Weight Loss Diet Pills Yellow:** The U.S. Food and Drug Administration warned that these weight loss products contain prescription drugs (sibutramine, ephedrine alkaloids) and unauthorized drugs (phenolphthalein, and substances similar to sibutramine).
Health Canada Jun/12 testing has identified that the weight loss product "**ZXT Gold**" bee pollen capsules contain sibutramine and phenolphthlalein.
Jebb SA, Ahern AL, Olson AD et al. Primary care **referral to a commercial provider** for weight loss treatment versus standard care: a randomized controlled trial. Lancet 2011
Lee JM, Gebremariam A, Vijan S, Gurney JG. **Excess Body Mass Index-Years**, a Measure of Degree and Duration of Excess Weight, and Risk for Incident Diabetes. Arch Pediatr Adolesc Med. 2011 Sep 12
McDonnell WM, et al. Fulminant Hepatic Failure After Use of the Herbal Weight-Loss Supplement **Exilis**. Ann Intern Med. 2009 Nov 3;151(9):673-674.
Mediterranean diet: [Mayo Clinic website] choose this heart-healthy diet option. Rochester, MN: Mayo Clinic; 2010. Available from: www.mayoclinic.com/health/mediterranean-diet/CL00011 . Accessed 2011 May 24.
Medical Letter. Treatment Guidelines. **Diet, Drugs & Surgery for weight loss**. April 2011.
MHRA Feb/12 Herbal sliming products found to contain potentially dangerous undeclared pharmaceuticals: **Expelling Grease Slimming Abdomen, V12 Fruit Slimming, 100% Natural Weight Loss Coffee, Leisure 18 Slimming Orange Juice, Fashion Slimming Milk Shake, Langli, Ya Buk & Fruit and vegetables lose weight**. MHRA has received advice from the Danish Medicines Agency that these unlicensed products have been tested and found to contain the Prescription Only Medicine Sibutramine.
MHRA Feb/12 Following a safety alert issued in October 2010 about slimming products containing Paiyouji the Agency has received a further complaint about a product called '**Paiyouji Plus - Fast Acting Slimming Tea**'. This product has been tested by the Agency and, as in the case of other Paiyouji products, found to contain sibutramine.
Mozaffarian Dariush, Hao Tao, Rimm Eric B., eft al. Changes in **Diet and Lifestyle and Long-Term Weight Gain** in Women and Men. N Engl J Med 2011; 364:2392-2404.
Padwal RS, Pajewski NM, Allison DB, Sharma AM. Using the **Edmonton obesity staging system to predict mortality** in a population-representative cohort of people with overweight and obesity. CMAJ. 2011 Aug 15.
Pharmacist's Letter: Health Benefits of Drinking Green Tea. Nov 2006.
Pharmacist's Letter. **PolyGlycopleX (PGX)** for Weight Loss. April 2010.
Pharmacist's Letter. **Raspberry ketone** for Weight Loss. May 2012.
Poirier P, Cornier MA, Mazzone T. **Bariatric surgery and cardiovascular risk factors**: A scientific statement from the American Heart Association (**AHA**). Circulation. 2011; DOI: 10.1161/CIR.0b013e3182149099. http://circ.ahajournals.org/cgi/reprint/123/15/1683
Read J. Leighton, Shortell Stephen M.. **Interactive Games** to Promote Behavior Change in Prevention and Treatment. JAMA. 2011;305(16):1704-1705.
Safe Use of Health Products for Weight Loss. Health Canada April 2007 http://www.hc-sc.gc.ca/iyh-vsv/med/weight-amaigr_e.html
Savitz DA, Chan RL, Herring AH, et al. **Caffeine** and miscarriage risk. Epidemiology. 2008 Jan;19(1):55-62. There is little indication of possible harmful effects of caffeine on miscarriage risk within the range of coffee and caffeine consumption reported, with a suggested reporting bias among women with losses before the interview.

TOP

Søvik TT, Aasheim ET, Taha O, Engstro¨m M, et al. Weight loss, cardiovascular risk factors, and quality of life **after gastric bypass and duodenal switch**. A randomized trial. Ann Intern Med. 2011;155: 281-91.

Spring B, Schneider K, McFadden HG, et al. Multiple behavior changes in diet and activity: A randomized controlled trial using **mobile technology**. Arch Intern Med 2012; 172:789-796.

Striano P, Zara F, Minetti C, Striano S. Chitosan may decrease serum valproate and increase the risk of seizure reappearance. BMJ. 2009 Sep 24;339:b3751. doi: 10.1136/bmj.b3751.

Tirosh A et al. Adolescent **BMI trajectory and risk of diabetes versus coronary disease**. N Engl J Med 2011 Apr 7; 364:1315.

Vanherweghem JL, et al. Rapidly progressive **interstitial renal fibrosis** in young women: association with **slimming regimen** including **Chinese herbs**. Lancet. 1993 Feb 13;341(8842):387-91.

Villareal DT, Chode S, Parimi N, et al. **Weight loss, exercise, or both** and physical function in obese older adults. N Engl J Med 2011; 364: 1218-29.

Weng X, Odouli R, Li DK. Maternal **caffeine** consumption during **pregnancy** and the risk of miscarriage: a prospective cohort study. Am J Obstet Gynecol. 2008 Jan 24; [Epub ahead of print] Our results demonstrated that high doses of caffeine intake during pregnancy increase the risk of miscarriage, independent of pregnancy-related symptoms.

TOP

Acknowledgements: Contributors & Reviewers: Norman Wong (Endocrinology, Calgary); Arthur Voth (Endocrinology, Edmonton); G. Casper-Bell (Endocrinology, Saskatoon); T. Arnason (Endocrinology, Saskatoon); D. Blackburn (PharmD, Col of Pharmacy, U of S.), R. Halil (PharmD, Ottawa) & the RxFiles Advisory Committee.

Prepared by: *Jason Kielly, B. Jensen* BSP, *L. Regier* BSP, BA

References: THYROID DISORDERS

[1] Toward Optimized Practice Clinical Practice Guideline Working Group. Clinical practice guidelines: investigation and management of primary thyroid dysfunction. Edmonton AB: Toward Optimized Practice Program: 2008 Update. Available from: www.topalbertadoctors.org/cpgs/thyroid_dysfunction.html (accessed September 2009).

[2] American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypothyroidism and hyperthyroidism. Endocr Pract 2002;8(6):457-69. Available from: http://www.aace.com/pub/pdf/guidelines/hypo_hyper.pdf (accessed September 2009).

[3] Sherman SI, Talbert RL,Thyroid disorders. In JT DiPiro, RL Talbert, GC Yee, et al (eds), Pharmacotherapy: A Pathophysiological Approach, 7th ed. On-line. www.accesspharmacy.com. New York, McGraw-Hill, 2008. (accessed September 2009).

[4] American Thyroid Association Professional Guidelines. Available from: http://thyroidguidelines.net/ (accessed September 2009).

[5] British Thyroid Association. UK Guidelines for the Use of Thyroid Function Tests. Available from: http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf (accessed September 2009).

[6]Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004 Jan 14;291(2):228-38.

[7] Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab. 2005 Jan;90(1):581-5; discussion 586-7.

[8] Jensen KA. Update on Nonmalignant Thyroid Disorders. Pharmacy Practice. Continuing Education Lesson. June 2009

[9] Vaidya B, Pearce SH. Management of hypothyroidism in adults. BMJ. 2008 Jul 28;337:a801. doi: 10.1136/bmj.a801

[10] U.S. Preventive Services Task Force. Screening for thyroid disease:recommendation statement. Ann Intern Med. 2004 Jan 20;140(2):125-7.

[11] American Thyroid Association. Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer 2006.
Hartl DM, Travagli JP. The updated American Thyroid Association Guidelines for management of thyroid nodules and differentiated thyroid cancer: a surgical perspective. Thyroid. 2009 Nov;19(11):1149-51. http://www.liebertonline.com/doi/pdfplus/10.1089/thy.2009.0110?cookieSet=1
Misra Madhusmita, Parangi Sareh,. Rosset Douglas S al. Case 38-2010 — A 13-Year-Old Girl with an Enlarging Neck Mass (Papillary thyroid carcinoma). N Engl J Med 2010; 363:2445-2454.

[12] Haugen BR, Cooper DS, Emerson CH, Luster M, Maciel RM, Biscolla RP, Mazzaferri EL, Medeiros-Neto G, Reiners C, Robbins RJ, Robinson BG, Schlumberger M, Yamashita S, Pacini F. Expanding indications for recombinant human TSH in thyroid cancer. Thyroid. 2008 Jul;18(7):687-94.

[13] Herrick B. Subclinical hypothyroidism. Am Fam Physician. 2008 Apr 1;77(7):953-5.

[14] Pham CB, Shaughnessy AF. Should we treat subclinical hypothyroidism? BMJ. 2008 Jul 16;337:a834. doi: 10.1136/bmj.a834.

[15] Ross DS. Subclinical hypothyroidism. In: UpToDate Online. UpToDate Waltham, MA. Available from: www.uptodate.com (accessed September 2009).
Rodondi N, den Elzen WP, Bauer DC, et al. Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010 Sep 22;304(12):1365-74. Subclinical hypothyroidism is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater.
Lee Jennifer S.; Buzkova Petra; Fink Howard A.; et al. Subclinical Thyroid Dysfunction and Incident Hip Fracture in Older Adults Arch Intern Med. 2010;170(21):1876-1883.

[16] VillarHCCE, Saconato H, Valente O, Atallah ÁN. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database of Systematic Reviews* 2007, Issue 3.Art.No.:CD003419.DOI: 10.1002/14651858.CD003419.pub2.

[17] Ross DS. Subclinical hyperthyroidism. In: UpToDate Online. UpToDate Waltham, MA. Available from: www.uptodate.com (accessed September 2009).
Donangelo I, Braunstein GD. Update on Subclinical Hyperthyroidism. Am Fam Physician. 2011;83(8):933-938.

[18] Therapeutic Choices 5rd Edition

[19] Micromedex 2011

[20] Repchinsky, *C.* Compendium of Pharmaceuticals and Specialties *(CPS)*, Ottawa: Canadian Pharmacists Association, 2009.

[21] Lexi-Comp 2009.

[22] Lau E. The 2008-2009 Drug Handbook and Formulary; The Hospital for Sick Children. Toronto: The Hospital for Sick Children, 2008.

[23] Dipchand A, Friedman J. The Hospital for Sick Children Handbook of Pediatrics. Toronto: The Hospital for Sick Children, 2008

[24] Pharmacist's Letter. Drugs & Substances that **Reduce Absorption** of Levothyroxine. Dec 2008.

[25] Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.

Additional References:

Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, Mandel SJ, Stagnaro-Green A. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007 Aug;92(8 Suppl):S1-47.

Abraham P, Avenell A, Watson WA, Park CM, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD003420. DOI: 10.1002/14651858.CD003420.pub3.

Alexander EK, Kennedy GC, Baloch ZW, et al. **Preoperative diagnosis of benign thyroid nodules** with indeterminate cytology. N Engl J Med 2012. DOI: 10.1056/NEJMoa1203208.

American Thyroid Association; Endocrine Society; American Association of Clinical Endocrinologists. Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. Thyroid. 2004 Jul;14(7):486.

Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab. 2005 May;90(5):2666-74

TOP

Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.
Arnason T, Clarke DB, Imran SA. Hyperthyroidism caused by a **pituitary adenoma**. CMAJ. 2011 Aug 9;183(11):E757.
Åsvold BO, Vatten LJ, Midthjell K, Bjøro T. **Serum TSH within the reference range** as a predictor of future hypothyroidism and hyperthyroidism: 11-year follow-up of the HUNT Study in Norway. J Clin Endocrinol Metab. 2012 Jan;97(1):93-9.
Bahn, Rebecca S. **Graves' Ophthalmopathy**. N Engl J Med 2010 362: 726-738.
Barczyński M, Konturek A, Gołkowski F, Hubalewska-Dydejczyk A, Cichoń S, Nowak W. Five-Year Follow-up of a Randomized Clinical Trial of **Unilateral Thyroid Lobectomy** with or Without Postoperative Levothyroxine Treatment. World J Surg. 2010 Feb 4. Prophylactic LT4 treatment significantly decreased the recurrence rate of nodular goiter in the contralateral thyroid lobe and the need for completion thyroidectomy, mostly among patients with iodine deficiency.
Bauer DC, McPhee SJ: Thyroid Disease. In: SJ McPhee, WF Ganong (eds), Pathophysiology of Disease: An Introduction to Clinical Medicine, 5th ed. On-line. www.statref.com. New York, McGraw-Hill, 2006. (accessed September 2009).
Becker DV, Braverman LE, Delange F, et al. **Iodine supplementation** for pregnancy and lactation—United States and Canada: recommendations of the American Thyroid Association. Thyroid 2006; 16: 949–51.
Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. **Higher maternal TSH levels in pregnancy** are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol* 2009;160:985-91.
Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008 Feb;29(1):76-131. Epub 2007 Nov 8.
Bochukova E et al. A **Mutation in the Thyroid Hormone Receptor Alpha Gene**. N Engl J Med. 2011 Dec 14.
Bogazzi F, Bartalena L, Martino E. Approach to the patient with **amiodarone-induced thyrotoxicosis**. J Clin Endocrinol Metab. 2010 Jun;95(6):2529-35.
Brent GA. Clinical practice. Graves' disease. N Engl J Med. 2008 Jun12;358(24):2594-605
Clyde PW, Harari AE, Getka EJ, Shakir KM. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. JAMA. 2003 Dec 10;290(22):2952-8.
Cooper DS. Antithyroid drugs. N Engl J Med. 2005 Mar 3;352(9):905-17.
Cooper DS. Approach to the patient with subclinical hyperthyroidism. J Clin Endocrinol Metab. 2007 Jan;92(1):3-9.
Cooper DS. Hyperthyroidism. Lancet. 2003 Aug 9;362(9382):459-68.
Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012 Jan 20.
Costeira MJ, Oliveira P, Santos NC, et al. Psychomotor development of children from an **iodine-deficient region**. J Pediatr. 2011 Sep;159(3):447-53.
Counts D, Varma SK. Hypothyroidism in children. Pediatr Rev. 2009 Jul;30(7):251-8.
Davies Louise; Welch H. Gilbert. **Thyroid Cancer** Survival in the United States: Observational Data From 1973 to 2005. Arch Otolaryngol Head Neck Surg. 2010;136(5):440-444.
De Pergola G, Ciampolillo A, Alò D, et al. Free Triiodothyronine is associated with **smoking** habit, independently of obesity, body fat distribution, insulin, and metabolic parameters. J Endocrinol Invest. 2010 Jul 13.
Dickerman AL, Barnhill JW. **Abnormal thyroid function tests in psychiatric patients**: a red herring? Am J Psychiatry. 2012 Feb 1;169(2):127-33.
Drugs for thyroid disorders. Treat Guidel Med Lett. 2009 Aug;7(84):57-64; quiz 2p following 64.
Duclos A, Peix JL, Colin C et al. Influence of **experience on performance of individual surgeons in thyroid surgery**: prospective cross sectional multicentre study. BMJ. 2012 Jan 10;344:d8041.
Escobar-Morreale HF, Botella-Carretero JI, Gómez-Bueno M, Galán JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med. 2005 Mar 15;142(6):412-24.
Faber J, Galløe AM. Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. Eur J Endocrinol. 1994 Apr;130(4):350-6.
FDA Propylthiouracil-Induced Liver Failure June/09 FDA has identified 32 AERS cases (22 adult and 10 pediatric) of serious liver injury associated with propylthiouracil use. Of the adult cases, 12 deaths and 5 liver transplants occurred. Among the pediatric patients, 1 case resulted in death and 6 in liver transplants. In contrast, for methimazole 5 AERS cases of serious liver injury were identified. All five cases were in adult patients and 3 resulted in death. (**April 21, 2010**: Propylthiouracil: FDA has added a Boxed Warning to the label for propylthiouracil, to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and pediatric patients using this medication. A boxed warning has been added to the hyperthyroidism drug propylthiouracil (PTU) to alert clinicians about the drug's risk for severe liver injury, the FDA announced on Wednesday. The new labeling is based in part on postmarketing safety reports of severe liver injury — including 15 deaths — in 23 adult and 11 pediatric patients taking PTU. A warning about the potential dangers of the drug was issued by the agency last June. The FDA recommends that PTU only be used in patients who cannot tolerate methimazole or other treatments for hyperthyroidism and in women just before and during their first trimester of pregnancy. Patients will now receive a medication guide upon filling a prescription for PTU. FDA drug safety communication)
Fiore E, Rago T, Provenzale MA, Scutari M, et al. L-thyroxine-treated patients with **nodular goiter** have lower serum TSH and lower frequency of **papillary thyroid cancer**: results of a cross-sectional study on 27 914 patients. Endocr Relat Cancer. 2010 Feb 18;17(1):231-9.
Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P. Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. Lancet. 1999 Jun 19;353(9170):2111-5.
Gerdes AM, Iervasi G. Thyroid replacement therapy and **heart failure**. Circulation. 2010 Jul 27;122(4):385-93.
Glinoer D, Riahi M, Grün JP, Kinthaert J. Risk of **subclinical hypothyroidism in pregnant** women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab* 1994;79:197-204.
Giovanella L. Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer. 2008 Jan 1;112(1):220; author reply 220-1.
Glatstein MM, Garcia-Bournissen F, Giglio N, Finkelstein Y, Koren G. Pharmacologic treatment of hyperthyroidism during lactation. Can Fam Physician. 2009 Aug;55(8):797-8.
Glinoer D, de Nayer P, Bex M; Belgian Collaborative Study Group on Graves' Disease. Effects of l-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study. Eur J Endocrinol. 2001 May;144(5):475-83.
Grogan RH, Mitmaker EJ, Hwang J, et al. A Population-Based Prospective Cohort Study of Complications after **Thyroidectomy in the Elderly**. J Clin Endocrinol Metab. 2012 Mar 14.
Haentjens P, Van Meerhaeghe A, Poppe K, Velkeniers B. Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. Eur J Endocrinol. 2008 Sep;159(3):329-41.
Harjai KJ, Licata AA. Effects of **amiodarone** on thyroid function. Ann Intern Med. 1997 Jan 1;126(1):63-73.
Haymart MR, Banerjee M, Stewart AK, et al.Use of **radioactive iodine for thyroid cancer**. JAMA. 2011 Aug 17;306(7):721-8.
Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones).
Inoue M, Arata N, Koren G, Ito S. Hyperthyroidism during pregnancy. Can Fam Physician. 2009 Jul;55(7):701-3.
Iyer NG, Morris LG, Tuttle RM, et al. Rising incidence of **second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine** therapy. Cancer. 2011 Oct 1;117(19):4439-46.
Kharlip J, Cooper DS. Recent developments in hyperthyroidism. Lancet. 2009 Jun 6;373(9679):1930-2.
Ladenson, Paul W., Kristensen, Jens D., Ridgway, E. Chester, et al. Use of the Thyroid Hormone Analogue **Eprotirome** in Statin-Treated Dyslipidemia. N Engl J Med 2010 362: 906-916.
LaFranchi S. Treatment and prognosis of congenital hypothyroidism . In: UpToDate Online. UpToDate Waltham, MA. Available from: www.uptodate.com (accessed September 2009).
Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized

TOP

study. Eur J Endocrinol. 2008 Jan;158(1):69-75.
Lazarus JH, Bestwick JP, Channon S, et al. **Antenatal thyroid screening** and childhood cognitive function. N Engl J Med 2012; 366:493-50. Prenatal screening and treatment for hypothyroidism do not lead to improved cognitive function in offspring at age 3 years.
Lee JY, Chung JH, Lee YJ, et al. **Propylthiouracil-induced nonspecific interstitial pneumonia**. Chest. 2011 Mar;139(3):687-90.
Mallick U, Harmer C, Yap B, et al. Ablation with **low-dose radioiodine and thyrotropin alfa in thyroid cancer**. N Engl J Med 2012;366:1674-85.
Marcocci Claudio, Kahaly George J, Krassas Gerasimos E., et al. for the European Group on Graves' Orbitopathy. **Selenium and the Course of Mild Graves' Orbitopathy**. N Engl J Med 2011; 364:1920-1931.
Marx H, Amin P, Lazarus JH. Hyperthyroidism and pregnancy. BMJ. 2008 Mar 22;336(7645):663-7.
McQueen MJ. Laboratory Reference Intervals: SI and Traditional Units. E-Therapeutics Online. Canadian Pharmacists Association. Ottawa, Ontario. www.e-therapeutics.ca (accessed September 2009).
Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P. Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer. 2007 May 15;109(10):1972-9.
Metso S, Jaatinen P, Huhtala H, Auvinen A, Oksala H, Salmi J. Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. J Clin Endocrinol Metab. 2007 Jun;92(6):2190-6.
Nakamura H et al. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab. 2007 Jun;92(6):2157 -62.
Negro R, Formoso G, Mangieri T, et al. **Levothyroxine** treatment in **euthyroid pregnant women** with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006;91:2587-91.
Negro R, Schwartz A, Gismondi R, et al. **Increased Pregnancy Loss Rate** in Thyroid Antibody Negative Women with TSH Levels between 2.5 and 5 in the First Trimester of Pregnancy. J Clin Endocrinol Metab.2010Jun 9.
Newman CM, Price A, Davies DW, Gray TA, Weetman AP. **Amiodarone** and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart. 1998 Feb;79(2):121-7.
Ng SM, Anand D, Weindling AM. High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD006972. DOI: 10.1002/14651858.CD006972.pub2.
Nolte MR, Muller R, Siggelkow H, et al. **Prophylactic application of thyrostatic drugs during excessive iodine exposure** in euthyroid patients with thyroid autonomy: a randomized study. Eur J Endocrinol. 1996;134(3):337-341.
Perros P, Kendall-Taylor P, Neoh C, Frewin S, Dickinson J. A prospective study of the effects of radioiodine therapy for hyperthyroidism in patients with minimally active graves' ophthalmopathy. J Clin Endocrinol Metab. 2005 Sep;90(9):5321-3.
Pramyothin P, Leung AM, Pearce EN, Malabanan AO, Braverman LE. Clinical problem-solving. A hidden solution. N Engl J Med. 2011 Dec 1;365(22):2123-7.
Rhee CM, Bhan I, Alexander EK, Brunelli SM. Association between **iodinated contrast media exposure** and incident hyperthyroidism and hypothyroidism. Arch Intern Med. 2012;172(2):153-159.
Rivkees SA, Mattison DR. **Ending propylthiouracil-induced liver failure** in children. N Engl J Med. 2009 Apr 9;360(15):1574-5.
Roos A, Linn-Rasker SP, van Domburg RT, Tijssen JP, Berghout A. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. Arch Intern Med. 2005 Aug 8 22;165(15):1714-20.
Rosenthal LJ, Goldner WS, O'Reardon JP. **T3 Augmentation** in Major Depressive Disorder: Safety Considerations. Am J Psychiatry 168:10, October 2011.
Ross DS. Thionamides in the treatment of Graves'disease. In: UpToDate Online. UpToDate Waltham, MA. Available from: www.uptodate.com (accessed September 2009).
Ross DS. Thyroid function in nonthyroidal illness. In: UpToDate Online. UpToDate Waltham, MA. Available from: www.uptodate.com (accessed September 2009).
Ross DS. Treatment of Hypothyroidism. In: UpToDate Online. UpToDate Waltham, MA. Available from: www.uptodate.com (accessed September 2009).
Ross DS. Treatment of Graves' Hyperthyroidism. In: UpToDate Online. UpToDate Waltham, MA. Available from: www.uptodate.com (accessed September 2009)
Ross DS. **Radioiodine therapy for hyperthyroidism**. N Engl J Med. 2011 Feb 10;364(6):542-50.
Sattar N, Lazare F, Kacer M, et al. **Celiac disease** in children, adolescents, and young adults with autoimmune thyroid disease. J Pediatr. 2011 Feb;158(2):272-5.e1.
Schlumberger M, Catargi B, Borget I, et al. Strategies of **radioiodine ablation in patients with low-risk thyroid cancer**. N Engl J Med 2012;366:1663-73.
Schvartz C, Bonnetain F, Dabakuyo S, et al. Impact on overall **survival of radioactive iodine in low-risk differentiated thyroid cancer** patients. J Clin Endocrinol Metab 2012 February 16
Selvaraj S, Klein I, Danzi S, et al. Association of Serum **Triiodothyronine** With B-Type Natriuretic Peptide and Severe Left Ventricular **Diastolic Dysfunction in Heart Failure** With Preserved Ejection Fraction. Am J Cardiol. 2012 Apr 11.
Shields B, Hill A, Bilous M, Knight B, Hattersley AT, Bilous RW, Vaidya B. Cigarette smoking during pregnancy is associated with alterations in maternal and fetal thyroid function. J Clin Endocrinol Metab. 2009 Feb;94(2):570-4.
Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Alvarez-Marfany M, Davies TF. Detection of **at-risk pregnancy** by means of highly sensitive assays for thyroid autoantibodies. *JAMA* 1990;264:1422-5.
Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association (**ATA**) for the diagnosis and management of **thyroid disease during pregnancy** and postpartum. Thyroid 2011;21.
Stuckey B, Kent G, Ward L, Brown S, Walsh J. **Postpartum thyroid dysfunction** and the long-term risk of **hypothyroidism**: results from a 12 year follow-up study of women with and without postpartum thyroid dysfunction. Clin Endocrinol (Oxf). 2010 Feb 23. Women who present with postpartum hypothyroidism or have positive TPOAb are at particularly high risk.
Tallstedt L, Lundell G, Tørring O, Wallin G, Ljunggren JG, Blomgren H, Taube A. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. N Engl J Med. 1992 Jun 25;326(26):1733-8.
Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between **thyroid autoantibodies and miscarriage and preterm** birth: meta-analysis of evidence. BMJ 2011;342:d2616.
Thyroid®. Product monograph. ERFA Canada. Available from: http://thyroid.erfa.net/index.php/en/thyroid-monograph.html (accessed September 2009).
Tzakas P, Sit SW. Progressive impairment of cognition and motor function: **Hashimoto encephalopathy**. CMAJ. 2011 Feb 14.
Vaidya B, Pearce SH. Management of hypothyroidism in adults. BMJ. 2008 Jul 28;337:a801. doi: 10.1136/bmj.a801.
Vanderpump MPJ, Lazarus JH, Smyth PP, et al, on behalf of the British Thyroid Association UK Iodine Survey Group. **Iodine status of UK schoolgirls**: a cross-sectional survey. *Lancet* 2011; published online June 2.
Villar HCCE, Saconato H, Valente O, Atallah ÁN. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database of SystematicReviews* 2007, Issue 3.Art.No.:CD003419.DOI: 10.1002/14651858.CD003419.pub2.
Viswanathan L, Vigersky RA. The effect of **herbal medications on thyroid hormone economy** and estrogen-sensitive hepatic proteins in a patient with prostate cancer. Arch Intern Med. 2012 Jan 9;172(1):58-60. (PC-SPES)
Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, Bucher HC, Müller-Brand J, Müller B. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomized controlled trials. BMJ. 2007 Mar 10;334(7592):514.
Walter MA, Christ-Crain M, Muller B. Graves' disease. N Engl J Med. 2008 Sep 25;359(13):1407; author reply 1409.

Hypothyroid

Akhoundi FH, Ghorbani A, Soltani A, Meysamie A. **Favorable functional outcomes in acute ischemic stroke patients with subclinical hypothyroidism**. Neurology. 2011 Jun 29.
Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during **pregnancy** in women with hypothyroidism. N Engl J Med. 2004 Jul 15;351(3):241-9.

TOP

Bach-Huynh TG, Nayak B, Loh J, et al. Timing of Levothyroxine Administration Affects Serum Thyrotropin Concentration. J Clin Endocrinol Metab. 2009 Jul 7. [Epub ahead of print]. Non-fasting regimens of levothyroxine administration are associated with higher and more variable serum thyrotropin concentrations. If a specific serum thyrotropin goal is desired, thereby avoiding iatrogenic subclinical thyroid disease, then fasting ingestion of levothyroxine ensures that thyrotropin concentrations remain within the narrowest target range.

Balhara B, Misra M, Levitsky LL. Clinical monitoring guidelines for **congenital hypothyroidism**: Laboratory outcome data in the first year of life. J Pediatr 2011;158:532-7.

Bolk Nienke; Visser Theo J.; Nijman Judy; et al. Effects of **Evening** vs Morning **Levothyroxine Intake**: A Randomized Double-blind Crossover Trial. Arch Intern Med. 2010;170(22):1996-2003.

Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of **thyroxine as compared with thyroxine plus triiodothyronine** in patients with hypothyroidism. N Engl J Med 1999;340:424-429.

Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.

Capalbo D, Lucariello A, Saccà L, et al. Long-term cardiovascular effects of levothyroxine therapy in young adults with congenital hypothyroidism. J Clin Endocrinol Metab. 2008 Jul;93(7):2486-91. Epub 2008 Apr 29.

Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA. 2006;295(9):1033-1041.

Cleary-Goldman J, et al. **Maternal thyroid hypofunction and pregnancy outcome.** Obstet Gynecol. 2008 Jul;112(1):85-92.

Clemens Kristin, Payne William, Van Uum Stan H.M.. **Central hypothyroidism** Can Fam Physician June 2011 57: 677-680.

Clemens K, Van Uum S. A **pituitary mass** as consequence of a **decimal error in levothyroxine dose**. CMAJ. 2012 Jan 16.

Committee on Patient Safety and Quality Improvement; Committee on Professional Liability. ACOG Committee Opinion No. 381: Subclinical hypothyroidism in pregnancy. Obstet Gynecol. 2007 Oct;110(4):959-60.

Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. L-thyroxine therapy in subclincial hypothyroidism. A double-blind, placebo-controlled trial. Ann Intern Med 1984;101:18-24.

Danese MD, Ladenson PW, Meinert CL, Powe NR. Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab. 2000;85(9):2993-3001.

Flynn RW, et al. Serum **Thyroid-Stimulating Hormone Concentration** and Morbidity from **Cardiovascular Disease and Fractures** in Patients on Long-Term Thyroxine Therapy. J Clin Endocrinol Metab. 2009 Nov 11.

Fox CS, Pencina MJ, D'Agostino RB, et al. Relations of thyroid function to **body weight**: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med. 2008 Mar 24;168(6):587-92.

Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, et al. Association between serum free thyroxine concentration and atrial fibrillation. Arch Intern Med 2007;167:928-34.

Girling J, Nelson-Piercy C. Hypothyroidism in pregnancy: Three unresolved issues. BMJ. 2007 Aug 25;335(7616):362.

Grebe SK, Cooke RR, Ford HC, et al. Treatment of hypothyroidism with once **weekly thyroxine**. J Clin Endocrinol Metab. 1997 Mar;82(3):870-5.

Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L. **Thyroxine-triiodothyronine combination therapy versus thyroxine** monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2006;91:2592-2599.

Hak AE, Pols HA, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for **atherosclerosis** and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 2000 Feb 15;132(4):270-8.

Heather N, Hall K, Neas K et al. Growth and development in a child with **resistance to thyroid hormone** and ectopic thyroid gland. Pediatrics. 2012 Mar;129(3):e817-20.

Herrick B. Subclinical hypothyroidism. Am Fam Physician. 2008 Apr 1;77(7):953-5.

Ineck BA, Ng TM. Effects of subclinical hypothyroidism and its treatment on serum lipids. Ann Pharmacother 2003;37:725-30.

Jorde R, Waterloo K, Storhaug H, Nyrnes A, et al. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab 2006;91:145-53.

Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M, et al. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Med 2002;112:348-54.

Lee Jennifer S.; Buzkova Petra; Fink Howard A.; et al. Subclinical Thyroid Dysfunction and Incident **Hip Fracture** in Older Adults Arch Intern Med. 2010;170(21):1876-1883.

Levine Richard J, Vatten Lars J, Horowitz Gary L, **Pre-eclampsia**, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested case-control and population based study**.** BMJ 2009;339:b4336, doi: 10.1136/bmj.b4336 (Published 17 November 2009)

Li Y, Shan Z, Teng W, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol (Oxf). 2009 Oct 31.

Lin HC, Kang JH, Jiang YD, et al. Hypothyroidism and the Risk of Developing Open-Angle **Glaucoma** A Five-Year Population-Based Follow-Up Study. Ophthalmology. 2010 Jun 15. Hypothyroid patients had a significantly increased risk of OAG development during the 5-year follow-up period. Levothyroxine seemed to be protective.

Loh JA, Wartofsky L, Jonklaas J, Burman KD.The magnitude of increased levothyroxine requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism. Thyroid. 2009;19:269-275.

McDermott Michael T. **In the Clinic**: **Hypothyroidism**. Ann Intern Med December 1, 2009 151:ITC6-1.

Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. **Universal Screening Versus Case Finding** for Detection and Treatment of Thyroid Hormonal Dysfunction During **Pregnancy**. J Clin Endocrinol Metab. 2010 Feb 3.

Nygaard B, Jensen EW, Kvetny J, Jarlov A, Faber J. Effect of **combination therapy with thyroxine (T4) and 3,5,3′-triiodothyroxine versus T4 monotherapy** in patients with hypothyroidism, a double-blind, randomised cross-over study. Eur J Endocrinol 2009;161:895-902.

Panicker V, Saravanan P, Vaidya B, et al. Common variation in the **DIO2 gene predicts baseline** psychological well-being and response to **combination thyroxine plus triiodothyronine** therapy in hypothyroid patients. J Clin Endocrinol Metab 2009;94:1623-1629.

Parle J, Roberts L, Wilson S, et al. A Randomized Controlled Trial of the Effect of Thyroxine Replacement on **Cognitive Function** in Community-Living Elderly Subjects with Subclinical Hypothyroidism: The Birmingham Elderly Thyroid Study. J Clin Endocrinol Metab. 2010 May 25. This RCT provides no evidence for treating elderly subjects with SCH with T4 replacement therapy to improve cognitive function.

Ramadhan A, Tamilia M. **Treatment-refractory** hypothyroidism. CMAJ. 2012 Feb 7;184(2):205-9. (May have a **supervised test for levothyroxine absorption**)

Razvi S, Ingoe L, Keeka G, et al. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. J Clin Endocrinol Metab 2007;92:1715-23.

Razvi S, Weaver JU, Butler TJ, Pearce SHS. **Levothyroxine treatment of subclinical hypothyroidism**, fatal and nonfatal cardiovascular events, and mortality. Arch Intern Med 2012.

Reid SM, Middleton P, Cossich MC, Crowther CA. Interventions for **clinical and subclinical hypothyroidism in pregnancy**. Cochrane Database Syst Rev. 2010 Jul 7;7:CD007752.

Levothyroxine treatment of clinical hypothyroidism in pregnancy is already standard practice given the documented benefits from earlier non-randomised studies. Whether levothyroxine should be utilised in autoimmune and subclinical hypothyroidism remains to be seen, but it may prove worthwhile, given a possible reduction in preterm birth and miscarriage.Selenomethionine as an intervention in women with thyroid autoantibodies is promising, particularly in reducing postpartum thyroiditis. There is a probable low incidence of adverse outcomes from levothyroxine and selenomethionine. High-quality evidence is lacking and large-scale randomised trials are urgently needed in this area. Until evidence for or against universal screening becomes available, targeted thyroid function testing in pregnancy should be implemented in women at risk of thyroid disease and levothyroxine utilised in hypothyroid women.

Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med. 2005;165(21):2460-2466.

Rodondi N, Aujesky D, Vittinghoff E, Cornuz J, Bauer DC. Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. Am J Med. 2006;119(7):541-551.

Salerno M, Oliviero U, Lettiero T, et al. Long-term cardiovascular effects of levothyroxine therapy in young adults with congenital hypothyroidism. J Clin Endocrinol Metab. 2008 Jul;93(7):2486-91. Epub 2008 Apr 29.

Shin DY, Kim EK, Lee EJ. Role of Ultrasonography in Outcome Prediction in Subclinical Hypothyroid Patients Treated with Levothyroxine. Endocr J. 2009 Oct 10.

Simonsick Eleanor M.; Newman Anne B.; Ferrucci Luigi; et al. for the Health ABC Study **Subclinical Hypothyroidism** and Functional Mobility in **Older** Adults. Arch Intern Med. 2009;169(21):2011-2017.

Singh S, Duggal J, Molnar J, Maldonado F, Barsano CP, Arora R. Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis. Int J Cardiol. In press.

Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association (**ATA**) for the diagnosis and management of **thyroid disease during pregnancy** and postpartum. Thyroid 2011;21.

Tan ZS, Beiser A, Vasan RS, Au R, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. Arch Intern Med. 2008 Jul 28;168(14):1514-20. Low and high thyrotropin levels were associated with

TOP

increased risk of incident AD in women but not in men.
Torpy Janet M., Lynm Cassio, Golub Robert M. JAMA Patient Page: **Hyperthyroidism**. JAMA. 2011;306(3):330.doi:10.1001/jama.306.3.330
Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon PA, et al. **Levothyroxine dose and risk of fractures** in older adults: nested case-control study. BMJ 2011;342:d2238.
Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. Clin Endocrinol 1995;43:55-68.
Villar HC, Saconato H, Valente O, Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev. 2007;(3):CD003419.
Wolter P, Stefan C, Decallonne B, et al. The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. Br J Cancer. 2008 Aug 5;99(3):448-54.
Woo CH, Lizarda A, Tucker R, Mitchell ML, Vohr G, OhW, Phornphutkul C. **Congenital hypothyroidism** with a delayed thyroid-stimulating hormone (TSH) elevation in very premature infants: Incidence and growth and developmental outcomes. J Pediatr 2011;158:538-42.
Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid Hormone Early Adjustment in **Pregnancy** (The THERAPY) Trial. J Clin Endocrinol Metab. 2010 May 12.

Hyperthyroid

Bahn R, Levy E, Wartofsky L. Graves' disease. J Clin Endocrinol Metab. 2007 Nov;92(11):2 p following 14A.
Bahn, Rebecca S. **Graves' Ophthalmopathy**. N Engl J Med 2010 362: 726-738.
Bahn RS, Burch HS, Cooper DS, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. Thyroid. 2009;19:673-674.
Bauer DC, Rodondi N, Stone KL, Hillier TA; Study of Osteoporotic Fractures Research Group: Universities of California (San Francisco), Pittsburgh, Minnesota (Minneapolis); Kaiser Permanente Center for Health Research, Portland. Thyroid hormone use, hyperthyroidism and mortality in older women. Am J Med. 2007 Apr;120(4):343-9.
Bogazzi F, Tomisti L, Rossi G, et al.. Glucocorticoids are preferable to thionamides as first-line treatment for **amiodarone-induced** thyrotoxicosis due to destructive thyroiditis: a matched retrospective cohort study. . J Clin Endocrinol Metab. 2009 Jul 21. [Epub ahead of print]
Bogazzi F, Bartalena L, Martino E. Approach to the patient with **amiodarone-induced thyrotoxicosis**. J Clin Endocrinol Metab. 2010 Jun;95(6):2529-35.
Chen CH, Xirasagar S, Lin CC, et al. Risk of adverse perinatal outcomes with **antithyroid treatment during pregnancy**: a nationwide population-based study. BJOG. 2011 Oct;118(11):1365-73.
Chattaway JM. Klepser TB. Propylthiouracil versus methimazole in treatment of Graves' disease during pregnancy. Ann Pharmacother. 2007;41:1018-1022.
Chen H. Pre-operative management of patients with Graves' disease. Surgery. 2008 Feb;143(2):292-3. Epub 2007 Dec 21.
Chung SD, Chen YK, Chen YH et al. **Hyperthyroidism** and female urinary incontinence: a population-based cohort study. Clin Endocrinol (Oxf). 2011 Nov;75(5):704-8.
Collet T-H, Gussekloo J, Bauer DC, et al; Thyroid Studies Collaboration.**Subclinical hyperthyroidism** and the risk of coronary heart disease and mortality [online April 23, 2012]. Arch Intern Med.
Cooper DS, Rivkees SA. Putting **propylthiouracil** in perspective. J Clin Endocrinol Metab. 2009;94:1881-1882.
Donangelo I, Braunstein GD. Update on **Subclinical Hyperthyroidism**. Am Fam Physician. 2011;83(8):933-938.
Douchement D, Rakza T, Holder M, Bonne NX, Fayoux P. **Choanal Atresia** Associated With Tracheoesophageal Fistula: The Spectrum of **Carbimazole** Embryopathy. Pediatrics. 2011 Aug 1.
England RJ, Atkin S. Total thyroidectomy is best operation for thyrotoxicosis. BMJ. 2007 Apr 7;334(7596):710.
Franklyn JA, Boelaert K. **Thyrotoxicosis**. Lancet. 2012 Mar 2.
Kampmann JP, Johansen K, Hansen JM, Helweg J. Propylthiouracil in human milk. Revision of a dogma. Lancet. 1980;1:736-737.
Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Torring O. **TSH-receptor autoimmunity in Graves' disease** after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. Eur J Endocrinol 2008;158:69-75.
Majlesi N, Greller HA, McGuigan MA, Caraccio T, Su MK, Chan GM. Thyroid storm after **pediatric levothyroxine ingestion**. Pediatrics. 2010 Aug;126(2):e470-3. Epub 2010 Jul 19.
Medical Letter, Inc. Drugs for hypothyroidism and hyperthyroidism. Treat Guidel Med Lett. 2006 Apr;4(44):17-24.
Nygaard B. Hyperthyroidism. Am Fam Physician. 2007 Oct 1;76(7):1014-6.
Ochs N, Auer R, Bauer DC, Nanchen D, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med. 2008 Jun 3;148(11):832-45. Epub 2008 May 19.
Ortiz GA et al. **Propylthiouracil-induced lupus, antiphospholipid syndrome**, and stroke in a patient with graves hyperthyroidism. Arch Neurol. 2011 Dec;68(12):1587-90.
Pantalone K Nasr C. **Approach to a low TSH level**: Patience is a virtue *Cleveland Clinic Journal of Medicine* 2010; 77(11):803-811; doi:10.3949/ccjm.77a.10056.
Pearce EN. Diagnosis and management of thyrotoxicosis. BMJ. 2006 Jun 10;332(7554):1369-73.
Pusl T, Jaehnig H, Dorn R. Thyrotoxicosis: a lesson from the **slaughterhouse**. Ann Intern Med. 2011 Nov 1;155(9):646.
Rhee EP, et al. Case records of the Massachusetts General Hospital. Case 4-2012. A 37-year-old man with muscle pain, weakness, and weight loss. (**thyrotoxic periodic paralysis**) N Engl J Med. 2012 Feb 9;366(6):553-60.
Rivkees SA, Mattison DR. Ending **propylthiouracil-induced liver failure** in children. N Engl J Med. 2009;360:1574-1575.
Ross DS. **Radioiodine therapy for hyperthyroidism**. N Engl J Med. 2011 Feb 10;364(6):542-50.
Tallstedt L, Lundell G, Torring O, et al. Occurrence of **ophthalmopathy** after treatment for Graves' hyperthyroidism. The Thyroid Study Group. N Engl J Med. 1992;326:1733-1738.
Takata K, Amino N, Kubota S, et al. Benefit of short-term iodide supplementation to antithyroid drug treatment of thyrotoxicosis due to Graves' disease. Clin Endocrinol (Oxf). 2009 Nov 11.
Tsang W, Houlden RL. **Amiodarone-induced** thyrotoxicosis: a review. Can J Cardiol. 2009 Jul;25(7):421-4
Toft A, Sandeep TC. Radioiodine treatment of hyperthyroidism. BMJ. 2007 Mar 10;334(7592):483-4.
Torpy JM, Lynm C, Golub RM. JAMA patient page. **Hyperthyroidism**. JAMA. 2011 Jul 20;306(3):330.
Wilhelm SM, McHenry CR. **Total Thyroidectomy** Is Superior to Subtotal Thyroidectomy for Management of Graves' Disease in the United States. World J Surg. 2009 Dec 23.
US Food and Drug Administration. Information for healthcare professionals - propylthiouracil-induced liver failure. June 4, 2009. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm162701.htm . Accessed February 9, 2010.

Given these potential adverse effects, the FDA issued an alert on June 4, 2009 that noted the risk of serious liver injury, including liver failure and death, with the use of PTU in adult (1:10,000) and pediatric (1:2,000) patients. These conferences focused on the relative safety of methimazole compared with PTU.[11-14,16] Approximately 30% of patients treated with PTU will have 1- to 2-fold elevations of serum aminotransferase levels. The liver disease associated with PTU can be severe. In the Adverse Event Reporting System (AERS), approximately 22 adult (12 deaths, 5 hepatic transplants) and 10 pediatric (1 death, 6 hepatic transplants) cases of serious hepatic injury associated with PTU treatment were reported. Methimazole, by contrast, was associated with 5 adult cases of serious hepatic injury with 3 deaths. In a system that may overlap with AERS, the United Network for Organ Sharing reported 23 hepatic transplants from 1990 to 2007 (16 adult, 7 children) related to PTU-associated hepatic failure.[11-13,16] Concurrently, no liver transplants related to the use of methimazole were reported. The average PTU dose in children and adults requiring liver transplant was 300 mg daily. Liver failure occurred between 6 and 450 days after starting treatment (median 120 days). Furthermore, there were 2 reports of serious maternal liver disease during pregnancy and 2 reports of liver injury in fetuses of mothers who ingested PTU during pregnancy.[11-14,16]

Guidelines

TOP

AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract. 2006 Jan-Feb;12(1):63-102.

American Association of Clinical Endocrinologists-**AACE**. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002 Nov-Dec;8(6):457-69.

American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with **thyroid nodules and differentiated thyroid cancer**. Thyroid. **2009** Nov;19(11):1167-214.

American Thyroid Association (ATA) Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr. **Medullary thyroid cancer**: management guidelines of the American Thyroid Association. Thyroid 2009 Jun;19(6):565-612.

American Thyroid Association (**ATA**): Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association (**ATA**) for the diagnosis and management of **thyroid disease during pregnancy** and postpartum. Thyroid 2011;21.

American Thyroid Association (**ATA**); American Association of Clinical Endocrinologists-AACE. Bahn Chair RS, Burch HB, Cooper DS, et al. **Hyperthyroidism** and other causes of thyrotoxicosis: management guidelines of the

American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011 Jun;21(6):593-646.

Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, Mandel SJ, Stagnaro-Green A. Management of thyroid dysfunction during **pregnancy and postpartum**: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007 Aug;92(8 Suppl):S1-47.

Cohen JI, Salter KD; American Thyroid Association-**ATA**; American Association of Clinical Endocrinologists; Associazione Medici Endocrinologi. Thyroid disorders: evaluation and management of thyroid nodules. Oral Maxillofac Surg Clin North Am. 2008 Aug;20(3):431-43.

Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM, The American Thyroid Association Guidelines Taskforce. Management guidelines for patients with **thyroid nodules and differentiated thyroid cancer**. Thyroid 2006 Feb;16(2):109-42.

Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with **thyroid nodules and differentiated thyroid cancer**. Thyroid 2009;19:1167-214.

Gharib H, Tuttle MH, Baskin J, Fish LH, Singer PA, McDermott MT. **Subclinical** thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrin Metab 2005;90:581-5.

Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT; American Association of Clinical Endocrinologists/American Thyroid Association/Endocrine Society. **Subclinical** thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. Endocr Pract. 2004 Nov-Dec;10(6):497-501.

Gharib H, Papini E, Paschke R, et al. AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of **thyroid nodules**: executive summary of recommendations. J Endocrinol Invest. 2010;33(5 Suppl):51-6.

Helfand M, Redfern CC. Clinical guideline, part 2. **Screening** for thyroid disease: an update. American College of Physicians [published correction appears in Ann Intern Med. 1999;130(3):246]. Ann Intern Med. 1998;129(2):144-158.

Inoue M, Arata N, Koren G, Ito S. Hyperthyroidism during **pregnancy**. Can Fam Physician. 2009 Jul;55(7):701-3.

Screening for thyroid disease: recommendation statement. Ann Intern Med 2004 Jan 20;140(2):125-7.

The Endocrine Society. Management of thyroid dysfunction during **pregnancy and postpartum**: an Endocrine Society clinical practice guideline. Chevy Chase (MD): The Endocrine Society; 2007. 79 p.

UK guidelines for the use of thyroid function **tests**. 2006. http://www.acb.org.uk/docs/TFTguidelinefinal.pdf

USPSTF- U.S. Preventive Services Task Force. Screening for thyroid disease: recommendation statement. Ann Intern Med. 2004 Jan 20;140(2):125-7.

USPSTF- US Preventive Services Task Force. Screening for congenital hypothyroidism: US Preventive Services Task Force reaffirmation recommendation. Ann Fam Med 2008 Mar-Apr;6(2):166.

USPSTF- US Preventive Services Task Force. Recommendation statement. Screening for thyroid disease. 2004. www.ahrq.gov/clinic/3rduspstf/thyroid/thyrrs.htm#recommendations

Web Sites:

Access information for patients with hypothyroidism prepared by the American College of Physicians.
www.acponline.org/patients_families/diseases_conditions/hypothyroidism/

Access information for patients with hypothyroidism prepared by the National Library of Medicine of the National Institutes of Health.
www.nlm.nih.gov/medlineplus/ency/article/000353.htm

Access information for patients with hypothyroidism prepared by the American Thyroid Association.
www.thyroid.org/patients/patient_brochures/hypothyroidism.html

American Thyroid Association. Questions and answers about potassium iodide (KI). http://www.thyroid.org/professionals/publications/statements/ki/02_04_09_ki_qa.html Accessed March 17, 2011.

US Nuclear Regulatory Commission. Use of potassium iodide. Available at:

http://www.nrc.gov/about-nrc/emerg-preparedness/about-emerg-preparedness/potassium-iodide-use.html Accessed March 17, 2011.

TOP

Other Agents	Prednisone (Glucocorticoid) 1, 5ᶜ, 50ᶜmg tab; 1mg/ml soln	-Suppresses adrenal function	Classic & Nonclassic congenital adrenal hyperplasia (NCCAH)	-Less effective compared to OCPs or anti-androgens[1]	Uncontrolled diabetes, Obesity	Changes typical of Cushing syndrome (weight gain, bone loss), adrenal atrophy	5-7.5mg po daily $8 (5mg tab)
	Ketoconazole NIZORAL 200ᶜmg tab ☎▼	-Adrenal enzyme inhibitor	For patients with Cushing's syndrome while waiting definite therapy	-Similar efficacy to CPA 2-50mg[20]	Hepatic dysfunction Pregnancy, BF	Gynecomastia, dry skin, hepatotoxicity, adrenocortical suppression	200mg po daily $38 (200mg tab)
	Leuprolide acetate depot (GnRH analog) LUPRON & DEPOT ☎▼ 5mg/ml vial ✗⊗; Depot: 3.75,7.5,11.25,22.5 ✗ &30✗ mg	-Potent inhibitor of ovarian steroidogenesis by suppressing LH & FSH	Severe hyperandrogenism of ovarian origin that does not respond to other drugs	-Similar efficacy to CPA 2-50mg, but more adverse effects[20]	Pregnancy, BF Osteoporosis	Osteoporosis Reversable induced menopause	3.75-7.5mg monthly IM, with 25-50ug transdermal estradiol 445_{$415 + $24-30}$
	Metformin GLUCOPHAGE 500ᶜ, 850mg tab	-improves insulin sensitivity	Used in polycystic ovary syndrome (PCOS). Not effective for idiopathic hirsutism	-Small benefit compared to placebo[23] -Inferior to OC or anti-androgen therapy for idiopathic hirsutism[23]	Renal failure	Gastrointestinal upset (minimize by starting low dose $_{250mg\ daily}$, then titrate)	500-2000mg/day (given 250-1000mg BID) $21-33 (500mg tab)

Thanks to everyone who helped with the development and review of this chart. Dr. D. Jubin and Dr. K. Insley (FM, Bella Sante MD and Laser Clinic, Saskatoon), Dr. D. Lichtenwald (Dermatol., Saskatoon), Dr. T. Arnason (U of S. Endocrin.), Dr. M. Markovski (FM, U of S. Regina), Dr. T. Laubscher (FM, U of S. Saskatoon). ***J Hall, M Jin, L Regier.***

References for Hirsutism, Idiopathic - Tables & Figures (RxFiles.ca)
http://www.rxfiles.ca/rxfiles/uploads/documents/members/Hirsutism-Treatment-Figure-Drug-Chart.pdf

RxFiles provides objective, comparative, evidence informed drug information for drug therapy decision making. One hallmark of the program is the academic detailing service or "office visit discussions" provided for physicians/others in Saskatchewan, Canada. A second hallmark that has evolved is the RxFiles Drug Therapy Charts book. For more information on our academic detailing, book, app or online info & services, see our website at www.RxFiles.ca.

Book Orderform: http://www.rxfiles.ca/rxfiles/uploads/documents/1A-CHT-Book-ORDERFORM.pdf
Online store: http://www.rxfiles.ca/rxfiles/modules/products/products.aspx

RxFiles is funded for academic detailing in SK by Saskatchewan Health. Production and updating of our drug comparison charts book is provided via additional revenue from the sale of books and online subscriptions. We are a not-for-profit information program. RxFiles does not receive any funding from the pharmaceutical industry.

[1] Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Human Reproduction Update Advanced Access published November 6, 2011
[2] Rosenfield, RL. Hirsutism. N Engl J Med 2005;353:2578-88
[3] e-CPS, Toronto, ON: Canadian Pharmacists Association. www-e-therapeutics-ca (accessed 2011 November)
[4] DRUGDEX System. Greenwood Village, CO: Thomson Micromedex. www.thomsonhc.com (accessed 2011 November)
[5] Kumar R, St John J, Devendra D. 10-MinuteConsultation: Hirsutism. BMJ 2009;339:b3090 doi: 10.1136/bmj.b3090
[6] Sathyapalan T, Atkin SL.. Rational Testing: Investigating hirsutism. BMJ 2009;338:912 doi:10.1136/bmj.b912
[7] Koulouri O, Conway GS. Clinical Review: Management of hirsutism. BMJ 2009;338:b847 doi:10.1136/bmj.b847
[8] Harrison S, Somani N, Bergfeld W. Update on the management of hirsutism. Cleveland Clinic J Med 2010;77(6): 338-98.
[9] Hamzavi I, Tan E, Shapiro J, Lui H. A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. J Am Acad Dermatol 2007;57:54-9.
[10] Smith SR, Piacquadio DJ, Beger B, Littler C. Eflornithine Cream Combined with Laser Therapy in the Management of Unwanted Facial Hair Growth in Women: A Randomized Trial. Dermatol Surg 2006;32:1237–1243.
[11] Wolf JE, Shander D, Huber F, Jackson J, Lin CS, Mathes BM et al. Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair. Int J Dermat 2007;46:94 –98.
[12] Regier L, Downey S. Contraceptive, Combination Hormonal Products – Prescription. *RxFiles drug comparison charts*. 8th ed. Saskatoon, SK: RxFiles; 2011. Available from: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-OCs-Color.pdf (accessed 2011 December)
[13] Batukan C, Muderris II. Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism. Fertil Steril 2006;85:436–40.
[14] Batukan C, Muderris II, Ozcelik B, Ozturk A. Comparison of two oral contraceptives containing either drospirenone or cyproterone acetate in the treatment of hirsutism. Gyne Endocrin 2007;23(1):38–44.
[15] Breitkopf DM, Rosen MP, Young SL, Nagamani M. Efficacy of second versus third generation oral contraceptives in the treatment of hirsutism. Contraception 2003;67:349–353.
[16] Bunka D, Hall J. YAZ / YASMIN: Safety Considerations related to Venous Thromboembolism (VTE). *RxFiles Q&A*. Saskatoon, SK: RxFiles; 2011. Available from: http://www.rxfiles.ca/rxfiles/uploads/documents/Yaz-Yasmin-Q-A.pdf (accessed 2011 December)
[17] Brown J, Farquhar C, Lee O, Toomath R, Jepson RG. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD000194. DOI: 10.1002/14651858.CD000194.pub2.

TOP

[18] Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, Erwin PJ, Montori VM. Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. J Clin Endocrinol Metab 2008b;93:1153–1160.

[19] Karakurt F. Comparison of the Clinical Efficacy of Flutamide and Spironolactone plus Ethinyloestradiol/Cyproterone Acetate in the Treatment of Hirsutism: a Randomised Controlled Study. *Adv Ther.* 2008;25(4):321–328.

[20] van der Spuy ZM, Le Roux PA, Matjila MJ. Cyproterone acetate for hirsutism. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001125. DOI: 10.1002/14651858.CD001125.

[21] Brahm J, Brahm M, Segovia R, Latorre R, Zapata R, Poniachik J et al. Acute and fulminant hepatitis induced by flutamide: Case series report and review of the literature. Ann Hepatology 2011;10(1):93-98.

[22] Calaf J, Lopez E, Millet A, Alcaniz J, Fortuny A, Vidal O, Callejo J, Escobar-Jimenez F, Torres E, Espinos JJ. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. J Clin Endocrinol Metab 2007;92:3446–3452.

[23] Cosma M, Swiglo BA, Flynn DN, Kurtz DM, LaBella ML, Mullan RJ, et al. Insulin Sensitizers for the Treatment of Hirsutism: A Systematic Review and Metaanalyses of Randomized Controlled Trials. J Clin Endocrinol Metab 2008;93:1135–1142.

TOP

Cochrane reviews CD:

- TNF-a for induction: data not combined. One RCT indicates single infusion may induce remission. CDP571 may induce remission; no evidence for etanercept. Need longer f/u to assess SE such as TB & lymphoma.
- MTX for induction: data not combined. Evidence from a single large trial suggests benefit of MTX 25 mg IM weekly for induction of remission & complete withdrawal from steroids in refractory disease. No evidence supports lower dose PO MTX.
- CsA for induction: low dose PO CsA does not induce remission. Higher PO or IV doses not adequately evaluated, but ↑risk SE such as nephrotoxicity. One study found clinical improvement on unvalidated scale, but remission not assessed.
- AZA and 6-MP effective for inducing remission (NNT=5); OR increases after 17 weeks of tx; NNT=3 for steroid sparing effect; NNT for SE=14.
- Budesonide: superior to placebo for induction & superior to mesalamine; budesonide was inferior to prednisone/prednisolone, but fewer SE. Note: in disease limited to ileum or ascending colon.
- Natalizumab: superior to placebo for induction, but trials halted after 2 cases fatal progressive multifocal leukoencephalopathy in MS.
- Corticosteroids superior to enteral nutrition therapy for induction.
- 5-ASA not superior to placebo in maintaining remission in CD.
- PO budesonide 6 mg/day not effective in maintaining remission.
- Anti-tubercular tx for maintaining remission: may be effective when remission induced by corticosteroids combined with anti-TB tx; however, this is based on subgroup analyses of 2 trials with small numbers
- Corticosteroids (maintenance): not effective and increased AE.
- Probiotics (maintenance): Lactobacilli GC, E. coli strain Nissle 1917, VSL#3, Saccharomyces boulardii-all not effective, but may be due to small sample size
- AZA (maintenance): effective NNT=7 for maintenance; NNT=3 for steroid sparing; NNH=19.

Cochrane reviews UC:

- 5-ASA superior to placebo to induce remission in UC & trended towards benefit over sulfasalazine (SSZ). However, cost an issue, therefore SSZ generally preferred. 5-ASA has fewer SE than SSZ. 5-ASA not associated with male infertility, but SSZ is.
- 5-ASA superior to placebo in maintaining remission for UC (NNT=6). 5-ASA NOT superior to SSZ (NNT= -19), indicating SSZ superior. HOWEVER, many trials required tolerance of SSZ as part of inclusion criteria (Bergman 2006)
- Transdermal nicotine superior to placebo for inducing remission in UC, however no benefit was seen when compared to standard therapy (oral prednisone or mesalamine). More patients on transdermal nicotine withdrew due to AE then placebo or standard therapy.
- Only 2 small trials identified for CsA; could not be pooled as major differences in design & patients involved. Quick response rates in severe disease appear beneficial, but long-term effects unknown.
- In moderate-severe, refractory disease, infliximab induces remission. NNT=5 at 8 weeks (based on ACT studies alone)
- Systematic review: Combination topical & oral 5ASA superior to oral 5ASA for induction of remission of mild-mod UC. Intermittent topical 5ASA superior to oral for prevention of relapse of quiescent UC.[Ford et al.]

Contributors and Reviewers: Dr. G. Bruce (SHR-Gastroent-Peds), Dr. L.J. Worobetz (SHR-Gastroent), Dr. P.C. Ganguli (SHR-Gastroent), Dr. P. Thomson (Winnipeg Health Sciences Centre – Pharmacy-GI)

RxFiles – Inflammatory Bowel Disease - References: (organization and formatting still in process);

[1] Kornbluth A, Sachar DB; Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology (ACG), Practice Parameters Committee. Am J Gastroenterol. 2004 Jul;99(7):1371-85.
[2] Dipiro JT, Schade RR. Inflammatory Bowel Disease. In: DipiroJT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: a pathophysiologic approach. Toronto, McGraw-Hill, 2005:649-64.
[3] Sandborn WJ, Feagan BG. Review article: mild to moderate Crohn's disease--defining the basis for a new treatment algorithm. Aliment Pharmacol Ther. 2003 Aug 1;18(3):263-77.
[4] Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. Aliment Pharmacol Ther. 2006 Apr 1;23(7):841-55.
[5] Hanauer SB, Sandborn W; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2001; Mar;96(3):635-43
[6] Hanauer SB, Stromberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. Clin Gastroenterol Hepatol. 2004; May;2(5):379-88.
[7] Simms L, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2001;(1):CD002913.
[8] Ardizzone S, Maconi G, Russo A, et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006; Jan;55(1):47-53.
[9] Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. Cochrane Database Syst Rev. 2000;(2):CD000545.
[10] Panaccione R, Fedorak RN, Aumais G, Bernstein CN, Bitton A, Croitoru K, Enns R, Feagan B, Fishman M, Greenberg G, Griffiths A, Marshall JK, Rasul I, Sadowski D, Seidman E, Steinhart H, Sutherland L, Walli E, Wild G, Williams CN, Zachos M; Canadian Association of Gastroenterology. Canadian Association of Gastroenterology Clinical Practice Guidelines: the use of infliximab in Crohn's disease. Can J Gastroenterol. 2004 Aug;18(8):503-8.
[11] Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. Cochrane Database Syst Rev. 2000;(2):CD000067.
[12] Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76. Erratum in: N Engl J Med. 2006 May 18;354(20):2200.
[13] Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology. 2003 Mar;124(3):795-841.
[14] Bernstein CN. Osteoporosis in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2006 Feb;4(2):152-6.
[15] SickKids Drug Handbook and Formulary 2006-2007 (25th Ed). Hospital for Sick Children, Toronto, ON, Canada.
[16] IBD guideline team, Cincinnati Children's Hospital Medical Centre: evidence-based care guideline for management of inflammatory bowel disease (IBD), http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/ibd.htm Guideline 29 pages 1-16, May 9, 2006.
[17] Pediatric Dosing Handbook, Health Sciences Centre, Winnipeg, MB.
[18] Micromedex 2010
[19] Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2006 Mar 1;23(5):577-85.
[20] Cohen RD, Woseth DM, Thisted RA, et al. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol. 2000 May;95(5):1263-76.
[21] Marteau P, Crand J, Foucault M, Rambaud JC. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. Gut. 1998 Feb;42(2):195-9.
[22] Beattie RM, Croft NM, Fell JM, Afzal NA, Heuschkel RB. Inflammatory bowel disease. Arch Dis Child. 2006 May;91(5):426-32. Review. PMID: 16632672
[23] Simms L, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2001;(1):CD002913.
[24] Sandborn 2003 - duplicate
[25] Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2006 Mar;130(3):940-87.
[26] Lichtenstein GR - Duplicate
[27] Siegel CA, Hur C, Korzenik JR, Gazelle GS, et al. Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol. 2006 Aug;4(8):1017-24; quiz 976. Epub 2006 Jul 14.
[28] Carter MJ, Lobo AJ, Travis SP; IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2004 Sep;53 Suppl 5:V1-16.
[29] Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD003459.

TOP

[30] Escher JC, Taminiau JA, Nieuwenhuis EE, Buller HA, Grand RJ. Treatment of inflammatory bowel disease in childhood: best available evidence. Inflamm Bowel Dis. 2003 Jan;9(1):34-58.
[31] Mack DR, Young R, Kaufman SS, Ramey L, Vanderhoof JA. Methotrexate in patients with Crohn's disease after 6-mercaptopurine. J Pediatr. 1998 May;132(5):830-5.
[32] Pham CQ, Efros CB, Berardi RR. Cyclosporine for severe ulcerative colitis. Ann Pharmacother. 2006 Jan;40(1):96-101. Epub 2005 Dec 20.
[33] Lichtenstein GR, Duplicate.
[34] Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. Drugs. 2005;65(16):2253-86.
[35] Chapman TM, Plosker GL, Figgitt DP. VSL#3 probiotic mixture: a review of its use in chronic inflammatory bowel diseases. Drugs. 2006;66(10):1371-87.
Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a Probiotic Preparation (VSL#3) on Induction and Maintenance of Remission in Children With Ulcerative Colitis. Am J Gastroenterol. 2009 Jan 20
Conen Anna, Zimmerer Stefan, Frei Reno, Et al. A Pain in the Neck: Probiotics for Ulcerative Colitis. Ann Intern Med December 15, 2009 151:895-897.
Tursi A, Brandimarte G, Papa A, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2010 Oct;105(10):2218-27.
[36] Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med. 1996 Jun 13;334(24):1557-60.
[37] Romano C, Cucchiara S, Barabino A, et al. Usefulness of omega-3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: a double-blind, randomized, placebo-controlled study. World J Gastroenterol. 2005 Dec 7;11(45):7118-21.
[38] MacLean CH, Mojica WA, Newberry SJ, et al. Systematic review of the effects of n-3 fatty acids in inflammatory bowel disease. Am J Clin Nutr. 2005 Sep;82(3):611-9.

Additional IBD References

1: MacLean CH, Mojica WA, Newberry SJ, et al. Systematic review of the effects of n-3 fatty acids in inflammatory bowel disease. Am J Clin Nutr. 2005 Sep;82(3):611-9.
2: Romano C, Cucchiara S, Barabino A, et al. Usefulness of omega-3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: a double-blind, randomized, placebo-controlled study. World J Gastroenterol. 2005 Dec 7;11(45):7118-21.
3: Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med. 1996 Jun 13;334(24):1557-60.
1: Thukral C, Cheifetz A, Peppercorn MA. Anti-tumour necrosis factor therapy for ulcerative colitis : evidence to date.Drugs. 2006;66(16):2059-65.
2: Gisbert JP, Gomollon F, Mate J, Pajares JM. Role of 5-aminosalicylic acid (5-ASA) in treatment of inflammatory bowel disease: a systematic review.Dig Dis Sci. 2002 Mar;47(3):471-88.
3: Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD003715.
4: Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology. 1979 Oct;77(4 Pt 2):847-69.
5: Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology. 1984 Feb;86(2):249-66.
6: Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. Aliment Pharmacol Ther. 2006 Apr 1;23(7):841-55.
7: Feagan BG. 5-ASA therapy for active Crohn's disease: old friends, old data, and a new conclusion. Clin Gastroenterol Hepatol. 2004 May;2(5):376-8.
8: Sandborn WJ, Feagan BG. Review article: mild to moderate Crohn's disease--defining the basis for a new treatment algorithm. Aliment Pharmacol Ther. 2003 Aug 1;18(3):263-77.
9: Kane SV, Schoenfeld P, Sandborn WJ, Tremaine W, Hofer T, Feagan BG. The effectiveness of budesonide therapy for Crohn's disease. Aliment Pharmacol Ther. 2002 Aug;16(8):1509-17.
10: Hanauer SB, Stromberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. Clin Gastroenterol Hepatol. 2004 May;2(5):379-88.
11: Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76. Erratum in: N Engl J Med. 2006 May 18;354(20):2200.
12: Hanauer SB, Feagan BG, Lichtenstein GR, et al.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.Lancet. 2002 May 4;359(9317):1541-9.
13: Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004 Feb 26;350(9):876-85.
14: Rutgeerts P, D'Haens G, Targan S, et al. Efficacy & safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology. 1999 Oct;117(4):761-9.
15: Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999 May 6;340(18):1398-405. (Targan SR, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. 1997 Oct 9;337(15):1029-35.)
16: Panaccione R, Fedorak RN, Aumais G, et al. Canadian Association of Gastroenterology. Canadian Association of Gastroenterology Clinical Practice Guidelines: the use of infliximab in Crohn's disease. Can J Gastroenterol. 2004 Aug;18(8):503-8.
17: Siegel CA, Hur C, Korzenik JR, Gazelle GS, et al. Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol. 2006 Aug;4(8):1017-24; quiz 976. Epub 2006 Jul 14.
18: Sandborn WJ. Evidence-based treatment algorithm for mild to moderate Crohn's disease. Am J Gastroenterol. 2003 Dec;98(12 Suppl):S1-5.
19: Hanauer SB, Sandborn W; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2001 Mar;96(3):635-43.
20: Papi C, Luchetti R, Gili L, Montanti S, Koch M, Capurso L. Budesonide in the treatment of Crohn's disease: a meta-analysis. Aliment Pharmacol Ther. 2000 Nov;14(11):1419-28.
21: Sandborn WJ, Hanauer SB. Infliximab in the treatment of Crohn's disease: a user's guide for clinicians. Am J Gastroenterol. 2002 Dec;97(12):2962-72.
22: Cunliffe RN, Scott BB. Review article: monitoring for drug side-effects in inflammatory bowel disease. Aliment Pharmacol Ther. 2002 Apr;16(4):647-62.
23: Carter MJ, Lobo AJ, Travis SP; IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2004 Sep;53 Suppl 5:V1-16.
24: Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2006 Mar;130(3):940-87.
25: Escher JC, Taminiau JA, Nieuwenhuis EE, Buller HA, Grand RJ. Treatment of inflammatory bowel disease in childhood: best available evidence. Inflamm Bowel Dis. 2003 Jan;9(1):34-58.
26: Chapman TM, Plosker GL, Figgitt DP. VSL#3 probiotic mixture: a review of its use in chronic inflammatory bowel diseases. Drugs. 2006;66(10):1371-87.
27: Beattie RM, Croft NM, Fell JM, Afzal NA, Heuschkel RB. Inflammatory bowel disease. Arch Dis Child. 2006 May;91(5):426-32. Review. PMID: 16632672
28: Podolsky DK. Inflammatory bowel disease. N Engl J Med. 2002 Aug 8;347(6):417-29.
29: Simms L, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2001;(1):CD002913.
30: Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD003459.
31: Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. Cochrane Database Syst Rev. 2000;(2):CD000545.
32: Akobeng AK, Zachos M. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2004;(1):CD003574.
33: Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for inducing remission of Crohn's disease. Cochrane Database Syst Rev. 2001;(3):CD000542.
34: McDonald JW, Feagan BG, Jewell D, Brynskov J, Stange EF, Macdonald JK. Cyclosporine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD000297.
35: Macdonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2006 Jul 19;3:CD006097.
36: Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2003;(4):CD000301.
37: Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004826.
38: Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. Cochrane Database Syst Rev. 2000;(2):CD000067.
39: Otley A, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD000296.
40: Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD000544.
41: Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD000543.
42: Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005112.
43: McGrath J, McDonald JW, Macdonald JK. Transdermal nicotine for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004722.
44: Shibolet O, Regushevskaya E, Brezis M, Soares-Weiser K. Cyclosporine A for induction of remission in severe ulcerative colitis. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD004277.
45: Ardizzone S, Maconi G, Russo A, et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006 Jan;55(1):47-53. Epub 2005 Jun 21.
46: Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2004 Jul;99(7):1371-85.
47: Collins P, Rhodes J. Ulcerative colitis: diagnosis and management. BMJ. 2006 Aug 12;333(7563):340-3.
48: Marteau P, Crand J, Foucault M, Rambaud JC. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. Gut. 1998 Feb;42(2):195-9.

TOP

49: Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. Am J Gastroenterol. 2005 Nov;100(11):2478-85.
50: Pham CQ, Efros CB, Berardi RR. Cyclosporine for severe ulcerative colitis. Ann Pharmacother. 2006 Jan;40(1):96-101. Epub 2005 Dec 20.
51: Mack DR, Young R, Kaufman SS, Ramey L, Vanderhoof JA. Methotrexate in patients with Crohn's disease after 6-mercaptopurine. J Pediatr. 1998 May;132(5):830-5.
52: Sandborn WJ. Rational selection of oral 5-aminosalicylate formulations and prodrugs for the treatment of ulcerative colitis. Am J Gastroenterol. 2002 Dec;97(12):2939-41.
53: Cohen RD, Woseth DM, Thisted RA, et al. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol. 2000 May;95(5):1263-76.
54: Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut. 1997 Jun;40(6):775-81.
55: Ogata H, Matsui T, Nakamura M, et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. Gut. 2006 Sep;55(9):1255-62. Epub 2006 Feb 16.
56: D'Haens G, Daperno M. Advances in biologic therapy for ulcerative colitis and Crohn's disease. Curr Gastroenterol Rep. 2006 Dec;8(6):506-12.
57: Medical Letter Mar 26,2007. Once daily mesalamine (Lialda) for ulcerative colitis.
58: Sands BE, Anderson FH, Bernstein CN, Chey WY, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004 Feb 26;350(9):876-85.
59. Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology. 2005 Jun;128(7):1805-11.
60. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, et al. Adalimumab Induction Therapy for Crohn Disease Previously Treated with Infliximab. A Randomized Trial. Ann Intern Med. 2007 Apr 30; [Epub ahead of print] n=325. Adalimumab induces remissions more frequently than placebo in adults with Crohn disease who cannot tolerate infliximab or have symptoms despite receiving infliximab therapy.
61. Gisbert JP, Gonzalez-Lama Y, Mate J. Systematic review:Infliximab therapy in ulcerative colitis. Aliment Pharmacol Ther. 2007Jan 1;25(1):19-37. Infliximab is more effective than placebo, with an NNT from 3 to 5, for the treatment of moderate-to-severe UC, achieving clinical remission in 40% of the patients at approximately 9 months of follow-up. Further studies are necessary to confirm the long-term efficacy of infliximab in ulcerative colitis.
62. Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007 Jul;66(7):921-6. Epub 2007 Feb 14. Serum antibodies against adalimumab are associated with lower serum adalimumab concentrations and non-response to adalimumab treatment.
63. Sandborn WJ, Feagan BG, Stoinov S, et al; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med. 2007 Jul 19;357(3):228-38.
64. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al; PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med. 2007 Jul 19;357(3):239-50.
65. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007 Jan;132(1):52-65. Epub 2006 Nov 29.
66. Sandborn WJ, Hanauer SB, Rutgeerts P, et al Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007 Sep;56(9):1232-9. Epub 2007 Feb 13. Adalimumab induced and maintained clinical remission for up to 56 weeks in patients with moderate to severe Crohn's disease naive to anti-TNF treatment.
67. Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B(12) deficiency in patients with Crohn's disease. Inflamm Bowel Dis. 2007 Sep 20; [Epub ahead of print] Vitamin B(12) abnormalities are common in patients with CD and patients with a prior ileal or ileocolonic resection are at particular risk.
68. Langan RC, Gotsch PB, Krafczyk MA, et al. Ulcerative Colitis: Diagnosis and Treatment. American Family Physician. Nov 1, 2007.
69. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut. 2004 Nov;53(11):1617-23.
70. Rembacken BJ, Snelling AM, et al. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet. 1999 Aug 21;354(9179):635-9.
71. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. Am J Gastroenterol. 2005 Jun;100(6):1345-53.
72. Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. Gastroenterology. 2007 Nov;133(5):1670-89.
73. Roberts SE, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. BMJ. 2007 Nov 17;335(7628):1033. Epub 2007 Oct 30. In England, the clinical threshold for elective colectomy in people with inflammatory bowel disease may be too high. Further research is now required to establish the threshold criteria and optimal timing of elective surgery for people with poorly controlled inflammatory bowel disease.
74. Langan RC, Gotsch PB, Krafczyk MA, Skillinge DD. Ulcerative colitis: diagnosis and treatment. Am Fam Physician. 2007 Nov 1;76(9):1323-30.
75. Panés J, Gomollón F, Taxonera C, Hinojosa J, Clofent J, Nos P. Crohn's disease : a review of current treatment with a focus on biologics. Drugs. 2007;67(17):2511-37.
76. Turner D, Grossman AB, Rosh J, et al. Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. Am J Gastroenterol. 2007 Dec;102(12):2804-12.
77. Orholm M, Fonager K, Sørensen HT. Risk of ulcerative colitis and Crohn's disease among offspring of patients with chronic inflammatory bowel disease. Am J Gastroenterol. 1999 Nov;94(11):3236-8.
78. Behm B, et al. Tumor necrosis factor-alpha antibody for maintenace of remission in Crohn`s disease. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006893. Infliximab 5 mg/kg or 10 mg/kg, given every 8 weeks, is effective for the maintenance of remission and maintenance of fistula healing in patients who have responded to infliximab induction therapy. Adalimumab 40 mg weekly or every other week is effective for the maintenance of remission in patients who have responded to adalimumab induction therapy. Certolizumab pegol 400 mg every 4 weeks is effective for the maintenance of remission in patients who have responded to certolizumab induction therapy.
79. D'Haens G, Baert F, van Assche G, et al; Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008 Feb 23;371(9613):660-7.
80. Feagan BG, et al. Omega-3 free fatty acids for maintenance of remission in Crohn disease: EPIC RCT. JAMA. 2008 Apr 9;299(14):1690-7. In these trials, omega-3 free fatty acids was not effective for the prevention of relapse in Crohn disease.
81. Cummings JR, Keshav S, Travis SP. Medical management of Crohn's disease. BMJ. 2008 May 10;336(7652):1062-6.
82. Akobeng AK. Crohn's disease: current treatment options. Arch Dis Child. 2008 May 2. [Epub ahead of print]
83. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. Am J Gastroenterol. 2008 May;103(5):1299-307.
84. Health Canada June/08 Reports of serious liver injury in patients receiving Tysabri, occurring as early as 6 days after first dose. Tysabri product label has been updated for liver injury, hypersensitivity reactions and herpes infections.
85. Kulnigg S, et al.. A novel intravenous iron formulation for anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. Am J Gastroenterol. 2008 May;103(5):1182-92. Epub 2008 Mar 26.
86. Ferguson CB, Mahsud-Dornan S, Patterson RN. Inflammatory bowel disease in pregnancy. BMJ. 2008 Jul 3;337:a427. doi: 10.1136/bmj.39566.681458.BE.
87. Brar H, Einarson A. Effects and treatment of inflammatory bowel disease during pregnancy. Can Fam Physician. 2008 Jul;54(7):981-3.
88. Strate LL, Liu YL, Syngal S, et al. Nut, corn, and popcorn consumption and the incidence of diverticular disease. JAMA. 2008 Aug 27;300(8):907-14. In this large, prospective study of men without known diverticular disease, nut, corn, and popcorn consumption did not increase the risk of diverticulosis or diverticular complications. The recommendation to avoid these foods to prevent diverticular complications should be reconsidered.
89. Kitazaki S, Mitsuyama K, Masuda J, et al. Clinical trial: comparison of alendronate & alfacalcidol in glucocorticoid-associated osteoporosis in patients with ulcerative colitis. Aliment Pharmacol Ther. 2008 Nov 25. [Epub ahead of print] Our study indicates that alendronate is a safe, well tolerated, and more effective therapy than alfacalcidol for preventing glucocorticoid-associated bone loss in patients with ulcerative colitis.
90. Infliximab for the treatment of acute exacerbations of ulcerative colitis NICE Guidance Dec 2008 http://www.nice.org.uk/TA163
91. Kane S, Ford J, Cohen R, Wagner C. Absence of Infliximab in Infant Sera and Breast Milk From Nursing Mothers Receiving Therapy for Crohn's Disease Before and After Delivery. J Clin Gastroenterol. 2009 Jan 12. [Epub ahead of print]n=3. Infliximab was detected in the mothers' sera, but not in the breast milk of nursing mothers or in the sera of the breast-fed newborns. Data from this small series of patients suggest that infliximab was not transferred from mother to child, either in utero or through breast milk. These data suggest that mothers receiving infliximab should not be discouraged from nursing their children.
92. Turner D, Zlotkin SH, Shah PS, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006320. Omega 3 fatty acids are safe but probably ineffective for maintenance of remission in CD. The existing data do not support routine maintenance treatment of Crohn's disease with omega 3 fatty acids.
93. Prefontaine E, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000067. Azathioprine and 6-mercaptopurine are more effective than placebo for maintenance of remission in Crohn's disease. Higher response rates were obtained with azathioprine than 6-mercaptopurine. However, the one study evaluating 6-mercaptopurine used a relatively low dose of the drug. Future studies should look at the effect of higher doses of 6-mercaptopurine. There is weak evidence for a steroid sparing effect with azathioprine treatment.
94. Benchimol EI, Seow CH, Otley AR, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD002913. Budesonide is not more effective than placebo or weaning prednisolone for maintenance of remission in Crohn's disease. Some modest benefits are noted in patients receiving budesonide compared with placebo in terms of lower CDAI scores and longer time to relapse of disease. However, these benefits are offset by higher treatment-related adverse event rates and more frequent adrenocorticoid suppression in patients receiving budesonide. Therefore, budesonide is not recommended for maintenance of remission in Crohn's disease.
95. Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology. 2009 Feb;136(2):441-50.e1; quiz 716. Epub 2008 Oct 31.
96. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a Probiotic Preparation (VSL#3) on Induction and Maintenance of Remission in Children With Ulcerative Colitis. Am J Gastroenterol. 2009 Jan 20. [Epub ahead of print] This is the first pediatric, n=29, randomized, placebo-controlled trial that suggests the efficacy and safety of a highly concentrated mixture of probiotic bacterial strains (VSL#3) in active UC and demonstrates its role in maintenance of remission.
97. Levine A, Kori M, Dinari G, Broide E, Shaoul R, Yerushalmi B, On A, Bujanover Y, Pröls M, Greinwald R; Israeli Pediatric Budesonide Study Group. Comparison of two dosing methods for induction of response and remission with oral budesonide in active pediatric Crohn's disease: A randomized placebo-controlled trial. Inflamm Bowel Dis. 2009 Feb 19. [Epub ahead of print] Group 1: Standard dose budesonide (9 mg/day) for 7 weeks followed by 6 mg budesonide daily for an additional 3 weeks. Group 2: Induction with 12 mg/day for the first month followed by the same regimen as Group 1. Use of an induction dose of budesonide followed by a budesonide taper resulted in a trend to higher rates of clinical remission and a decrease in inflammation, without an increase in steroid-associated side effects. Budesonide was also useful for patients with ileocolonic disease.
98. Patel H, Barr A, Jeejeebhoy KN. Renal effects of long-term treatment with 5-aminosalicylic acid. Can J Gastroenterol. 2009 Mar;23(3):170-6. The present study is the first to demonstrate a significant dose- and treatment duration-dependant decline in CrCl.

TOP

be further evaluated because 5-ASA is widely used for long-term maintenance therapy in patients with IBD.
99. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. Lancet. 2006 Mar 11;367(9513):839-46.
100. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet. 2009 May 30;373(9678):1905-17.
101. Hindorf U, Johansson M, Eriksson A, Kvifors E, Almer SH. Mercaptopurine treatment should be considered in azathioprine intolerant patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2009 Mar 15;29(6):654-61. Epub 2008 Dec 22.
102. Peyrin-Biroulet L, Deltenre P, Ardizzone S, D'Haens G, et al. Azathioprine and 6-Mercaptopurine for the Prevention of Postoperative Recurrence in Crohn's Disease: A Meta-Analysis. Am J Gastroenterol. 2009 Jun 30. [Epub ahead of print]
103. Sandborn WJ, Rutgeerts P, Feagan BG, et a;l Colectomy Rate Comparison After Treatment of Ulcerative Colitis With Placebo or Infliximab. Gastroenterology. 2009 Jul 10. [Epub ahead of print] Patients with moderately-to-severely active ulcerative colitis treated with infliximab were less likely to undergo colectomy through 54 weeks than those receiving placebo.
104. Bernstein CN, et al. Isotretinoin Is Not Associated With Inflammatory Bowel Disease: A Population-Based Case-Control Study. Am J Gastroenterol. 2009 Jul 21. [Epub ahead of print]
105. Cassinotti A, Actis GC, Duca P, et al. Maintenance Treatment With Azathioprine in Ulcerative Colitis: Outcome and Predictive Factors After Drug Withdrawal. Am J Gastroenterol. 2009 Jul 21. [Epub ahead of print
106. Sadowski DC, Bernstein CN, et al.; the CAG Crohn's Consensus Group. Canadian Association of Gastroenterology Clinical Practice Guidelines: The use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease. Can J Gastroenterol. 2009 Mar;23(3):185-202.
107. Drugs for Inflammatory Bowel Disease. Treatment Guidelines- Medical Letter Sept/09. Updated Mar 2012.
108. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology (ACG). Management of Crohn's disease in adults. Am J Gastroenterol. 2009 Feb;104(2):465-83; quiz 464, 484. Epub 2009 Jan 6.
109. Hart AR. Linoleic Acid, a Dietary N-6 Polyunsaturated Fatty Acid, and the Aetiology of Ulcerative Colitis - A European Prospective Cohort Study. Gut. 2009 Jul 23. [Epub ahead of print]
110. Assasi N, Blackhouse G, Xie F, Gaebel K, Marshall J, Irvine EJ, Giacomini M, Robertson D, Campbell K, Hopkins R, Goeree R. Anti-TNF-α drugs for refractory inflammatory bowel disease: Clinical- and cost-effectiveness analyses [Technology report number 120] and Overview of anti-TNF-α drugs for refractory inflammatory bowel disease [Technology overview number 52].
111. Beaugerie L, Brousse N, Bouvier AM, et al. for the CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009 Oct 16. [Epub ahead of print]
FDA Apr/11 Warning of Tumor Necrosis Factor (TNF) blockers, Azathioprine and/or Mercaptopurine: Update on Reports of Hepatosplenic T-Cell Lymphoma in Adolescents and Young Adults.
Chiorean MV, Pokhrel B, Adabala J, et al. Incidence and risk factors for lymphoma in a single-center inflammatory bowel disease population. Dig Dis Sci. 2011 May;56(5):1489-95.
112. Gisbert JP. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. Inflamm Bowel Dis. 2009 Nov 2.
113. WGO Practice Guidelines Inflammatory bowel disease: a global perspective - June 2009 http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/21_inflammatory_bowel_disease.pdf
114. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009 Dec;68(12):1833-8. Epub 2008 Dec 9.
115. Papay P, Reinisch W, Ho E, Gratzer C, et al.. The Impact of Thiopurines on the Risk of Surgical Recurrence in Patients With Crohn's Disease After First Intestinal Surgery. Am J Gastroenterol. . [Epub ahead of print]
116. Rosh JR, Lerer T, Markowitz J, et al. Retrospective Evaluation of theSafety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease. Am J Gastroenterol. 2009 Dec;104(12):3042-9.
117. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut. 2010 Jan;59(1):49-54.
(Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol. 2006 Oct;4(10):1248-54. Epub 2006 Aug 22.)
118. Sandborn WJ, Korzenik J, Lashner B, et al. Once Daily Dosing of Delayed-Release Oral Mesalamine (400 mg Tablet) for Maintenance of Remission of Ulcerative Colitis: The ODIEM Trial. Gastroenterology. 2010 Jan 8.[Epub ahead of print]
119. Sandborn WJ, Regula J, Feagan BG, et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. Gastroenterology. 2009 Dec;137(6):1934-43.e1-3. Epub 2009 Sep 18. (ASCEND III)
120. Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD004115.
121. El-Matary W, Vandermeer B, Griffiths AM. Methotrexate for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007560.
122. Hyams JS, Lerer T, Griffiths A, et al. Outcome Following Infliximab Therapy in Children With Ulcerative Colitis. Am J Gastroenterol. 2010 Jan 26.
123. Wasan SK, Baker SE, Skolnik PR, Farraye FA. A Practical Guide to Vaccinating the Inflammatory Bowel Disease Patient. Am J Gastroenterol. 2010 Jan 26. [Epub ahead of print]
Rahier JF, Ben-Horin S, Chowers Y, et al. on behalf of the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2009 Jun;3(2):47-91.
124. Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010 Feb;138(2):746-74.
125. Farraye FA, Odze RD, Eaden J, Itzkowitz SH; AGA Institute Medical Position Panel on Diagnosis and Management of Colorectal Neoplasia in Inflammatory Bowel Disease, McCabe RP, Dassopoulos T, Lewis JD, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010 Feb;138(2):738-45.
NICE: Guideline 118 Mar 2011. Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. http://www.nice.org.uk/nicemedia/live/13415/53641/53641.pdf Guick Guide http://www.nice.org.uk/nicemedia/live/13415/53592/53592.pdf
126. Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. Clin Gastroenterol Hepatol. 2010 Feb 4.
127. Afif W, Loftus EV Jr, Faubion WA, Kane SV, Bruining DH, Hanson KA, Sandborn WJ. Clinical Utility of Measuring Infliximab and Human Anti-Chimeric Antibody Concentrations in Patients With Inflammatory Bowel Disease. Am J Gastroenterol. 2010 Feb 9.
128. Bezabeh S, Flowers CM, Kortepeter C, Avigan M. Review article: clinically significant liver injury in patients treated with natalizumab (TYSABRI). Aliment Pharmacol Ther. 2010 Feb 16.
129. Fournier MR, Klein J, Minuk GY, Bernstein CN. Changes in Liver Biochemistry During Methotrexate Use for Inflammatory Bowel Disease. Am J Gastroenterol. 2010 Feb 16. Methotrexate is commonly associated with LET abnormalities, but these frequently normalize while still on therapy, and in only 5% will drug discontinuation be necessary. Liver biopsies rarely have substantive abnormalities
130. Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy (PML) and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010 Apr;9(4):425-37.
131. Schreiber S, Colombel JF, Bloomfield R, et al. Increased Response and Remission Rates in Short-Duration Crohn's Disease With Subcutaneous Certolizumab Pegol: An Analysis of PRECiSE 2 Randomized Maintenance Trial Data. Am J Gastroenterol. 2010 Mar 16.f
132. Colombel, Jean Frederic, Sandborn, William J., Reinisch, Walter, et al., the SONIC Study Group, Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. N Engl J Med 2010 362: 1383-1395.
133. Gisbert JP, Linares PM, McNicholl AG, Maté J, Gomollón F. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. Aliment Pharmacol Ther. 2009 Jul 1;30(2):126-37. Epub 2009 Apr 15.
134. Gisbert JP, Niño P, Cara C, Rodrigo L. Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: prospective, long-term, follow-up study of 394 patients. Aliment Pharmacol Ther. 2008 Jul;28(2):228-38. Epub 2008 May 12.
135. Crockett SD et al. Isotretinoin use and the risk of inflammatory bowel disease: A case–control study. Am J Gastroenterol 2010 Mar 30; [e-pub ahead of print].
136. NICE 2010: Use of tumour necrosis factor alpha (TNF a) inhibitors (adalimumab, and infliximab [review]) for Crohn's disease (review of TA40) http://guidance.nice.org.uk/TA187
137. Ducharme J, Pelletier C, Zacharias R. The safety of infliximab infusions in the community setting. Can J Gastroenterol. 2010 May;24(5):307-11.
138. Jones DW, Finlayson SR. Trends in Surgery for Crohn's Disease in the Era of Infliximab. Ann Surg. 2010 Jun 25.
139. Gisbert JP. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. Inflamm Bowel Dis. 2010 May;16(5):881-95.
140. Bermejo F, López-Sanromán A, Algaba A, et al. Mercaptopurine rescue after azathioprine-induced liver injury in inflammatory bowel disease. Aliment Pharmacol Ther. 2010 Jan;31(1):120-4.
141. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ. 2010 Jul 15;341
142. Turner D, Griffiths AM. Acute severe ulcerative colitis in children: Asystematic review. Inflamm Bowel Dis. 2010 Jul 19.
143. Hussain SW, Pardi DS. Inflammatory bowel disease in the elderly. Drugs Aging. 2010 Aug 1;27(8):617-24. doi: 10.2165/11537340-000000000-00000.
144. Teruel C, Román AL, Bermejo F, et al. Outcomes of Pregnancies Fathered by Inflammatory Bowel Disease Patients Exposed to Thiopurines. Am J Gastroenterol. 2010 Aug 10.
145. Van Assche G, Vermeire S, Rutgeerts P. Management of acute severe ulcerative colitis. Gut. 2010 Oct 28.
146. Chi AC, Neville BW, Krayer JW, Gonsalves WC. Oral manifestations of systemic disease. Am Fam Physician. 2010 Dec 1;82(11):1381-8. (Oral cavity changes may be first sign of Crohn's disease)
147. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104:228-233.
148. Mahadevan U, Cucchiara S, Hyams JS, et al. The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: Pregnancy and Pediatrics. Am J Gastroenterol. 2010 Dec 14.
149. Hyams JS, Lerer T, Griffiths A, et al. Pediatric Inflammatory Bowel Disease Collaborative Research Group. Outcome following infliximab therapy in children with ulcerative colitis. Am J Gastroenterol. 2010 Jun;105(6):1430-6.
150. Hyams JS, Lerer T, Mack D, Bousvaros A, et al. Outcome Following Thiopurine Use in Children With Ulcerative Colitis: A Prospective Multicenter Registry Study. Am J Gastroenterol. 2011 Jan 11.
151. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology (ACG). Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23.
152. Tursi A, Brandimarte G, Papa A, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2010 Oct;105(10):2218-27.
153. Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. Gut. 2005 Jul;54(7):960-5.
154. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol. 1997 Oct;92(10):1867-71.
155. Timmer A, McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD000478.
156. Goodhand JR, Kamperidis N, Nguyen H, et al. Application of the WHO fracture risk assessment tool (FRAX) to predict need for DEXA scanning and treatment in patients with inflammatory bowel disease at risk of osteopo rosis.Aliment Pharmacol Ther. 2011 Mar;33(5):551-8.
157. Riquelme AJ, Calvo MA, Guzmán AM, Depix MS, García P, Pérez C, Arrese M, Labarca JA. Saccharomyces cerevisiae fungemia after Saccharomyces boulardii treatment in immunocompromised patients. J Clin Gastroenterol. 2003 Jan;36(1):41-3.
158. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD008794. DOI: 10.1002/14651858.CD008794.pub2. Overall, in the short term biologics were associated with significantly higher rates of total adverse events, withdrawals due to adverse events and TB reactivation. Some biologics had a statistically higher association with certain adverse outcomes compared to control, but there was no consistency across the outcomes so caution is needed in interpreting these results.
159. Bernstein CN, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, et al. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. Inflamm Bowel Dis. 2010 Jan;16(1):112-24.
160. Nikfar S, Ehteshami-Ashar S, Rahimi R, et al. Systematic review and meta-analysis of the efficacy and tolerability of nicotine preparations in active ulcerative colitis. Clin Ther. 2010 Dec;32(14):2304-15. The findings from this meta-analysis do not support the efficacy or tolera

preparations in inducing remission in UC.
161. Yarur AJ, Deshpande AR, Pechman DM, et al. Inflammatory Bowel Disease Is Associated With an Increased Incidence of Cardiovascular Events. Am J Gastroenterol. 2011 Mar 8.
162. NICE: Guideline 118 Mar 2011. Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. http://www.nice.org.uk/nicemedia/live/13415/53641/53641.pdf Guick Guide http://www.nice.org.uk/nicemedia/live/13415/53592/53592.pdf
163. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of Biological Therapies in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. Am J Gastroenterol. 2011 Mar 15.
164. Wee JS, Marinaki A, Smith CH. Life threatening myelotoxicity secondary to azathioprine in a patient with atopic eczema and normal thiopurine methyltransferase activity. BMJ. 2011 Mar 25;342:d1417. doi: 10.1136/bmj.d1417.
165. Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):630-42.
166. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):661-73.
167. Talley NJ, Abreu MT, Achkar J for the American College of Gastroenterology (ACG) IBD Task Force. An evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease. Am J Gastroenterol. 2011 Apr;106(Supp 1).
168. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):601-16. Epub 2011 Mar 15.
169. Bartelds Geertje M., Krieckaert Charlotte L. M., Nurmohamed Michael T., et al. Development of Antidrug Antibodies Against Adalimumab and Association With Disease Activity and Treatment Failure During Long-term Follow-up. JAMA. 2011;305(14):1460-1468.doi:10.1001/jama.2011.406
170. Korswagen LA, Bartelds GM, Krieckaert CL, et al. Venous and arterial thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies: a case series and cohort study. Arthritis Rheum. 2011 Apr;63(4):877-83. doi: 10.1002/art.30209.
171. Chande N, McDonald JW, Macdonald JK, Wang JJ. Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD006774.
172. Chiorean MV, Pokhrel B, Adabala J, et al. Incidence and risk factors for lymphoma in a single-center inflammatory bowel disease population. Dig Dis Sci. 2011 May;56(5):1489-95. (not higher than general population)
173. Frankel Jonathan K, Packer Clifford D. Cushing's Syndrome Due to Antiretroviral Ritonaivr-Budesonide Interaction. Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1P731. Ann Pharmacother ;45:823-824.
174. Booth Ronald A., Ansari Mohammed T., Loit Evelin, et al. Assessment of Thiopurine S-Methyltransferase Activity in Patients Prescribed Thiopurines: A Systematic Review. Ann Intern Med June 21, 2011 154:814-823.
175. Mahadevan U, Cucchiara S, Hyams JS, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. Am J Gastroenterol. 2011 Feb;106(2):214-23; quiz 224.
176. Baumgart DC, Macdonald JK, Feagan B. Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. Cochrane Database Syst Rev. 2008;(3):CD007216.
177. Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):590-9.
178. Sang LX, Chang B, Zhang WL, Wu XM, Li XH, Jiang M. Remission induction and maintenance effect of probiotics on ulcerative colitis: a meta-analysis. World J Gastroenterol [Internet]. 2010 Apr 21 [cited 2011 Jun 2];16(15):1908-15.
179. Sherlock ME, Seow CH, Steinhart AH, Griffiths AM. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010;(10):CD007698.
180. Wall GC, Schirmer LL, Anliker LE, Tigges AE. Pharmacotherapy for acute pouchitis. Ann Pharmacother. 2011 Sep;45(9):1127-37.
181.FDA Nov/11 FDA continues to receive reports of a rare cancer of white blood cells (known as Hepatosplenic T-Cell Lymphoma or HSTCL, primarily in adolescents and young adults being treated for Crohn's disease and ulcerative colitis with medicines known as tumor necrosis factors (TNF) blockers, as well as with azathioprine, and/or mercaptopurine. TNF blockers include Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab pegol) and Simponi (golimumab).
182. Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.
183. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med. 2011 Nov 3;365(18):1713-25.
184. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Cesame Study Group. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011 Nov;141(5):1621-1628.e5.
185. Sanaee F, Clements JD, Waugh AW, et al. Drug-disease interaction: Crohn's disease elevates verapamil plasma concentrations but reduces response to the drug proportional to disease activity. Br J Clin Pharmacol. 2011 Nov;72(5):787-97. doi: 10.1111/j.1365-2125.2011.04019.x.
186. Hoentjen F, et al "Long-term effectiveness and tolerability of allopurinol and thiopurine combination therapy in inflammatory bowel disease patients" *ACG* 2011; Abstract 27. http://www.medpagetoday.com/MeetingCoverage/ACG/29402
187. Natekar A, Pupco A, Bozzo P and Koren G. Safety of azathioprine use during pregnancy. Can Fam Physician December 2011 57: 1401-1402.
188. Leiper K, Martin K, Ellis A, et al. Randomised placebocontrolled trial of rituximab (anti-CD20) in active ulcerative colitis. Gut 2011;60:1520 –1526.
189. Wilkins T, Jarvis K, Patel J. Diagnosis and management of Crohn's disease. American Family Physician December 2011; 84(12):1365-75.
190. Jess T, Frisch M, Jørgensen KT, Pedersen BV, Nielsen NM. Increased risk of inflammatory bowel disease in women with endometriosis: a nationwide Danish cohort study. Gut. 2011 Dec 19.
191. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a populationbased nationwide study. Gut 2011;60:937–943.
192. Sandborn WJ, van Assche G, Reinisch W et al. Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology. 2011 Nov 4.
193. Merrill A, Millham F. Increased Risk of Postoperative Deep Vein Thrombosis and Pulmonary Embolism in Patients With Inflammatory Bowel Disease: A Study of National Surgical Quality Improvement Program Patients. Arch Surg. 2011 Oct 17.
194. Molodecky NA et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42.
195. Louis E et al. Groupe D'etudes Thérapeutiques Des Affections Inflammatoires Digestives. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012 Jan;142(1):63-70.e5.
196. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin d status is associated with reduced risk of Crohn's disease. Gastroenterology. 2012 Mar;142(3):482-9.
197. Prantera C, Lochs H, Grimaldi M et al. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. Gastroenterology. 2012 Mar;142(3):473-481.e4.
198. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, Nonsteroidal Anti-inflammatory Drug Use, and Risk for Crohn Disease and Ulcerative Colitis: A Cohort Study (NHS). Ann Intern Med. 2012 Mar 6;156(5):350-9.
199. National Institute for Health and Clinical Excellence (NICE). Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. (Guideline no. 118).
200. Ford AC, Khan KJ, Achkar JP, et al. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in Ulcerative Colitis: systematic review and meta-analysis. Am J Gastroenterol. 2012 Feb;107(2):167-76. Combined 5-ASA therapy appeared superior to oral 5-ASAs for induction of remission of mildly to moderately active UC. Intermittent topical 5-ASAs appeared superior to oral 5-ASAs for preventing relapse of quiescent UC.
201. Fiehn C, Vay S. Golimumab can induce flares of inflammatory bowel disease: Report of three cases with enteropathic spondyloarthritis or ankylosing spondylitis and comorbid colitis. Arthritis Rheum. 2011 Jul 18.
202. Levesque BG, Loftus EV Jr. Initiating azathioprine for Crohn's disease. Clin Gastroenterol Hepatol. 2012 May;10(5):460-5.
203. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab Induces and Maintains Mucosal Healing in Patients With Crohn's Disease: Data From the EXTEND Trial. Gastroenterology. 2012 May;142(5):1102-1111.e2.
204. Román M, Cabaleiro T, Ochoa D, et al. Validation of a Genotyping Method for Analysis of TPMT Polymorphisms. Clin Ther. 2012 Mar 13.
205. Lakhi N, Govind A. Unplanned pregnancy in a woman with Crohn disease. Can Fam Physician. 2012 May;58(5):531-2.
206. Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K; AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012 Apr;99(4):532-9.
207. Crandall WV, Margolis PA, Kappelman MD, et al. Improved Outcomes in a Quality Improvement Collaborative for Pediatric Inflammatory Bowel Disease. Pediatrics. 2012 Apr;129(4):e1030-e1041
208. Clarke K, Regueiro M. Stopping immunomodulators and biologics in inflammatory bowel disease patients in remission. Inflamm Bowel Dis. 2012 Jan;18(1):174-9.

TOP

Additional references: GASTROINTESTINAL - ACID SUPPRESSION DRUGS: EVIDENCE, TIPS AND PEARLS

Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of **antiplatelet therapy and NSAID** use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol***.** 2008; *Circulation*. 2008; DOI: DOI: 10.1161/CIRCULATIONAHA.108.191087. Available at: http://circ.ahajournals.org

Chan FKL, et al Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding. N Engl J Med 2005;352:238-44. n=320 1yr (InfoPOEMs: For patients with a history of bleeding peptic ulcer, aspirin and a proton pump inhibitor twice a day was safer in terms of bleeding side effects than clopidogrel. While esomeprazole was used in this study, generic omeprazole 20 mg give twice a day provides nearly the same degree of acid suppression at a much lower cost. This study calls into question the overall safety of clopidogrel, which has been promoted as not increasing the risk of bleeding significantly. (LOE = 1b))

Giannini EG, Zentilin P, Dulbecco P, Vigneri S, Scarlata P, Savarino V. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. Am J Gastroenterol. 2008 Feb;103(2):267-75. Early endoscopy for patients with gastroesophageal reflux disease (GERD) without alarm symptoms does not improve symptoms or quality of life, but increases costs. (LOE = 1b)

Graham DY, Agrawal NM, Campbell DR, et al. NSAID-Associated Gastric Ulcer Prevention Study Group. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of **misoprostol vs lansoprazole**. Arch Intern Med. 2002 Jan 28;162(2):169-75.

Hsu PI, Lai KH, Liu CP. **Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone**, in patients with atherosclerosis. Gastroenterology. 2011 Mar;140(3):791-8.

Hudson N, Taha AS, Russell RI, et al. **Famotidine** for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration. Gastroenterology. 1997 Jun;112(6):1817-22.

Lai KC, et al. Esomeprazole 20mg/d + ASA (100mg/d) vs clopidogrel 75mg od for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol. 2006 Jul;4(7):860-5. Epub 2006 Jun 22. n=170 1yr 0 esomeprazole + ASA vs 13.6% clopidogrel recurrent ulcer complications)

Lin KJ, Hernández-Díaz S, García Rodríguez LA. **Acid suppressants reduce risk of gastrointestinal bleeding in patients on antithrombotic** or anti-inflammatory therapy. Gastroenterology. 2011 Jul;141(1):71-9.

Liu CP, Chen WC, Lai KH, et al. **Esomeprazole Alone Compared with Esomeprazole Plus Aspirin** for the Treatment of Aspirin-Related Peptic Ulcers. Am J Gastroenterol. 2012 Apr 17.

Luo JC, Huang KW, Leu HB, et al. Randomised clinical trial: **rabeprazole plus aspirin is not inferior to rabeprazole plus clopidogrel** for the healing of aspirin-related peptic ulcer. Aliment Pharmacol Ther. 2011 Sep;34(5):519-25.

Mastronarde JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, Wise RA. American Lung Association Asthma Clinical Research Centers. Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med. 2009 Apr 9;360(15):1487-99. Abstract: http://content.nejm.org/cgi/content/short/360/15/1487

Srygley FD, Gerardo CJ, Tran T, Fisher DA. Does this **patient have a severe upper gastrointestinal bleed**? JAMA. 2012 Mar 14;307(10):1072-9. . Melena, nasogastric lavage with blood or coffee grounds, or serum urea nitrogen:creatinine ratio of more than 30 increase the likelihood of a UGIB. Blood clots in the stool make a UGIB much less likely. The Blatchford clinical prediction score, which does not require nasogastric lavage, is very efficient for identifying patients who do not require urgent intervention.

Taha AS, McCloskey C, Prasad R, Bezlyak V. **Famotidine** for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (**FAMOUS**): a phase III, randomised, double-blind, placebo-controlled trial. Lancet. 2009 Jul 11;374(9684):119-25.

Taha AS, Hudson N, Hawkey CJ, et al. **Famotidine** for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med. 1996 May 30;334(22):1435-9.

Treatment Guidelines: Drugs for **Peptic Ulcers & GERD**. **The Medical Letter**: February, **2004**; 2(18) pp. 9-12. New & Updated August 2008. **New & Updated Sept 2011**

van Marrewijk CJ, Mujakovic S, Fransen GA, Numans ME. Effect and cost-effectiveness of step-up versus step-down treatment with antacids, H2-receptor antagonists, and proton pump inhibitors in patients with new onset dyspepsia (DIAMOND study): a primary-care-based randomised controlled trial. Lancet. 2009 Jan 17;373(9659):215-25.

TOP

References

[1] Micromedex 2011

[2] Van Zanten V, Lauritsen K, Delchier JC, Labenz J, De Argila CM, Lind T. One-week triple therapy with esomeprazole provides effective eradication of Helicobacter pylori in duodenal ulcer disease. Aliment Pharmacol Ther. 2000 Dec;14(12):1605-11.

[3] Wong BC, Wong WM, Yee YK, et al. Rabeprazole-based 3-day and 7-day triple therapy vs. omeprazole-based 7-day triple therapy for the treatment of Helicobacter pylori infection. Aliment Pharmacol Ther. 2001 Dec;15(12):1959-65.

[4] Gottrand F, Kalach N, Spyckerelle C, et al. Omeprazole combined with amoxicillin and clarithromycin in the eradication of Helicobacter pylori in **children** with gastritis: A prospective randomized double-blind trial. J Pediatr. 2001 Nov;139(5):664-8.

[5] Lind T, Veldhuyzen van Zanten S, Unge P. Eradication of Helicobacter pylori using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I Study. Helicobacter 1996;1(3):138-44.

[6] Hunt R, Fallone C, Veldhuyzan van Zanten S, et al. CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of Helicobacter pylori--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H pylori infection. Can J Gastroenterol. 2004 Sep;18(9):547-54.

[7] Jones NL. A review of current guidelines for the management of Helicobacter pylori infection in **children** and adolescents. Paediatr Child Health 2004;9(10):709-713.

[8] Duck WM, et al. Antimicrobial resistance incidence & risk factors among Helicobacter pylori-infected persons, United States. Emerg Infect Dis. 2004 Jun;10(6):1088-94.

[9] Liu CC, Lee CL, Chan CC, et al. Maintenance treatment is not necessary after Helicobacter pylori eradication and healing of bleeding peptic ulcer: a 5-year prospective, randomized, controlled study. Arch Intern Med. 2003 Sep 22;163(17):2020-4.

[10] Treiber G, Wittig J, Ammon S, Walker S, van Doorn LJ, Klotz U. Clinical outcome and influencing factors of a new short-term quadruple therapy for Helicobacter pylori eradication: a randomized controlled trial (**MACLOR** study). Arch Intern Med. 2002 Jan 28;162(2):153-60.

[11] Lara LF, Cisneros G, Gurney M, Van Ness M, Jarjoura D, Moauro B, Polen A, Rutecki G, Whittier F. One-day quadruple therapy compared with 7-day triple therapy for Helicobacter pylori infection. Arch Intern Med. 2003 Sep 22;163(17):2079-84.

[12] Hunt R, Thomson AB. Canadian Helicobacter pylori consensus conference. Canadian Association of Gastroenterology. Can J Gastroenterol. 1998 Jan-Feb;12(1):31-41.

[13] Hunt R, Fallone C, Veldhuyzan van Zanten S, et al.; CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of Helicobacter pylori--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H pylori infection. Can J Gastroenterol. 2004 Sep;18(9):547-54.

[14] Iacopini F, et al. One-week once-daily triple therapy with esomeprazole, levofloxacin and azithromycin compared to a standard therapy for Helicobacter pylori eradication. Dig Liver Dis. 2005 Aug;37(8):571-6.

Federico A, Nardone G, Gravina AG, et al. Efficacy of 5-day **levofloxacin**- containing concomitant therapy in eradication of Helicobacter pylori infection. Gastroenterology 2012;142:000–000.

[15] Best L, Cooper-Lesins G, Haldane D, et al. Helicobacter pylori antibiotic resistance in Canadian populations. (Abstr) Gastroenterology 2004;126:S1293

Additional sources:

Ables AZ, Simon I, Melton ER. **Update on Helicobacter pylori treatment**. Am Fam Physician. 2007 Feb 1;75(3):351-8.

Albrecht P, Kotowska M, Szajewska H. **Sequential therapy** compared with standard triple therapy for helicobacter pylori eradication in **children**: a double-blind, randomized, controlled trial. J Pediatr. 2011 Jul;159(1):45-9.

Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/

BC 2010 Guidelines.

Bentur Y, Matsui D, Koren G. Safety of **14C-UBT** for diagnosis of Helicobacter pylori infection in **pregnancy**. Can Fam Physician. 2009 May;55(5):479-80.

Bourke B, Ceponis P, Chiba N, et al.; Canadian Helicobacter Study Group. Canadian Helicobacter Study Group Consensus Conference: Update on the approach to Helicobacter pylori infection in children and adolescents--an evidence-based evaluation. Can J Gastroenterol. **2005** Jul;19(7):399-408.

Braden B. **Diagnosis** of Helicobacter pylori infection. BMJ. 2012 Feb 24;344:e828.

Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.

Buonavolontà R, Miele E, Russo D, Vecchione R, et al. Helicobacter pylori **Chronic Gastritis in Children**: To Eradicate or Not to Eradicate? J Pediatr. 2011 Jul;159(1):50-6.

Centanni M, et al. **Thyroxine** in goiter, Helicobacter pylori infection, and chronic gastritis. N Engl J Med. 2006 Apr 27;354(17):1787-95.

Cheng HC, Chang WL, Chen WY, et al. Levofloxacin-Containing Triple Therapy to Eradicate the Persistent H. pylori after a Failed Conventional Triple Therapy. Helicobacter. 2007 Aug;12(4):359-63. n=124. One-week levofloxacin 500 mg daily-based triple therapy is effective for eradicating the persistent H. pylori after a failed triple therapy with amoxicillin, clarithromycin, and omeprazole.

TOP

Chey WD, Moayyedi P. Review article: uninvestigated dyspepsia and non-ulcer dyspepsia-the use of endoscopy and the roles of Helicobacter pylori eradication and antisecretory therapy. Aliment Pharmacol Ther. 2004 Feb;19 Suppl 1:1-8.

Chey WD, Wong BC; Practice Parameters Committee of the **American** College of Gastroenterology (**ACG**). American College of Gastroenterology Guideline on the Management of **Helicobacter pylori Infection**. Am J Gastroenterol. 2007 Aug;102(8):1808-25. Epub 2007 Jun 29.

Chiba N, Van Zanten SJ, Sinclair P, Ferguson RA, Escobedo S, Grace E. Treating Helicobacter pylori infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment-Helicobacter pylori positive (CADET-Hp) randomised controlled trial. BMJ. 2002 Apr 27;324(7344):1012-6.

Czinn SJ. Helicobacter pylori infection: detection, investigation, and management. J Pediatr. 2005 Mar;146(3 Suppl):S21-6.

Deguchi R, et al. Effect of Pretreatment with **Lactobacillus gasseri OLL2716** on First-line Helicobacter pylori Eradication Therapy. J Gastroenterol Hepatol. 2011 Nov 18.

Delaney BC, Qume M, Moayyedi P, et al. **Helicobacter pylori test and treat versus proton pump inhibitor** in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). BMJ. 2008 Feb 29; [Epub ahead of print] Test and treat and acid suppression are equally cost effective in the initial management of dyspepsia. Empirical acid suppression is an appropriate initial strategy. As costs are similar overall, general practitioners should discuss with patients at which point to consider H pylori testing.

FDA has announced approval of a breath test for *Helicobacter pylori* for use in children aged 3 to 17 years. **BreathTek UBT** was previously approved for adult use. The first breath test for use in children ages 3 to 17 years to detect *Helicobacter pylori* (*H. pylori*) bacterial infections, responsible for chronic stomach inflammation (gastritis) and ulcers, was approved by the U.S. Food and Drug Administration (FDA) on Feb. 22, 2012.

Federico A, Nardone G, Gravina AG, et al. Efficacy of 5-day **levofloxacin**- containing concomitant therapy in eradication of Helicobacter pylori infection. Gastroenterology 2012;142:000–000.

Fischbach W, Goebeler ME, et al.; EGILS (European Gastro-Intestinal Lymphoma Study) Group. Most patients with minimal histological residuals of gastric **MALT lymphoma** after successful eradication of Helicobacter pylori can be managed safely by a watch and wait strategy: experience from a large international series. Gut. 2007 Dec;56(12):1685-7. Epub 2007 Jul 16.

Fletcher EH, Johnston DE, Fisher CR, et al. Systematic review: Helicobacter **pylori and the risk of upper gastrointestinal bleeding** risk in patients taking aspirin. Aliment Pharmacol Ther. 2010 Oct;32(7):831-9. doi: 10.1111/j.1365-2036.2010.04415.x.

Ford A, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD003840.

Francavilla R, et al. Improved efficacy of 10d **sequential** treatment for Helicobacter pylori eradication in children:a randomized trial. Gastroenterology.2005 Nov;129(5):1414-9.

Fuccio L, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for Helicobacter pylori eradication. Ann Intern Med. 2007 Oct 16;147(8):553-62. Available data suggest that extending triple therapy beyond 7 days is unlikely to be a clinically useful strategy. {InfoPOEMs Dec 2007: Seven days of treatment with triple therapy -- a proton pump inibitor (PPI) + clarithromycin (Biaxin) + amoxicillin or metronidazole -- produces rates of eradication that are nearly as good as 10 days to 14 days of treatment, and are equally good if only high-quality research is considered. (LOE = 1a-) }

Fuccio L, Laterza L, Zagari RM, Cennamo V, Grilli D, Bazzoli F. **Treatment of Helicobacter pylori** infection. BMJ. 2008 Sep 15;337:a1454. doi: 10.1136/bmj.a1454.

Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis:can Helicobacter pylori eradication treatment reduce the risk for **gastric cancer**? Ann Intern Med. 2009 Jul21;151(2):121-8.

Fukase K, Kato M, Kikuchi S,et al. Japan Gast Study Group. Effect of **eradication of Helicobacter pylori** on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet. 2008 Aug 2;372(9636):392-7. Prophylactic eradication of H pylori after endoscopic resection of early gastric cancer should be used to prevent the development of metachronous gastric carcinoma.

Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential Therapy or **Triple Therapy** for Helicobacter pylori Infection: Systematic Review and Meta-Analysis of Randomized Controlled Trials in Adults and Children. Am J Gastroenterol. 2009 Oct 20.

Gene E, Calvet X, et al. Triple vs quadruple therapy for treating Helicobacter pylori infection: an updated meta-analysis. Aliment Pharmacol Ther. 2003 Sep 1;18(5):543-4. Giannini EG, et al. Can Helicobacter pylori eradication regimens be shortened in clinical practice? An open-label, randomized, pilot study of 4 and 7-day triple therapy with rabeprazole, high-dose levofloxacin, and tinidazole. J Clin Gastroenterol. 2006 Jul;40(6):515-20.

Giannini EG, et al. A study of **4- and 7-day** triple therapy with rabeprazole, high-dose levofloxacin and tinidazole rescue treatment for Helicobacter pylori eradication. Aliment Pharmacol Ther. 2006 Jan 15;23(2):281-7.

Gisbert JP, Pajares JM. Systematic review and meta-analysis: is 1-week proton pump inhibitor-based triple therapy sufficient to heal peptic ulcer? Aliment Pharmacol Ther. 2005 Apr 1;21(7):795-804. CONCLUSION: In pts with peptic ulcer & H. pylori infection, prolonging therapy with proton pump inhibitor after a triple therapy for 7 days with a PPI & two antibiotics is not necessary to induce ulcer healing.

Gisbert JP. Potent gastric acid inhibition in Helicobacter pylori eradication. Drugs. 2005;65 Suppl 1:83-96.

Gisbert JP, et al. Systematic review & meta-analysis: **levofloxacin**-based rescue regimens after H. pylori treatment failure. Aliment Pharmacol Ther. 2006 Jan 1;23(1):35-44.

Gisbert JP, et al.; The H. pylori Study Group of the Asociacion Espanola de Gastroenterologia. Third-line rescue therapy with levofloxacin after two H. pylori treatment failures. Am J Gastroenterol. 2006 Feb;101(2):243-7.

Gisbert JP, Abraira V. Accuracy of Helicobacter pylori Diagnostic Tests in Patients with Bleeding Peptic Ulcer: A Systematic Review and Meta-analysis. Am J Gastroenterol. 2006 Feb 22; [Epub ahead of print]

Gisbert JP, Calvet X. Review article: the effectiveness of **standard triple therapy for Helicobacter pylori has not changed over the last decade**, but it is not good enough. Aliment Pharmacol Ther. 2011 Oct 21. doi:10.1111/j.1365-2036.2011.04887.x.

TOP

Graham DY, Lu H, Yamaoka Y. Therapy for Helicobacter pylori Infection Can be Improved : **Sequential Therapy and Beyond**. Drugs. 2008;68(6):725-36.
Graham DY, Fischbach L. Helicobacter pylori treatment in the era of **increasing antibiotic resistance**. Gut. 2010 Aug;59(8):1143-53.
Greenberg ER, Anderson GL, Morgan DR, et al. **14-day triple**, 5-day concomitant, and 10-day sequential therapies for Helicobacter pylori infection in seven Latin American sites: a randomised trial. Lancet 2011; published online July 20.
Harvey RF, Lane JA, Nair P, Egger M, Harvey I, Donovan J, et al. Clinical trial: **prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia** consultations—the Bristol Helicobacter Project. Aliment Pharmacol Ther 2010;32:394-400.
Hassan-Alin M, et al.Studies on drug interactions between **esomeprazole**, amoxicillin and **clarithromycin** in healthy subjects. Int J Clin Pharmacol Ther. 2006 Mar;44(3):119-27.
Hsu PI, et al. A prospective randomized trial of **esomeprazole**-versus pantoprazole-based triple therapy for H. pylori eradication. Am J Gastroenterol. 2005 Nov;100(11):2387-92.
Hsu PI, Lai KH, Lin CK, et al. A Prospective Randomized Trial of **Esomeprazole**- versus Pantoprazole-Based Triple Therapy for Helicobacter pylori Eradication. Am J Gastroenterol. 2005 Nov;100(11):2387-92.
Jafri NS, Hornung CA, Howden CW. Meta-analysis: **Sequential Therapy** Appears Superior to Standard Therapy for Helicobacter pylori Infection in Patients Naive to Treatment. Ann Intern Med. 2008 May 19. [Epub ahead of print] Sequential therapy appears superior to standard triple therapy for eradication of H. pylori infection. If RCTs in other countries confirm these findings, 10-day sequential therapy could become a standard treatment for H. pylori infection in treatment-naive patients.
Jarbol DE, et al. **Proton pump inhibitor or testing** for Helicobacter pylori as the first step for patients presenting with dyspepsia? A cluster-randomized trial. Am J Gastroenterol. 2006 Jun;101(6):1200-8. (InfoPOEMs: A test-and-treat strategy is the most cost-effective approach to dyspepsia in the primary care setting. (LOE = 1b))
Jones NL, Sherman P, et al. Canadian Helicobacter Study Group Consensus Conference: Update on the approach to Helicobacter pylori infection in **children** and adolescents - An evidence-based evaluation. Can J Gastroenterol. 2005 Jul;19(7):399-408.
Khan S, Sharrack B, Sewell WA. **Metronidazole-induced aseptic meningitis** during Helicobacter pylori eradication therapy. Ann Intern Med 146 (5): 395-6, 2007.
Kuo SH, Yeh KH, Wu MS, et al. Helicobacter pylori eradication therapy is effective in the treatment of early-stage H pylori-positive gastric diffuse large **B-cell lymphomas**. Blood. 2012 May 24;119(21):4838-44.
Laine L, Estrada R, Trujillo M, et al. Effect of proton-pump inhibitor therapy on diagnostic testing for Helicobacter pylori. Ann Intern Med. 1998 Oct 1;129(7):547-50.
Lane JA, Murray LJ, Noble S, et al. Impact of Helicobacter pylori eradication on **dyspepsia**, health resource use, and quality of life in the Bristol helicobacter project: randomised controlled trial. BMJ. 2006 Jan 28;332(7535):199-204. Epub 2006 Jan 20.
Liou JM, Lin JT, Chang CY, et al. **Levofloacin-based and clarithromycxin-based** triple therapies as first-line and second-line treatments for Helicobacter pylori infection: a randomised comparative trial with crossover design. Gut. 2010 May;59(5):572-8.
Liou JM, Chen CC, Chen MJ, et al. Empirical modified sequential therapy containing **levofloxacin and high-dose esomeprazole** in second-line therapy for Helicobacter pylori infection: a multicentre clinical trial. J Antimicrob Chemother. 2011 May 31.
Luther J, Higgins PD, Schoenfeld PS, Moayyedi P, et al. Empiric **Quadruple vs. Triple** Therapy for Primary Treatment of Helicobacter pylori Infection: Systematic Review and Meta-Analysis of Efficacy and Tolerability. Am J Gastroenterol. 2009 Sep 15.
Luther J, Higgins PD, Schoenfeld PS, et al. Empiric **quadruple vs. triple** therapy for primary treatment of Helicobacter pylori infection: Systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol. 2010 Jan;105(1):65-73.
Malfertheiner P, Bazzoli F, Delchier JC, et al. for Pylera Study Group. Helicobacter pylori eradication with a capsule containing **bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy**: a randomised, open-label, non-inferiority, phase 3 trial. Lancet. 2011 Feb 22.
Mazzoleni LE, Sander GB, Francesconi CFM, et al. Helicobacter pylori eradication in **functional dyspepsia**: **HEROES** Trial. Arch Intern Med. 2011;171 (21):1929-1936.
For every 8 patients treated with eradication therapy instead of placebo, one additional patient will have a 50% improvement in symptoms 1 year later. However, the range of this estimate is quite large (4.6 - 38.8).
Mazzoleni LE, Francesconi CF, Sander GB. **Mass eradication** of Helicobacter pylori: feasible and advisable? Lancet. 2011 Aug 6;378(9790):462-4.
McColl, Kenneth E.L. **Helicobacter pylori Infection**. N Engl J Med 2010 362: 1597-1604.
Miehlke S, Krasz S, Schneider-Brachert W, et al. Randomized Trial on 14 versus 7 days with esomeprazole, moxifloxacin and amoxicillin for Second-line or Rescue Treatment of Helicobacter pylori Infection. Helicobacter. 2011 Dec;16(6):420-426. doi: 10.1111/j.1523-5378.2011.00867.x.
Moayyedi P, Soo S, Deeks J, et al. Eradication of Helicobacter pylori for **non-ulcer dyspepsia**. Cochrane Database Syst Rev 2006 Apr 19;(2):CD002096.
Nam SY, Choi IJ, Ryu KH, et al. Effect of Helicobacter pylori Infection and Its Eradication on **Reflux Esophagitis and Reflux Symptoms**. Am J Gastroenterol. 2010 Jun 22.
Nista EC, et al. **Levofloxacin**-Based Triple Therapy in First-Line Treatment for Helicobacter pylori Eradication. Am J Gastroenterol. 2006 Sep;101(9):1985-90.
Oderda G, Rapa A, Bona G. A systematic review of Helicobacter pylori eradication treatment schedules in **children**. Aliment Pharmacol Ther. 2000 Oct;14 Suppl 3:59-66.
Ozdil K, Calhan T, Sahin A, et al. **Levofloxacin** based sequential and triple therapy compared with standart plus probiotic combination for helicobacter pylori eradication. Hepatogastroenterology. 2011 Jul-Aug;58(109):1148-52.
Pierantozzi M, et al. Helicobacter pylori eradication and l-**dopa absorption in patients with PD** and motor fluctuations. Neurology. 2006 Jun 27;66(12):1824-9.
Raju D, Hussey S, Ang M, et al. **Vacuolating cytotoxin and variants in Atg16l1** that disrupt autophagy promote Helicobacter pylori infection in humans. Gastroenterology 2012;142:1160–1171.
Ramakrishnan K, Salinas RC. Peptic ulcer disease. Am Fam Physician. 2007 Oct 1;76(7):1005-12.

TOP

Rokkas T, Sechopoulos P, Robotis I, Margantinis G, Pistiolas D. Cumulative H. pylori eradication rates in clinical practice by adopting first and second-line regimens proposed by the **Maastricht III consensus** and a third-line empirical regimen. Am J Gastroenterol. 2009 Jan;104(1):21-5. A sequence of 3 strategies was successful in eradicating H. pylori in 89% of patients by intention-to-treat analysis and in 98% of patients by per-protocol analysis. (LOE = 2b)

Ruggiero F, Elena L, Stefania C et al. **Clarithromycin-Resistant Genotypes** and Eradication of Helicobacter Pylori, The Journal of Pediatrics, Vol 157, Issue 2, Aug10, 228-232.

Sabbi T, et al. Efficacy of noninvasive tests in the diagnosis of Helicobacter pylori infection in **pediatric** patients. Arch Pediatr Adolesc Med 2005; 159:238-41. (InfoPOEMs: In children with significant & persistent or recurrent symptoms of upper gastrointestinal disease, fecal antigen testing for Helicobacter pylori is more reliable than serology. Although not part of this study (since serology is unreliable for monitoring response to treatment), direct testing of the stool also provides a more reliable means of evaluating treatment response.(LOE = 1c-))

Saad RJ, et al. **Levofloxacin**-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis. Am J Gastroenterol. 2006 Mar;101(3):488-96. (InfoPOEMs: A 10-day regimen of levofloxacin, amoxicillin, and a proton pump inhibitor (PPI) is more effective and better tolerated than the traditional 7-day 4-drug bismuth-based regimen for patients who have persistent Helicobacter pylori (HP) infection despite previous treatment. (LOE = 1a)) (see also Pharmacist's Letter: Levofloxacin for Persistent H. Pylori Infection, May 2006)

Saad AM, Choudhary A, Bechtold ML. Effect of Helicobacter **pylori treatment on gastroesophageal reflux disease** (GERD): meta-analysis of randomized controlled trials. Scand J Gastroenterol 2012;47:129-35

Sarker SA, Mahmud H, et al. Causal relationship of Helicobacter pylori with iron-deficiency anemia or failure of iron supplementation in children. Gastroenterology. 2008 Nov;135(5):1534-42. Epub 2008 Aug 5. H pylori is neither a cause of IDA/ID nor a reason for treatment failure of iron supplementation in young Bangladeshi children.

Scaccianoce G, et al. Helicobacter pylori eradication with either 7day or 10day triple therapies, and with a 10-day **sequential** regimen. Can J Gastroenterol. 2006 Feb;20(2):113-7.

Spee, Leo A. A., Madderom, MB., Pijpers, M, et al. Association Between Helicobacter pylori and **Gastrointestinal Symptoms** in **Children**. Pediatrics 2010 125: e651-e669.

Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: the effects of **Saccharomyces boulardii** supplementation on Helicobacter pylori eradication rates and side effects during treatment. Aliment Pharmacol Ther. 2010 Nov;32(9):1069-79. doi: 10.1111/j.1365-2036.2010.04457.x.

Talley NJ, Fock KM, Moayyedi P. Gastric Cancer Consensus conference recommends Helicobacter pylori screening and treatment in asymptomatic persons from high-risk populations to prevent **gastric cancer**. Am J Gastroenterol. 2008 Mar;103(3):510-4.

Treatment Guidelines: Drugs for **Peptic Ulcers & GERD**. **The Medical Letter**: February, **2004**; 2(18) pp. 9-12. New & Updated August 2008. **New & Updated Sept 2011**

Vaira D, et al. **Sequential** therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized trial. Ann Intern Med. 2007 Apr 17;146(8):556-63. n=300 Sequential therapy is statistically significant compared with standard therapy for eradicating H. pylori infection and is statistically significantly more effective in patients with clarithromycin-resistant strains. Side effects are similar with both treatment regimens and are rarely severe enough to cause discontinuation of therapy.

Valle PC, et al. "Test, score and scope": a selection strategy for safe reduction of upper gastrointestinal endoscopies in young dyspeptic patients referred from primary care. (InfoPOEMs: For men younger than 45 years, the endoscopic yield is very low for those without Helicobacter pylori infection, nonsteroidal anti-inflammatory drug (NSAID) use, unintended weight loss, or anemia. (LOE = 2b))

Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, Barkun A, Thomson A, et al. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in helicobacter pylori negative, primary care patients with dyspepsia: the CADET-HN Study. Am J Gastroenterol. 2005 Jul;100(7):1477-88. Treatment with omeprazole provides superior symptom relief compared to ranitidine, cisapride, and placebo in the treatment of H. pylori negative primary care dyspepsia patients.

Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003 Sep 15;18(6):647-54. The efficacy of various proton-pump inhibitors seems to be similar when used for H. pylori eradication in standard triple therapy.

Vergara M, Catalán M, Gisbert JP, Calvet X. Meta-analysis: role of Helicobacter **pylori eradication in the prevention of peptic ulcer in NSAID** users. Aliment Pharmacol Ther. 2005 Jun 15;21(12):1411-8.

Wang C, Yuan Y, Hunt RH. Helicobacter pylori infection and **Barrett's esophagus**: a systematic review and meta-analysis. Am J Gastroenterol. 2009 Feb;104(2):492-500.

Wilhelm SM, Johnson JL, Kale-Pradhan PB. Treating bugs with bugs: the role of **probiotics** as adjunctive therapy for Helicobacter pylori. Ann Pharmacother. 2011 Jul;45(7-8):960-6.

Wong BC, Lam SK, et al. Helicobacter pylori eradication to **prevent gastric cancer** in a high-risk region of China: a randomized controlled trial. JAMA 2004; 291: 187–94.

Zapata-Colindres JC,et al. The association of **Helicobacter pylori infection and nonsteroidal anti-inflammatory drugs** in peptic ulcer disease. Can J Gastroenterol. 2006 Apr;20(4):277-80. The development of PUD was observed earlier in the combined H pylori and NSAID group than in patients with only NSAID use. This suggests a synergic effect between the two risks factors in the development of PUD.

Zagari RM, et al. Comparison of **one and two weeks** of omeprazole, amoxicillin and clarithromycin treatment for Helicobacter pylori eradication: the HYPER study. Gut. 2006 Oct 6; [Epub ahead of print] n=909 One-week and two-week PPI-based triple therapies (omeprazole, amoxicillin and clarithromycin) for H. pylori eradication are similar in terms of efficacy, safety and patient compliance.

Zagari RM, Bianchi-Porro G, et al. Comparison of 1 and 2 weeks of omeprazole, amoxicillin and clarithromycin treatment for Helicobacter pylori eradication: the HYPER Study. Gut. 2007 Apr;56(4):475-9. Epub 2006 Oct 6. n=909. CONCLUSIONS: 1-week and 2-week triple treatments for H pylori eradication are similar in terms of efficacy, safety and patient compliance. (InfoPOEMs: One week of omeprazole, amoxicillin, and clarithromyin given twice daily is as effective at eradicating Helicobacter pylori (HP) as 2 weeks of treatment. It also costs less and is less burdensome for patients. (LOE = 1b))

TOP

Zojaji H, Talaie R, Mirsattari D, et al. The efficacy of Helicobacter pylori eradication regimen with and without **vitamin C** supplementation. Dig Liver Dis. 2009 Jun 1. [Epub ahead of print] Addition of vitamin C to H. pylori treatment regimen of amoxicillin, metronidazole and bismuth can significantly increases H. pylori eradication rate.

Zullo A, et al. High rate of H. pylori eradication with **sequential therapy** in elderly pts with peptic ulcer:a prospective controlled study.Aliment Pharmacol Ther.2005;21:1419-24.

Zullo A, Hassan C, Andriani A, et al.. Eradication Therapy for Helicobacter pylori in Patients With Gastric **MALT Lymphoma**: A Pooled Data Analysis. Am J Gastroenterol. 2009 Jun 16. [Epub ahead of print] This was the first comprehensive (approximately 1,300 patients) analysis of the therapeutic management of H. pylori in gastric lymphoma patients. Data suggest that this infection is easily managed in these patients, being cured in nearly all cases.

TOP

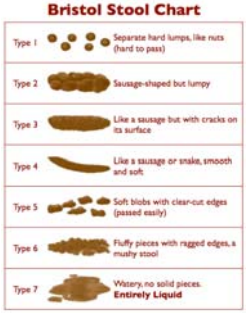
Extras:

Discontinued Drugs: Alosetron LOTRONEX (2000 -severe constipation & ischemic colitis) avail. in USA ♀ special access 5HT3 antagonist. Not avail. in Canada.

Tegaserod ZELNORM: Mar07- suspended due to CV ischemic events; but Apr08-FDA for Emergency IND situations only use in IBS-constipation & chronic idiopathic constipation in ♀<55yr with no hx of heart problems. 6 mg po bid $160 (NNT=14) 5HT4 agonist Not avail in Canada.

Notes:

- Children with IBS or functional abdominal pain: probiotic Lactobacillus rhamnosus GG 3 billion colony forming units twice daily reduced # of pain episodes & pain intensity by ≥50% more in Tx vs Pl group (8wks; ave age 6).[53]
- A high-fiber diet and increased frequency of bowel movements may not protect against diverticulosis.[72]



References – IBS – www.RxFiles.ca {Originally prepared by Lynette Kolodziejak for the RxFiles Academic Detailing Program}

1. Micromedex. 2010.
2. Association CP. *Compendium of Pharmaceuticals and Specialties*; 2010.
3. Briggs G, Freeman, Roger, Yaffe, Sumner, ed. *Drugs in **Pregnancy** and Lactation.* 9th ed: TechBooks 2011.
4. Kumar A KN, Vij JC, Sarin SK, Anand BS. Optimum dosage of ispaghula husk in patients with irritable bowel syndromw: correlation of symptom relief with whole gut transit time and stool weight. *Gut.* 1987;28(2):150-155.
5. Zuckerman MJ. The role of **fiber** in the treatment of irritable bowel syndrome: therapeutic recommendations. *J Clin Gastroenterol.* Feb 2006;40(2):104-108.
6. Efskind PS BT, Vatn MH. A double-blind placebo-controlled trial with **loperamide** in irritable bowel syndrome. *Scandanvian Journal of Gastroenterology.* 1996;31:463-468.
7. Cann PA RN, Holdsworth CD et al. Role of **loperamide** and placebo in management of irritable bowel syndrome (IBS). *Digestive diseases and sciences.* 1984;29:239-247.
8. Hadley SK, Gaarder SM. **Treatment** of irritable bowel syndrome. *Am Fam Physician.* Dec 15 2005;72(12):2501-2506.
9. Wald A. **Psychotropic** Agents in Irritable Bowel Syndrome. *J Clin Gastroenterol.* 2002;35(Suppl):S53-S57.
10. Abramowicz M. **Treatment** Guidelines: Drugs for Irritable Bowel Syndrome. *The Medical Letter.* March 2006;4(43):11-16. (**see also July 2011**)
11. Tabas G BM, Wang J, Friday P, Mardini H, Arnold G. **Paroxetine** to treat Irritable Bowel Syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. *American Journal of Gastroenterology.* 2004;99(5):914-920.
12. Vahedi H, Merat S, Rashidioon A, Ghoddoosi A, Malekzadeh R. The effect of **fluoxetine** in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. *Aliment Pharmacol Ther.* Sep 1 2005;22(5):381-385.
13. Talley NJ KJ, Boyce P, Tennant C, Huskie S, Jones M. **Antidepressant** Therapy (Imipramine and Citalopram) for Irritable Bowel Syndrome: A double-blind, randomized, placebo-controlled trial. *Digestive diseases and sciences*; 2007.
14. DiPiro, ed. **Pharmacotherapy***: A Pathophysiologic Approach.* 6th ed. New York: McGraw-Hill Companies; 2005.
15. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the **management** of irritable bowel syndrome in family practice. IBS Consensus Conference Participants. *Cmaj.* Jul 27 1999;161(2):154-160.
16. Evidence-based position statement on the **management** of irritable bowel syndrome in North America. *Am J Gastroenterol.* Nov 2002;97(11 Suppl):S1-5.
17. American Gastroenterological Association medical **position** statement: irritable bowel syndrome. *Gastroenterology.* Dec 2002;123(6):2105-2107.
    December 18, 2008 -- The **American College of Gastroenterology (ACG)** has today published a new evidence-based systematic review on the management of Irritable Bowel Syndrome (IBS) as a supplement to the **January 2009** issue of *The American Journal of Gastroenterology*. "For the gastroenterologist seeing patients with IBS, the new ACG recommendations specify whether or not the range of potential therapies are better than placebo for resolving IBS symptoms," said Lawrence J. Brandt, MD, ACG IBS Task Force, Bethesda, Maryland. The ACG Evidence-Based Systematic Review on IBS can be accessed here: **http://www.acg.gi.org/media/releases/ajg_ibs_supp_0109.pdf**
    American College of Gastroenterology (AJG) Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol. 2009 Jan;104 Suppl 1:S1-35.
18. Pharmacist's Letter. FDA Permits restricted use of **Zelnorm** for Qualifying patients. Sept 2007.

TOP

April/08 FDA: Zelnorm for Emergency use only http://www.fda.gov/cder/drug/infopage/zelnorm/default.htm
19. Wilson, J. Irritable Bowel Syndrome: In the clinic. Annals of Int Med. 2007, July.
20. Jailwala J, et al. Pharmacologic treatment of IBS: a systematic review of randomized, controlled trials. Ann Intern Med. 2000 Jul 18;133(2):136-47.
21. Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care **NICE** Guidelines Feb/08 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11927#summary
22. Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, Hughes AO. Defecation frequency and timing, and stool form in the general population: a prospective study. Gut. 1992 Jun;33(6):818-24. (Type 1: separate hard lumps, like nuts, Type 2: sausage shaped but lumpy, Type 3: Like sausage or snake but with cracks on its surface, Type 4: Like sausage or snake, smooth and soft, Type 5: Soft blobs with clear cut edges, Type 6: Fluffy pieces with ragged edges, a mushy stool , Type 7: Watery, no solid pieces, entirely liquid)
23. Vahedi H, et al. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2008 Apr;27(8):678-84. Epub 2008 Jan 30. **Amitriptyline 10mg** daily may be effective in the treatment of diarrhoea-predominant irritable bowel syndrome and at low dose is well tolerated.
24. Mayer EA. Clinical practice. **Irritable bowel syndrome**. N Engl J Med. 2008 Apr 17;358(16):1692-9.
25. Drossman DA. The functional gastrointestinal disorders and **Rome III** process. Gastroenterology. 2006 Apr;130(5):1377-90. http://www.romecriteria.org
26. Drossman DA, Toner BB, Whitehead WE, et al. **Cognitive-behavioral therapy** versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology. 2003 Jul;125(1):19-31.
27. Spiller R, Aziz Q, Creed F, et al. Clinical Services Committee of The **British** Society of Gastroenterology. **Guidelines** on the irritable bowel syndrome: mechanisms and practical management. Gut. 2007 Dec;56(12):1770-98. Epub 2007 May 8.
28. Wilhelm SM, Brubaker CM, Varcak EA, Kale-Pradhan PB. Effectiveness of probiotics in the treatment of irritable bowel syndrome. Pharmacotherapy. 2008 Apr;28(4):496-505. As probiotics have shown benefit and possess a favorable adverse-effect profile, their use may represent an option for symptom relief in patients with IBS. However, additional data are necessary before probiotics can become a standard of care in the treatment of IBS.

Additional References (post Feb 2008)

29. Bahar RJ, Collins BS, Steinmetz B, Ament ME. Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. J Pediatr 2008;152:685-9.
30. Vahedi H, Merat S, Momtahen S, Kazzazi AS, et al. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2008;27:678-84.
31. Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med. 2008 May 29;358(22):2344-54. n=620. Over 12 weeks, prucalopride 2-4mg po daily x 12 weeks significantly improved bowel function and reduced the severity of symptoms in patients with severe chronic constipation. Larger and longer trials are required to further assess the risks and benefits of the use of prucalopride for chronic constipation.
32. Ford AC, Talley NJ, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ. 2008 Nov 13;337:a2313. doi: 10.1136/bmj.a2313. Fibre, antispasmodics, & peppermint oil were all more effective than placebo in treatment of irritable bowel syndrome. Fiber provides minimal likelihood of benefit in patients with irritable bowel syndrome (IBS). Antispasmodics, particularly scopolamine (hyoscine) and otilonium, are effective in 50% to 70% of patients. Peppermint oil is also effective, with approximately 75% of patients responding (number needed to treat = 2.5). (LOE = 1a-)
33. Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the therapy of irritable bowel syndrome: a systematic review. Gut. 2008 Dec 17. [Epub ahead of print] Probiotics appear to be efficacious in IBS but the magnitude of benefit and the most effective species and strain are uncertain.
34. Nikfar S, Rahimi R, Rahimi F, Derakhshani S, Abdollahi M. Efficacy of probiotics in irritable bowel syndrome: a meta-analysis of randomized, controlled trials. Dis Colon Rectum. 2008 Dec;51(12):1775-80. Epub 2008 May 9. This systematic review/meta-analysis of randomized trials found a significant benefit of probiotics (number needed to treat [NNT] = 12) for improving symptoms of irritable bowel syndrome (IBS). Given the frequent difficulty in adequately treating this illness and the generally benign effects of probiotics, clinicians should strongly consider them for their patients with IBS. (LOE = 1a)b
35. Jones R. Treatment of irritable bowel syndrome in primary care. BMJ. 2008 Nov 13;337:a2213. doi: 10.1136/bmj.a2213.
36. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of Antidepressants and Psychological Therapies in Irritable Bowel Syndrome: Systematic Review and Meta-analysis. Gut. 2008 Nov 10. [Epub ahead of print]
37. Zijdenbos IL, de Wit NJ, van der Heijden GJ, Rubin G, Quartero AO. Psychological treatments for the management of irritable bowel syndrome. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006442. Psychological interventions may be slightly superior to usual care or waiting list control conditions at the end of treatment although the clinical significance of this is debatable. Except for a single study, these therapies are not superior to placebo and the sustainability of their effect is questionable. The meta-analysis was significantly limited by issues of validity, heterogeneity, small sample size and outcome definition. Future research should adhere to current recommendations for IBS treatment trials and should focus on the long-term effects of treatment.
38. Ford AC, Talley NJ, Veldhuyzen van Zanten SJ, Vakil NB, Simel DL, Moayyedi P. Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? JAMA. 2008 Oct 15;300(15):1793-805.
39. Agrawal A, Whorwell PJ. Irritable bowel syndrome: diagnosis and management. BMJ. 2006 Feb 4;332(7536):280-3.
40. Ford AC, et al. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in IBS: systematic review and meta-analysis. Am J Gastroenterol. 2009 Jul;104(7):1831-43; quiz 1844.
41. Jones R, Rubin G. Acute diarrhoea in adults (Post Infective IBS). BMJ. 2009 Jun 15;338:b1877. doi: 10.1136/bmj.b1877.

TOP

42. 1) Bijkerk C J, de Wit N J, Muris J W M, et al. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. BMJ 2009;339:b3154, doi: 10.1136/bmj.b3154 (Published 27 August 2009).
2) Luther J, Chey WD. ACP Journal Club. Psyllium increased symptom relief in patients with the irritable bowel syndrome more than bran or placebo. Ann Intern Med. 2010 Jan 19;152(2):JC1-11. PubMed PMID: 20083814.
43. Saps M, Youssef N, Miranda A, Nurko S, et al. Multicenter, Randomized, Placebo-Controlled Trial of Amitriptyline in Children With Functional Gastrointestinal Disorders. Gastroenterology. 2009 Jul 30. [Epub ahead of print] Both amitriptyline and placebo were associated with excellent therapeutic response.
44. WGO Practice Guidelines Irritable bowel syndrome: a global perspective - April 2009 http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/20_irritable_bowel_syndrome.pdf
45. Saito YA, Rey E, Almazar-Elder AE, et al. A randomized, double-blind, placebo-controlled trial of St John's wort for treating irritable bowel syndrome. Am J Gastroenterol. 2010 Jan;105(1):170-7.Epub 2009 Oct 6. SJW was a less effective treatment for IBS than placebo.
46. Chey WD, Nojkov B, Rubenstein JH, et al. The Yield of Colonoscopy in Patients With Non-Constipated Irritable Bowel Syndrome: Results From a Prospective, Controlled US Trial. Am J Gastroenterol. 2010 Feb 23. The prevalence of structural abnormalities of the colon is no higher in suspected non-constipation IBS patients than in healthy controls. Microscopic colitis can be identified in a small proportion of persons with IBS sx.
47. Jung HK et al. Diarrhea-predominant irritable bowel syndrome is associated with diverticular disease: A population-based study. Am J Gastroenterol 2010 Mar; 105:652. These results indicate that the association between diverticulosis and IBS is real and that it is stronger for diarrhea-predominant IBS and mixed or alternating IBS than for constipation-predominant IBS.
48. Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2009 Oct;30(7):707-17.
49. Primavera G, Amoroso B, et al. Clinical utility of Rome criteria managing functional gastrointestinal disorders in pediatric primary care. Pediatrics. 2010 Jan;125(1):e155-61.
50. Friedrich M, Grady SE, Wall GC. Effects of antidepressants in patients with irritable bowel syndrome and comorbid depression. Clin Ther. 2010 Jul;32(7):1221-1233.
51. Zhou Q, Souba WW, Croce CM, et al. MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome. Gut. 2010 Jun;59(6):775-84.
52. Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. Gut. 2010 Mar;59(3):325-32. Epub 2008 Dec 17. Probiotics appear to be efficacious in IBS, but the magnitude of benefit and the most effective species and strain are uncertain.
53. Francavilla R, Miniello V, Magistà AM, et al. A Randomized Controlled Trial of Lactobacillus GG in Children With Functional Abdominal Pain. Pediatrics. 2010 Nov 15.
54. Pimentel Mark, Lembo Anthony, Chey William D. et al.. for the TARGET Study Group. Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation. N Engl J Med 2011; 364:22-32.
55. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation:systematic review and meta-analysis.Gut.2011Feb;60(2):209-18.
56. Crowe Sheila E. In the Clinic: Celiac Disease. *Ann Intern Med* May 3, 2011 154:ITC5-1.
57. Smith Janette, Humes David J, Spiller Robin C. Uncertainties Page: Should we treat uncomplicated symptomatic diverticular disease with fibre? BMJ 2011;342.
58. Tabbers Merit M., Chmielewska Ania, Roseboom Maaike G., et al. Fermented Milk Containing Bifidobacterium lactis DN-173 010 in Childhood Constipation: A Randomized, Double-Blind, Controlled Trial. Pediatrics 2011; 127:6 e1392-e1399; published ahead of print May 23, 2011, doi:10.1542/peds.2010-2590
59. Liu JP, Yang M, Liu Y, et al. Herbal medicines for treatment of irritable bowel syndrome. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004116. DOI: 10.1002/14651858.CD004116.pub2.
60. Crowe FL, Appleby PN, Allen NE, Key TJ. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. BMJ 2011;343:d4131. (Vegetarian and high-fiber diets are each associated with lower risk for hospitalization or death from diverticular disease)
61. Kaminski A, Kamper A, Thaler K, et al. Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents. Cochrane Database Syst Rev. 2011 Jul 6;7:CD008013. Clinicians must be aware that for the majority of antidepressant medications no evidence exists that supports their use for the treatment of abdominal pain-related FGIDs in children and adolescents. The existing randomised controlled evidence is limited to studies on amitriptyline and revealed no statistically significant differences between amitriptyline and placebo for most efficacy outcomes. Amitriptyline does not appear to provide any benefit for the treatment of FGIDs in children and adolescents.
62. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011 Aug 11;365(6):527-36.
63. Ruepert L, Quartero AO, de Wit NJ, et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2011 Aug 10;(8):CD003460. There is no evidence that bulking agents are effective for treating IBS. There is evidence that antispasmodics are effective for the treatment of IBS. The individual subgroups which are effective include: cimetropium/dicyclomine, peppermint oil, pinaverium and trimebutine. There is good evidence that antidepressants are effective for the treatment of IBS. The subgroup analyses for SSRIs and TCAs are unequivocal and their effectiveness may depend on the individual patient.
64.Tabbers Merit M., Boluyt Nicole, Berger Marjolein Y.,et al. Nonpharmacologic Treatments for Childhood Constipation: Systematic Review. Pediatrics 2011; peds.2011-0179; published ahead of print September 26, 2011, doi:10.1542/peds.2011-0179
65.Ljotsson B, Hedman E, Andersson E, et al. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. Am J Gastroenterol. 2011 Aug;106(8):1481-91.
66. Guglielmetti S, Mora D, Gschwender M, Popp K. Randomised clinical trial: Bifidobacterium bifidum MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life--a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011 May;33(10):1123-32. doi: 10.1111/j.1365-2036.2011.04633.x.
67. Gaylord SA et al. Mindfulness training reduces the severity of irritable bowel syndrome in women: Results of a randomized controlled trial. Am J Gastroenterol 2011 Sep; 106:1678.
68. Torpy JM, Golub RM. JAMA patient page. Irritable bowel syndrome. JAMA. 2011 Oct 5;306(13):1501.
69. Cash BD, Rubenstein JH, Young PE, et al. The prevalence of celiac disease among patients with nonconstipated irritable bowel syndrome is similar to controls. Gastroenterology. 2011 Oct;141(4):1187-93.
70. Zucchelli Marco, Camilleri Michael, Andreasson AN, et al. Association of TNFSF15 polymorphism with irritable bowel syndrome. Gut 2011;60:1671-1677 2 June 2011.
71. Park JM, Choi MG, Cho YK. Cannabinoid receptor 1 gene polymorphism and irritable bowel syndrome in the Korean population: a hypothesis-generating study.

TOP

J Clin Gastroenterol 2011;45:45–49.
72. Peery AF, Barrett PR, Park D, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology. 2012 Feb;142(2):266-272.e1.
73. Menees SB, Maneerattannaporn M, Kim HM et al. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol. 2012 Jan;107(1):28-35.
74. Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler SM, et al. Chronic constipation in the elderly. Am J Gastroenterol. 2012 Jan;107(1):18-25.
75. Vlieger AM, Rutten JM, Govers AM, et al. Long-Term Follow-Up of Gut-Directed Hypnotherapy vs. Standard Care in Children With Functional Abdominal Pain or Irritable Bowel Syndrome. Am J Gastroenterol. 2012 Apr;107(4):627-31.

TOP

N&V EXTRAS:

NHS – CKS: Nausea and Vomiting in Pregnancy - management: http://www.cks.library.nhs.uk/nausea_vomiting_in_pregnancy ; NGC: ACCC Netherlands: http://www.guideline.gov/summary/summary.aspx?doc_id=11793
CINV Guidelines: 1) MASCC: http://www.mascc.org/content/1.html ; 2) ASCO: http://www.asco.org/portal/site/ASCO/
BWH-Overtreatment of PONV: 1) low doses of ondansetron, 1mg iv q6h, adequate ; 2) allow for onset, 30 minutes http://www.brighamandwomens.org/pharmacoepid/Research/EduMaterials/antiemetics3.05.04-web.pdf
Other: Fosapreitant: Injectible form of EMEND, 150mg vial in Canada.

Acknowledgements: Contributors & Reviewers: K. Stakiw (SHR Palliative Care), N. McKee, (Family Medicine, Saskatoon), S. Shepphard (SHR-Anaesthesia, V. Walker (Saskatoon-Cancer Centre), Pharmacists – Saskatoon Cancer Centre, & the RxFiles Advisory Committee.
Adapted from Timmins Palliative Care (P. Critchley MD, T. Dolanjski Pharmacist) Prepared by: *L. Regier* BSP, BA, B. *Jensen* BSP

References: RxFiles Nausea & Vomiting – Management / Treatment Chart www.rxfiles.ca

[1] General references:
a) Mannix KA. Palliation of nausea and vomiting. Oxford Text Palliative Med. Third ed. 2004. Doyle D, Hanks G, Cherney N, Calman K (Eds). Oxford: Oxford. U. Press, 459-468.
b) Quigley EM, Hasler WL, Parkman HP. AGA Technical Review on Nausea and Vomiting. *Gastroenterolgy* 2001; 120(1):263-286
c) Weissman, D. Fast Fact and Concepts #05: Treatment of Nausea and Vomiting. June, 2000. End-of-Life Physician Education Resource Center www.eperc.mcw.edu.
d) Neron A (Ed). Care Beyond Cure: A Pharmacotherapeutic Guide to Palliative Care Pharmacy. 2000. Specialty Group on Palliative Care. 73-81
e) Symptom Management Guidelines. Kingston, Frontenac, Lennox and Addington Palliative Care Integration Project. August 2003 57-61
f) MacLean C. Nausea. Therapeutic Choices. Fifth ed. 2007. Gray J (Ed). Canadian Pharmacists Association
g) Compendium of Pharmaceuticals and Specialties. 2007. Canadian Pharmacists Association
h) Scorza K, Williams A, Phillips DJ, Shaw J. Evaluation of Nausea and Vomiting. AFP 2007;76;76-84. Accessed online:
I) Micromedex Drug Database 2007 (Thomson Healthcare)
j) Dunsfield L, Fitsimmons. CADTH Health Technology Inquiry Service (HTIS): Serotonin (5-HT3) antagonists as anti-emetics. Systematic Review. Feb 6, 2007. www.cadth.ca , htis@cadth.ca .
k) Australian Family Physician September 2007 - Nausea & vomiting collection. http://www.racgp.org.au/afp/200709 {e.g. Hyperemesis gravidarum http://www.racgp.org.au/afp/200709/18538 ; The vomiting child http://www.racgp.org.au/afp/200709/18542 ; Diagnostic Approach http://www.racgp.org.au/afp/200709/18541 }
[2] Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2003;(4):CD000145.
Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med. 2010 Oct 14;363(16):1544-50.
[3] Motherrisk (Hospital for Sick Children, Toronto. http://www.motherisk.org/index.jsp ; N&V in Pregnancy - Algorithm Link (2007): http://www.cfp.ca/cgi/reprint/53/12/2109.pdf
[4] Drugs in Pregnancy and Lactation, 8th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Baltimore, MD: 2011.
[5] Micromedex Drug Database 2008 (Thomson Healthcare)
[6] Czeizel AE, Vargha P. A case-control study of congenital abnormality and dimenhydrinate usage during pregnancy. Arch Gynecol Obstet. 2005 Feb;271(2):113-8. Epub 2004 Oct 23.
[7] Briggs Pregnancy & Lactation 9th Edition 2011; {CPP= Collaborative Perinatal Project}
[8] Einarson A, Maltepe C, Navioz Y, Kennedy D, et al. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG. 2004 Sep;111(9):940-3.
[9] Evidence link: http://clinicalevidence.bmj.com/ceweb/conditions/pac/1405/1405_I2.jsp; P6 Picture link: http://www.pyroenergen.com/articles07/images/neiguan-acupressure-point.jpg
[10] Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006 Jul 19;3:CD004125.
Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative nausea and vomiting prophylaxis. Clin Ther. 2012 Feb;34(2):282-94.
[11] Lee A, Done ML. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2004;(3):CD003281.
[12] Golembiewski, J; Chernin E; Chopra T. Prevention and Treatment of Postoperative Nausea and Vomiting. Am J Health-Syst Pharm. 2005;62(12):1247-1260. ©2005 ASHSP Posted 06/27/2005. http://www.medscape.com/viewarticle/506997_print
[13] Kranke P, Morin AM, Roewer N, Eberhart LH. Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trial s. Acta Anaesthesiol Scand. 2002 Mar;46(3):238-44.
[14] Lee Y, Wang PK, Lai HY, Yang YL, Chu CC, Wang JJ. Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting. Can J Anaesth. 2007 May;54(5):349-54.
[15] www.Cancercare.on.ca : Hesketh Classification of Emetogenic Potential; www.cancercare.on.ca/pdfchemo/NVFIGURE%20II.pdf
[15b] Hesketh PJ, Chemotherapy-Induced Nausea and Vomiting. N Engl J Med 2008;358:2482-94.
[16] Peterson K, McDonagh M, Carson S, Lopez S. Drug class review on newer antiemetics: final report. Portland (OR): Oregon Evidence-based Practice Centre, 2006 Jan. Available: http://www.ohsu.edu/drugeffectiveness/reports/documents/Antiemetics%20Final%20Report.pdf
(Updated by Alison Little, Feb 2009 in a P&T Committee Brief)
[17] Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. Drug Saf. 2003;26(4):227-59.
[18] Gan TJ, Meyer TA, Apfel CC, Chung F,et al; Society for Ambulatory Anesthesia. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2007 Dec;105(6):1615-28,
[19] Koivuranta M, Läärä E, Snåre L, Alahuhta S. A survey of postoperative nausea and vomiting. Anaesthesia. 1997 May;52(5):443-9.
[20] Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999 Sep;91(3):693-700.
[21] Szajewska H, Gieruszczak-Białek D, Dylag M. Meta-analysis: ondansetron for vomiting in acute gastroenteritis in children. Aliment Pharmacol Ther. 2007 Feb 15;25(4):393-400.
Alhashimi D, Al-Hashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD005506. The small number of included trials provided some limited evidence favouring the use of ondansetron and metoclopramide over placebo to reduce the number of episodes of vomiting due to gastroenteritis in children. The increased incidence of diarrhea with both ondansetron and metoclopramide was considered to be as a result of retention of fluids and toxins that would otherwise have been eliminated through the process of vomiting.
Uhlig, Ulrike, Pfeil, Nicole, Gelbrich, Gotz, et al. Dimenhydrinate in Children With Infectious Gastroenteritis: A Prospective, RCT. Pediatrics 2009 0: peds.2008-1650.
Gouin S, Vo TT, Roy M, et al. Oral Dimenhydrinate Versus Placebo in Children With Gastroenteritis: A Randomized Controlled Trial. Pediatrics. 2012 May 14. (dimenhydrinate did not decrease frequency of vomiting)
[22] Leung AK, Robson WL. Acute gastroenteritis in children: role of anti-emetic medication for gastroenteritis-related vomiting. Paediatr Drugs. 2007;9(3):175-84. {also: http://www.racgp.org.au/afp/200709/18542}
[23] Freedman SB, Adler M, Seshadri R, Powell EC. Oral ondansetron for gastroenteritis in a pediatric emergency department. N Engl J Med. 2006 Apr 20;354(16):1698-705.
Fedorowicz Z, Jagannath VA, Carter B. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD005506. DOI: 10.1002/14651858.CD005506.pub5. Oral ondansetron increased the proportion of patients who had ceased vomiting and reduced the number needing intravenous rehydration and immediate hospital admission. Intravenous ondansetron and metoclopramide reduced the number of episodes of vomiting and hospital admission, and dimenhydrinate as a suppository reduced the duration of vomiting.
[24] 2006-2007 Drug Handbook & Formulary 25th Ed. SickKids – The Hospital for Sick Children, Toronto, ON, Canada.
[25] Nuttall GA, Eckerman KM, Jacob KA, Pawlaski EM, et al. Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? Anesthesiology. 2007 Oct;107(4):531-6. [Health Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/index-eng.php]
[26] Systematic Treatment Disease Site Group. Use of 5-HT3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy [Practice guideline; no 12-3]. Toronto(ON):Cancer Care Ontario (CCO);2003. Available: http://www.cancercare.on.ca/pdf/pebc12_3f.pdf (Accessed 2008, Jan 22).
[27] Geling O, Eichler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. J Clin Oncol. 2005 Feb 20;23(6):1289-94.
[28] Spinks AB, Wasiak J, Villanueva EV, Bernath V. Scopolamine (hyoscine) for preventing and treating motion sickness. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD002851.
Apfel Christian C., Zhang Kun, Georgeet Elizabeth al. Transdermal scopolamine for the prevention of postoperative nausea and vomiting: A systematic review and meta-analysis, Clinical Therapeutics, Volume 32, Issue 12, November 2010.
[29] Motherisk website: nausea and vomiting in pregnancy. Including video tutorial. Accessed Dec 10, 2007. http://www.motherisk.org/prof/morningSickness.jsp
[30] Richter J. "Heartburn, Nausea, Vomiting during pregnancy" in Pregnancy in Gastrointestinal Disorders. American College of Gastroenterology 2007. Accessed online Dec 10, 2007 at http://www.acg.gi.org/physicians/pdfs/PregnancyMonograph.pdf .
[31] Arsenault MY, Lane CA, MacKinnon CJ, Bartellas E, Cargill YM, Klein MC, Martel MJ et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002 Oct;24(10):817-31; quiz 832-3.

TOP

Nulman, Irena, Koren, Gideon. Diclectin for morning sickness: Long-term neurodevelopment. Can Fam Physician 2011 57: 193-194.
Jarvis Sheba, Nelson-Piercy Catherine. Management of nausea and vomiting in pregnancy. BMJ 2011;342:doi:10.1136/bmj.d3606 (Published 17 June 2011)
[32] Holmgren C, Aagaard-Tillery KM, Silver RM, Porter TF, Varner M. Hyperemesis in pregnancy: an evaluation of treatment strategies with maternal and neonatal outcomes. Am J Obstet Gynecol. 2008 Jan;198(1):56.e1-4. Maternal complications associated with PICC line placement are substantial despite no difference in neonatal outcomes, suggesting that the use of PICC lines for treatment of HEG patients should not be routinely used.
[32b] Matok I et al. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med 2009 Jun 11; 360:2528.
[33] Cyclic Vomiting Syndrome. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH. http://digestive.niddk.nih.gov/ddiseases/pubs/cvs/index.htm#6
[34] Talley NJ. Functional nausea and vomiting. Aust Fam Physician. 2007 Sep;36(9):694-7. Accessed online: http://www.racgp.org.au/Content/NavigationMenu/Publications/AustralianFamilyPhys/2007issues/afp200709/200709tally.pdf
[35] Czarnetzki C, Elia N, Lysakowski C, Dumont L, Landis BN, Giger R, Dulguerov P, Desmeules J, Tramèr MR. Dexamethasone and risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children: a randomized trial. JAMA. 2008 Dec 10;300(22):2621-30.
[36] DeCamp LR, Byerley JS, Doshi N, Steiner MJ. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. Arch Pediatr Adolesc Med. 2008 Sep;162(9):858-65.

Additional Reverences:
Allan M, Wilson E, Ivers N. Can ondansetron help children with vomiting due to gastroenteritis? Canadian Family Physician February 2012 vol. 58 no. 2167.
Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update. J Clin Oncol. 2011 Sep 26. http://jco.ascopubs.org/content/early/2011/09/25/JCO.2010.34.4614.full.pdf
Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006272.
Campbell-Yeo, Marsha L., Allen, Alexander C., Joseph, K. S., et al. Effect of Domperidone on the Composition of Preterm Human Breast Milk. Pediatrics 2010 125: e107-e114 .
Cheng A. Emergency department use of oral ondansetron for acute gastroenteritis-related vomiting in infants and children. Paediatr Child Health 2011;16:177-9.
Clary PL, Lawson P. Pharmacologic Pearls for End-of-Life Care. Am Fam Physician. 2009 Jun 15;79(12):1059-65.
Duval, Arnaud, Dubertret, Louis. Aprepitant as an Antipruritic Agent? N Engl J Med 2009 361: 1415-1416
Enarson Paul, Gouin Serge, Goldman Ran D. Dimenhydrinate use for children with vomiting Can Fam Physician April 2011 57: 431-432.
FDA Warning regarding metoclopramide & tardive dyskinesia (Feb 2009): http://www.fda.gov/bbs/topics/NEWS/2009/NEW01963.html
FDA Sep/09 notified healthcare professionals that a Boxed Warning is being added to the prescribing information for Promethazine Hydrochloride products, describing the risks of severe tissue injury, including gangrene, requiring amputation following intravenous administration of promethazine.
FDA Dec/09 The Texas Department of State Health Services and FDA notified healthcare professionals and consumers, especially pregnant or breastfeeding women, to avoid consuming a product called "Nzu", taken as a traditional remedy for morning sickness,because of the potential health risks from high levels of lead and arsenic, noted on laboratory analysis by Texas DSHS. Nzu, which is sold at African specialty stores is also called Calabash clay, Calabar stone, Mabele, Argile and La Craie. It generally resembles balls of clay or mud and is usually sold in small plastic bags with a handwritten label identifying it as "Nzu" or "Salted Nzu."
FDA Dec/10 The injectable form of dolasetron mesylate (Anzemet) should not be used to prevent nausea or vomiting related to chemotherapy because the drug increases the risk for torsade de pointes. The FDA recommends against using Anzemet injections in patients with congenital long-QT syndrome. The warning does not apply to Anzemet tablets because the risks for developing an abnormal heart rhythm are not as high as with the injections. FDA MedWatch alert (Free)
FDA Sep/11 The U.S. Food and Drug Administration (FDA) is informing the public of an ongoing safety review of the anti-nausea drug Zofran (ondansetron, ondansetron hydrochloride and their generics). Ondansetron may increase the risk of developing abnormal changes(QT prolongation & torsades) in the electrical activity of the heart
Fujii Y, Itakura M. Comparison of propofol, droperidol, and metoclopramide for prophylaxis of postoperative nausea and vomiting after breast cancer surgery: a prospective, randomized, double-blind, placebo-controlled study in Japanese patients. Clin Ther. 2008 Nov;30(11):2024-9.
Freedman SB, Parkin PC, Willan AR, Schuh S. Rapid versus standard intravenous rehydration in paediatric gastroenteritis: pragmatic, blinded, randomised clinical trial. BMJ 2011;343:d6976.
Gouin S, Vo TT, Roy M, et al. Oral Dimenhydrinate Versus Placebo in Children With Gastroenteritis: A Randomized Controlled Trial. Pediatrics. 2012 May 14.
Health Canada May/11 ANZEMET (dolasetron mesylate) - Withdrawal of 20 mg/mL Intravenous Injection Due to Potential Risk of Arrhythmias. New data suggest that intravenous administration of the injectable form of ANZEMET (dolasetron mesylate) may result in serious arrhythmias.
Health Canada July/11 is informing health professionals and consumers that the labelling information for the drug metoclopramide is being updated to include stronger warnings on the risk of a movement disorder known as "tardive dyskinesia."
Health Canada Mar/12: Domperidone should be used at the lowest possible dose. The risk of serious ventricular arrhythmias (QT) and sudden cardiac death may be higher in patients taking daily doses greater than 30 mg, and in patients over 60 years old.
Jarvis Sheba, Nelson-Piercy Catherine. Management of nausea and vomiting in pregnancy. BMJ 2011;342:doi:10.1136/bmj.d3606 (Published 17 June 2011)
Koren G, Clark S, Hankins GD, et al. Effectiveness of delayed-release doxylamine and pyridoxine (Diclectin) for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010 Sep 13.
Matthews A, Dowswell T, Haas DM, Doyle M, O'Mathúna DP. Interventions for nausea and vomiting in early pregnancy. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD007575. DOI: 10.1002/14651858.CD007575.pub2. There is a lack of high-quality evidence to support advice.
McCracken G, Houston P, Lefebvre G, Society of Obstetricians and Gynecologists of Canada (SOGC). Guideline for the management of postoperative nausea and vomiting. J Obstet Gynaecol Can 2008 Jul;30(7):600-7. http://www.sogc.org/guidelines/documents/gui209CPG0807.pdf
Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med. 2009 Jun, 11;360(24):2528-35.
Murdin L, Golding J, Bronstein A. Managing motion sickness. BMJ. 2011 Dec 2;343:d7430.
Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med. 2010 Oct 14;363(16):1544-50.
Phillips RS, Gopaul S, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD007786. DOI: 10.1002/14651858.CD007786.pub2. Our overall knowledge of themost effective antiemetics to prevent chemotherapy-induced nausea and vomiting in childhood is incomplete. This review suggests that 5-HT3 antagonists with dexamethasone added are effective in patients who are to receive highly emetogenic chemotherapy although the risk-benefit profile of additional steroid remains uncertain.
POGO Antineoplastic-Induced Nausea and Vomiting Guideline Development Panel. Guideline for classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. Toronto (ON): Pediatric Oncology Group of Ontario (POGO); 2010 Aug 11.
Powell CV, Priestley SJ, Young S, et al. Randomized clinical trial of rapid versus 24-hour rehydration for children with acute gastroenteritis. Pediatrics. 2011 Oct;128(4):e771-8.
Public Health Agency of Canada. Canada Communicable Disease Report. Committee to Advise on Tropical Medicine and Travel (CATMAT) statement. Statement on pregnancy and travel. Mar 2010. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-2/index-eng.php
Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc. 2012 Feb;87(2):114-9.
Shoemaker LK. Estfan B Induru R et al. Symptom management: An important part of cancer care. Cleveland Clinic Journal of Medicine 2011; 78(1):25-34; doi:10.3949/ccjm.78a.10053.
Sturm JJ, Hirsh DA, Schweickert A, et al. Ondansetron use in the pediatric emergency department and effects on hospitalization and return rates: are we masking alternative diagnoses?. Ann Emerg Med. 2010 May;55(5):415-22. Epub 2010 Jan 19.
Tan PC, Khine PP, Vallikkannu N, Omar SZ. Promethazine compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. Obstet Gynecol. 2010 May;115(5):975-81.
Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative nausea and vomiting prophylaxis. Clin Ther. 2012 Feb;34(2):282-94.
Vikanes Åse, Skjærven Rolv, Grjibovski Andrej M, et al. Recurrence of hyperemesis gravidarum across generations: population based cohort study. BMJ 2010;340:c2050, doi: 10.1136/bmj.c2050 (Published 29 April 2010)
Vincenzi B, Tonini G, Santini D. Aprepitant for erlotinib-induced pruritus. N Engl J Med. 2010 Jul 22;363(4):397-8.

TOP

RA - EXTRAS

Approach & Considerations for Drug Tx in RA

- Initial: DMARD + NSAID +/- Corticosteroid for symptoms. MTX often the DMARD of choice, however, HCQ is safer but suitable only for mild cases.
  -NSAIDs now used primarily for bridging and pain management.
  -Oral corticosteroids associated with complications, so use controversial. Short courses &/or low doses for ≤2yrs sometimes used (↓ joint pain & systemic symptoms). Intra-articular injections useful & few AEs.
  -Earlier combo DMARD or biologic tx warranted for those with high disease activity & poor prognositic factors.
  {Features of poor prognosis include: functional limitation, extraarticular disease rheumatoid nodules, RA vasculitis, Felty's syndrome, +'ve rheumatoid factor, anti-cyclic citrullinated peptide antibodies, bony erosions radiographic.}
- TNF inhibitors - 1st line biologics after an inadequate response to a DMARD. They are given +/- MTX (synergistic). Note, infliximab given with MTX (not recommended for monotherapy).
  - Initial TNF inhibitor choice: varies with clinician (often etanercept rapid onset, short t ½ or infliximab)
  - Relative to other agents, TNF-inhibitors may be more effective in relieving symptoms & limiting joint destruction. They often also act more rapidly.
  - AEs: 1) Injection site reactions (back pain, fever, urticaria, dyspnea, ↓BP): common with etanercept, golimumab, certolizumab, & adalimumab.
    2) Cytopenia: uncommon, but can occur with any anti-TNF tx. Monitor CBC.
    3) The potential for Serious Infections: (eg. bacterial sepsis, TB reactivated & disseminated, fungal, viral & opportunistic unusual eg. *p. jiroveci*) are important; screen for active infection, latent TB, etc.
    4) Malignancies (esp. lymphomas): reported but causality not established. The condition of RA ↑ lymphoma risk on its own. Avoid anti-TNF tx in patients with recent ca.
    5) Other AEs: (rare) – CHF, reversible lupus-like syndrome, demyelinating conditions eg. M.S. (avoid if hx), hepatoxicity (caution with infliximab).
  - If 1st TNF inhibitor is not effective, switching to a 2nd TNF inhibitor may be effective; however, many specialists will opt for a non-TNF biologic for a different mechanism of action.
- Non-TNF Biologics – include rituximab co-admin with a DMARD; pre-treat to prevent infusion reaction, abatacept +/- a DMARD, tocilizumab may work in ≥2wks, AEs (many; severe complications reported), anakinra less effective.
- Aggressive early therapy with MTX &/or a biologic ⇨ longer remissions, less joint destruction & improved quality of life.
- Combination Tx with 2-3 DMARDs (or a DMARD + biologic): often more effective than monotherapy without more toxicity.
  - Triple DMARD Tx: MTX +SSZ + HCQ (+/- prednisone low-dose ≤7.5-10mg/day) effective. ◆MTX + Biologic more efficatious than either alone. ◆Combination of 2+ Biologics NOT recommended as ↑ toxicity!
- Comorbidity & biologics ACR RA 2012:
  - 1) Hepatitis: a) Hep C ⇨ potentially recommend etanercept;
    b) Hep B: untreated chronic or treated chronic with Child-Pugh class B or higher: avoid any biologic!
  - 2) Malignancy: a) treated solid malignancy >5yrs or non-melanoma skin ca >5ys ago – recommend any biologic;
    b) treated solid malignancy <5yr or treated non-melanoma skin ca within 5yr – recommend rituximab;
    c) treated skin melanoma, & treated lymphoproliferative malignancy – recommend rituximab;
  - 3) CHF: a) NYHA class III-IV with ejection fraction ≤50%: avoid anti-TNF biologics!

Vaccinations: before DMARD or biologic, immunize for influenza, pneumococcal, hep-B & HZV. Live vaccines should not be given to patients on biologics (should be given ≥1 month prior to starting tx).

Pain Management in RA:

- Neuromodulators: Cochrane Review RCT, placebo controlled - few trials, all short term (~2-5 weeks) with high risk of bias (ie. Weak evidence)
  1) Nefopam (ACUPAN): not in Canada; 5HT, NE & DA receptor blocking; NNT=2 for pain relief, offset by significant SE's
  2) Topical capsaicin: reasonable add-onn option; NNT=2-3 for pain relief, offset by some burning at application site
  3) Oromucosal cannabis: small reduction in pain, highly offset by SE's leading to withdrawal (NNH=3) including dizziness 26%, dry mouth 13% & lightheadedness (10%)
  4) Lack of data for other agents included: anticonvulsants, ketamine, bupropion, methylphenidate

RHEUMATOID ARTHRITIS: DMARD Comparison Chart References (www.RxFiles.ca):

1. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46. http://www.rheumatology.org/publications/guidelines/raguidelines02.asp?aud=mem
   Guidelines for the management of rheumatoid arthritis: 2008 Update. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008 Jun 15;59(6):762-84. http://www.rheumatology.org/publications/guidelines/recommendations.asp?aud=mem
   Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39.
2. Treatment Guidelines: Drugs for Rheumatoid Arthritis. The Medical Letter: January, 2003; (5) pp. 25-32. Updated Vol 3 (Issue 40) Dec 2005. Updated Vol 7 (Issue 81) May 2009. May 2012.
3. Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. 1996 May;39(5):713-22.
4. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. 1996 May;39(5):723-31.
5. Drugs for Rheumatoid Arthritis. The Medical Letter July 10, 2000; (1082) pp. 57-64.
6. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001 Sep 15;358(9285):903-11.
7. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med. 2000 Mar 13;160(5):610-9.
8. Anakinra (Kineret) for Rheumatoid Arthritis. The Medical Letter: February 18, 2002; (1124) pp. 18-19.
9. Aletaha D, Kapral T, Smolen JS. Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. Ann Rheum Dis. 2003 May;62(5):482-6.
10. Adalimumab (Humira) for Rheumatoid Arthritis. The Medical Letter: March 31, 2003; (1153) pp. 25-27.
11. Micromedex 2011
12. Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2008.
13. Drug Information Handbook 10th edition, 2002-2003
14. Drugs in Pregnancy & Lactation 9th edition, 2011.
15. Geriatric Dosage Handbook 7th Edition, 2002

TOP

16. Handbook of Clinical Drug Data 10th edition, 2002
17. Therapeutic Choices 4rd edition, 2003
18. Moreland LW, O'Dell JR. Glucocorticoids and rheumatoid arthritis: back to the future? Arthritis Rheum. 2002 Oct;46(10):2553-63.
19. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.
20. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med. 2004 May 20;350(21):2167-79.
21 . USA Food & Drug Administration: Safety update meeting on TNF blocking agents Mar 4 & 5, 2003 http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t1.htm , http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t2.htm
22. O'Dell, James R., Therapeutic Strategies for Rheumatoid Arthritis. N Engl J Med 2004 350: 2591-2602.
Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580-8. In the new criteria set, classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in four domains: number and site of involved joints (range 0-5), serological abnormality (range 0-3), elevated acute-phase response (range 0-1) and symptom duration (two levels; range 0-1).
23. Fleischmann RM, Cohen SB, Moreland LW, et al.; iRAMT Study Group. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin. 2005 Aug;21(8):1181-90.
24. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1414-20.
25. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2005 Sep 15;72(6):1037-47.
26. Health Canada Jan/06 Hepatitis B Reactivation assoc. with the anti-TNFα products ENBREL (etanercept), HUMIRA (adalimumab), and REMICADE (infliximab)http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/anti-tnf_therap_hpc-cps_e.pdf
27. New drug: Orencia (abatacept). Pharmacist's Letter/Prescriber's Letter 2006;22(2):220207. (& also Medical Letter Feb 27,2006.)
28. Emery P. Treatment of rheumatoid arthritis. BMJ. 2006 Jan 21;332(7534):152-5.
29. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, et al. Canadian Rheumatology Association (CRA) Recommendations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs. J Rheumatol. 2011 Sep 15.

Additional references:

Agarwal SK, et al. Pattern of **infliximab utilization** in rheumatoid arthritis patients at an academic medical center. Arthritis Rheum. 2005 Dec;53(6):872-8.
Alarcon GS, McGwin G, Bertoli AM, et al. Effect of **hydroxychloroquine** on the survival of patients with systemic **lupus** erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). Ann Rheum Dis 2007;66:1168-72.
Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of **pemphigus vulgaris** with **rituximab** and intravenous immune globulin. N Engl J Med. 2006 Oct 26;355(17):1772-9.
Aletaha D, Neogi T, Silman AJ, et al. **2010 rheumatoid arthritis classification criteria**: an American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580-8. In the new criteria set, classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in four domains: number and site of involved joints (range 0-5), serological abnormality (range 0-3), elevated acute-phase response (range 0-1) and symptom duration (two levels; range 0-1).
Aletaha Daniel, Funovits Julia, Smolen Josef S. **Physical disability** in rheumatoid arthritis is associated with cartilage damage rather than bone destruction. Ann Rheum Dis 2011;70:733-739 Published Online First: 14 February 2011.
Aletaha D, Alasti F, Smolen JS. **Rheumatoid arthritis near remission**: clinical rather than laboratory inflammation is associated with radiographic progression. Ann Rheum Dis. 2011 Nov;70(11):1975-80.
Aksentijevich I, Masters SL, Ferguson PJ,et al. An Autoinflammatory Disease with Deficiency of the Interleukin-1-Receptor Antagonist. (**DIRA**) N Engl J Med. 2009 Jun 4;360(23):2426-2437.
Arabelovic S, et al. Preliminary evidence shows that folic acid fortification of the food supply is associated with higher methotrexate dosing in patients with rheumatoid arthritis. J Am Coll Nutr. 2007 Oct;26(5):453-5.This preliminary study suggests that folic acid supplementation may contribute to higher MTX dosing in patients with RA.
Arkema EV, Neovius M, Joelsson JK, et al. Is there a **sex bias in prescribing anti-tumour necrosis factor** medications to patients with rheumatoid arthritis? A nation-wide cross-sectional study. Ann Rheum Dis. 2012 Apr 13.
Arts E E A, Jansen T L, Broeder A Den, et al. **Statins inhibit the antirheumatic effects of rituximab** in rheumatoid arthritis: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Ann Rheum Dis 2011;70:877-878 Published Online First: 18 October 2010 doi:10.1136/ard.2010.136093.
Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the **EULAR** recommendations for the management of **psoriatic arthritis**. Ann Rheum Dis. 2011 Jul 28.
Askling J, van Vollenhoven RF, Granath F, et al. **Cancer risk** in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: Does the risk change with the time since start of treatment? Arthritis Rheum. 2009 Oct 29;60(11):3180-3189. During the first 6 years after the start of anti-TNF therapy in routine care, no overall elevation of cancer risk and no increase with followup time were observed.
Au WY, Ma ES, Choy C, Chung LP, Fung TK, Liang R, Kwong YL. Therapy-related **lymphomas** in patients with autoimmune diseases after treatment with disease-modifying anti-rheumatic drugs. Am J Hematol. 2006 Jan;81(1):5-11.
Bacani AK, Gabriel SE, Crowson CS, et al. Noncardiac vascular disease in rheumatoid arthritis: increase in **venous thromboembolic** events?. Arthritis Rheum. 2012 Jan;64(1):53-61.
Bakker MF, Jacobs JW, Welsing PM, et al. the Utrecht Arthritis Cohort Study Group. **Early clinical response to treatment predicts 5-year outcome** in RA patients: follow-up results from the CAMERA study. Ann Rheum Dis. 2011 Mar 15.
Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, et al. **Low-dose prednisone** inclusion into a **methotrexate-based**, tight control strategy for early rheumatoid arthritis. A randomized trial. Ann Intern Med. 2012;156:329-39.
Baranauskaite A, Raffayová H, Kungurov N, et al. **Infliximab plus methotrexate** is superior to methotrexate alone in the treatment of **psoriatic arthritis** in methotrexate-naive patients: the **RESPOND** study. Ann Rheum Dis. 2012 Apr;71(4):541-8.
Barnes PJ, Adcock IM. **Glucocorticoid resistance** in inflammatory diseases. Lancet. 2009 May 30;373(9678):1905-17.
Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. **Anti-infliximab and anti-adalimumab antibodies** in relation to response to adalimumab in infliximab switchers and anti-TNF naive patients: a cohort study. Ann Rheum Dis. 2009 Jul 5.
Bartelds Geertje M., Krieckaert Charlotte L. M., Nurmohamed Michael T., et al. Development of **Antidrug Antibodies Against Adalimumab** and Association With Disease Activity and Treatment Failure During Long-term Follow-up. *JAMA*. 2011;305(14):1460-1468.doi:10.1001/jama.2011.406
Baszis K, Garbutt J, Toib D, et al. Clinical outcomes after **withdrawal of anti-tumor necrosis factor-alpha therapy in juvenile idiopathic arthritis**: A twelve-year experience. Arthritis Rheum. 2011 Jun 23. doi: 10.1002/art.30502.
Bathon JM, Martin RW, et al A comparison of **etanercept** and **methotrexate** in patients with **early** rheumatoid arthritis. (**ERA trial**) N Engl J Med. 2000 Nov 30;343(22):1586-93.
Bathon J, Robles M, et al. Sustained disease remission and inhibition of radiographic progression in methotrexate-naïve patients with rheumatoid arthritis and poor prognostic factors treated with **abatacept**: 2-year outcomes. (**AGREE**) Ann Rheum Dis. 2011 Nov;70(11):1949-56.
Bernatsky S, Clarke AE, Suissa S. Hematologic **malignant neoplasms** after drug exposure in rheumatoid arthritis. Arch Intern Med. 2008 Feb 25;168(4):378-81. In this large cohort of patients with rheumatoid arthritis, the greatest relative risk for hematologic malignant neoplasms was noted after use of cyclophosphamide.
Beukelman T, Patkar NM, Saag KG, et al. **2011 American College of Rheumatology** recommendations for the treatment of **juvenile idiopathic arthritis**: Initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res(Hoboken). 2011 Apr;63(4):465-82. doi: 10.1002/acr.20460. http://www.rheumatology.org/practice/clinical/guidelines/ACR_2011_jia_full_manuscript.pdf
Beukelman T, Haynes K, Curtis JR, et al. Rates of **malignancy associated with juvenile idiopathic arthritis** and its treatment. Arthritis Rheum. 2012 Feb 10.
Beukelman T, Xie F, Chen L, et al; On behalf of the Safety Assessment of Biological ThERapeutics (SABER) Collaboration. Rates of **hospitalized bacterial infection** associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012 May 8.
Bingham CO 3rd, et al. **Immunization** responses in rheumatoid arthritis patients treated with **rituximab**: Results from a controlled clinical trial. Arthritis Rheum. 2009 Dec 28;62(1):64-74.
Bisset L, et al. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for **tennis elbow**: randomised trial. BMJ. 2006 Nov 4;333(7575):939. Epub 2006 Sep 29.
Bliddal H, et al. A randomized, controlled study of a single **intra-articular** injection of **etanercept** or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Sep-Oct;35(5):341-5.
Bodar EJ, Kuijk LM, Drenth JP, et al. On-demand **anakinra** treatment is effective in **mevalonate kinase deficiency**. Ann Rheum Dis. 2011 Dec;70(12):2155-8.
Boers M, Verhoeven AC, et al. Randomised comparison of combined step-down **prednisolone**, **methotrexate and sulphasalazine** with **sulphasalazine alone** in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18.
Bongartz T, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of **serious infections & malignancies**: systematic review & meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. (see also Pharmacist's Letter July 2006) Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI, 39-125) within a treatment period of 3 to 12 months. (Health Canada July/06 Possible Association of REMICADE® with hepatosplenic T-cell lymphoma in pediatric and young adult patients with Crohn's disease http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/remicade_3_hpc-cps_e.html) (Setoguchi S, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rh Arthritis Rheum. 2006 Aug 31;54(9):2757-2764 [Epub ahead of print] Our results indicate that users of biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with MTX users. Despite the use of large combined data

TOP

effect of an infrequent exposure (biologic DMARDs) on rare diseases (hematologic malignancies) remains a challenge.) (Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007 May;56(5):1433-9. In a study of lymphoma in 19,591 RA patients over 89,710 person-years of followup, which included exposure to anti-TNF therapy in 10,815 patients, we did not observe evidence for an increase in the incidence of lymphoma among patients who received anti-TNF therapy.)

Bose N, Calabrese LH. Q: Should I **order an anti-CCP antibody test** to diagnose rheumatoid arthritis? Cleve Clin J Med. 2012 Apr;79(4):249-52.

Bourre-Tessier J, Haraoui B. **Methotrexate drug interactions** in the treatment of rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jul;37(7):1416-21. Epub 2010 May 1.

Brandt J, Khariouzov A, et al. Six-month results of a double-blind, placebo-controlled trial of **etanercept** treatment in patients with active **ankylosing spondylitis**. Arthritis Rheum. 2003 Jun;48(6):1667-75.

Braun J, Brandt J, et al. Treatment of active **ankylosing spondylitis** with **infliximab**: a randomised controlled multicentre trial. Lancet. 2002 Apr 6;359(9313):1187-93.

Braun J, et al. Long-term efficacy & safety of **infliximab** in **ankylosing spondylitis**: an open, observational, extension study of a 3month, randomized, placebo-controlled trial. Arthritis Rheum. 2003 Aug;48(8):2224-33.

Braun J, Kästner P, Flaxenberg P, et al; MC-MTX.6/RH Study Group. Comparison of the clinical efficacy and safety of **subcutaneous (15-20mg) versus oral administration of methotrexate** (15mg) in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008 Jan;58(1):73-81. This 6-month prospective, randomized, controlled trial is the first to examine oral versus SC administration of MTX. We found that SC administration was significantly more effective than oral administration of the same MTX dosage. There was no difference in tolerability.

Braun J, Davis J, Dougados M, et al. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with **ankylosing spondylitis**. Ann Rheum Dis 2006; 65: 316–20.

Braun J, van den Berg R, Baraliakos X, et al. **2010 update of the ASAS/EULAR recommendations** for the management of **ankylosing spondylitis**. Ann Rheum Dis 2011;70:896-904 doi:10.1136/ard.2011.151027.

Braun J, Deodhar A, Inman RD, van et al. **Golimumab** administered subcutaneously every 4 weeks in **ankylosing spondylitis**: 104-week results of the GO-RAISE study. Ann Rheum Dis. 2011 Nov 11.

Braun J, Baraliakos X, Hermann KG, et al. **Golimumab** reduces spinal inflammation in **ankylosing spondylitis**: MRI results of the randomised, placebo- controlled GO-RAISE study. Ann Rheum Dis. 2012 Jun;71(6):878-84.

Breedveld FC, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2005 Dec 29;54(1):26-37 [Epub ahead of print]

Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of **anakinra** monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol. 2004 Jun;31(6):1103-11.

Buch MH, Smolen JS, Betteridge N, et al. for the **Rituximab Consensus** Expert Committee. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Mar 6.

Buchbinder R, Barber M, Heuzenroeder L, et al. Incidence of **melanoma** and other malignancies among rheumatoid arthritis patients treated with **methotrexate**. Arthritis Rheum. 2008 May 30;59(6):794-799.[Epub ahead of print]Compared with the general population, methotrexate-treated RA patients have an increased incidence of melanoma, non-Hodgkin's lymphoma, and lung cancer.

Bulatović M, Heijstek MW, Verkaaik M, et al. High prevalence of **methotrexate intolerance in juvenile** idiopathic arthritis: Development and validation of a methotrexate intolerance severity score. Arthritis Rheum. 2011 Mar 24. doi: 10.1002/art.30367.

Burmester Gerd R, Feist E, Kellner H, et al. Effectiveness and safety of the interleukin 6-receptor antagonist **tocilizumab** after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). Ann Rheum Dis 2011;70:755-759 Published Online First: 27 December 2010 doi:10.1136/ard.2010.139725.

Burmester Gerd, Lanas Angel, Biasucci Luigi, et al. The appropriate use of **non-steroidal anti-inflammatory drugs** (NSAIDS) in rheumatic disease: opinions of a multidisciplinary **European expert panel**. Ann Rheum Dis 2011;70:818-822 Published Online First: 10 September 2010 doi:10.1136/ard.2010.128660.

Burmester GR, Panaccione R, Gordon KB, et al. **Adalimumab: long-term safety (up to 12yrs)** in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2012 Jun 26.

Buszewicz M, et al. **Self management** of arthritis in primary care: randomised controlled trial. BMJ. 2006 Oct 13; [Epub ahead of print]

Buttgereit F. Do the treatment with **glucocorticoids** and/or the disease itself drive the impairment in glucose metabolism in patients with rheumatoid arthritis? Ann Rheum Dis. 2011 Nov;70(11):1881-3.

Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, et al. **Canadian Rheumatology Association** Recommendations for Pharmacological Management of **Rheumatoid Arthritis with Traditional and Biologic** Disease-modifying Antirheumatic Drugs. J Rheumatol. **2011** Sep 15.

Calguneri M, Pay S, et al. **Combination therapy** versus **monotherapy** for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1999 Nov-Dec;17(6):699-704.

Cameron M, Gagnier JJ, Chrubasik S. **Herbal therapy** for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD002948. Several herbal interventions are inadequately justified by single studies or non-comparable studies in the treatment of rheumatoid arthritis. There is moderate evidence that oils containing GLA (evening primrose, borage, or blackcurrant seed oil) afford some benefit in relieving symptoms for RA, while evidence for Phytodolor® N is less convincing.Tripterygium wilfordii products may reduce some RA symptoms, however, oral use may be associated with several side effects.

Campbell L, Chen C, Bhagat SS, et al. Risk of adverse events including **serious infections** in rheumatoid arthritis patients treated with **tocilizumab**: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2011 Mar;50(3):552-62.

Cassina M, Johnson D, Robinson L, et al. **Pregnancy outcome in women exposed to leflunomide** before or during pregnancy. Arthritis Rheum. 2012 Feb 3. n=45

Chakravarty EF, Michaud K, Wolfe F. **Skin cancer**, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005 Nov;32(11):2130-5. CONCLUSION: In this large, national cohort, RA was associated with an increased risk for development of NMSC. Among patients with RA, use of TNF inhibitors and prednisone were associated with an increased risk of NMSC.

Chambers CD, Johnson DL, Robinson LK, et al.. Birth outcomes in **pregnant women taking leflunomide**. Arthritis Rheum. 2010 Jan 28.

Chatzidionysiou K, Lie E, Nasonov E, et al. Effectiveness of disease-modifying antirheumatic drug **co-therapy with methotrexate and leflunomide in rituximab**-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. Ann Rheum Dis. 2012 Mar;71(3):374-7.

Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of **infliximab** monotherapy for plaque-type **psoriasis**: a randomised trial. Lancet. 2001 Jun 9;357(9271):1842-7.

Chen YF, et al. A systematic review of the effectiveness of **adalimumab**, **etanercept** and **infliximab** for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):1-248.

Chen YJ et al. Association between systemic **anti-psoriatic drugs and cardiovascular risk** in patients with psoriasis and psoriatic arthritis: A nationwide cohort study. Arthritis Rheum. 2011 Dec 12.

Chilibeck PD, Vatanparast H, Cornish SM, Abeysekara S, Charlesworth S. Evidencebased risk assessment and recommendations for **physical activity**: arthritis, osteoporosis, and low back pain. Appl Physiol Nutr Metab 2011;36(Suppl 1):S49-S79.

Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. **Methotrexate and mortality** in patients with rheumatoid arthritis: a prospective study. Lancet. 2002 Apr 6;359(9313):1173-7.

Chung ES, Packer M, et al. Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of **infliximab**, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive **Heart Failure** (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40.

Chung HY, Machado P, van der Heijde D, et al. **Smokers in early axial spondyloarthritis** have earlier disease onset, more disease activity, inflammation and damage, and poorer function and healthrelated quality of life: results from the DESIR cohort. Ann Rheum Dis. Published Online First: 11 Oct 2011.

Clifford DB, Ances B, Costello C,et al. **Rituximab-Associated Progressive Multifocal Leukoencephalopathy** (PML) in Rheumatoid Arthritis. Arch Neurol. 2011 May 9.

Cochrane Musculoskeletal Group- **Patient Decision Aids** http://musculoskeletal.cochrane.org/decision-aids

Cohen S, Cannon GW, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with **leflunomide** compared with **methotrexate**. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group.(**ULTRA**) Arthritis Rheum. 2001 Sep;44(9):1984-92.

Cohen S, Hurd E, et al. Treatment of rheumatoid arthritis with **anakinra**, a recombinant human interleukin-1 receptor antagonist, in combination **with methotrexate**: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.

Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, Hanrahan PS, Kraishi MM, Patel A, Sun G, Bear MB; 990145 Study Group. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8. Epub 2004 Apr 13.

Cohen SB, Emery P, Greenwald MW, Dougados M, et al. **REFLEX** Trial Group. **Rituximab** for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006 Sep;54(9):2793-806.

Cohen SB, et al. **Rituximab** for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006 Aug 31;54(9):2793-2806 [Epub ahead of print]

Combe B, et al. Etanercept European Investigators Network (Etanercept Study 309 Investigators). **Etanercept and sulfasalazine**, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a do comparison. Ann Rheum Dis. 2006 Oct;65(10):1357-62. Epub 2006 Apr 10.

TOP

Conaghan PG, Emery P, et al. Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving **golimumab**: results of the **GO-FORWARD** trial. Ann Rheum Dis. 2011 Nov;70(11):1968-74.

Coulson E, Saravanan V, Hamilton J, et al. **Pneumococcal antibody levels after pneumovax** in patients with rheumatoid arthritis on methotrexate. Ann Rheum Dis. 2011 Jul;70(7):1289-91.

Crowson CS, et al. How much of the increased incidence of **heart failure** in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? Arthritis Rheum. 2005 Oct;52(10):3039-44.

Crowson Cynthia S, Gabriel Sherine E. Towards improving **cardiovascular risk management** in patients with rheumatoid arthritis: the need for accurate risk assessment. Ann Rheum Dis 2011;70:719-721 Published Online First: 22 February 2011 doi:10.1136/ard.2010.145482.

Coulson E, Saravanan V, Hamilton J, et al. **Pneumococcal antibody levels after pneumovax** in patients with rheumatoid arthritis on methotrexate. Ann Rheum Dis. 2011 Apr 22.

Curtis JR, Beukelman T, Onofrei A, Cassell S, et al. **Elevated liver enzyme tests** among patients with rheumatoid arthritis or psoriatic arthritis treated with **methotrexate and/or leflunomide**. Ann Rheum Dis [Internet]. 2010 Jan;69(1):43-7.

Curtis JR, Chen L, Luijtens K, et al. **No additional efficacy with dose escalation of certolizumab** pegol from 200 mg to 400 mg every other week: An analysis of individual patient-level data from RAPID 1. Arthritis Rheum. 2011 Apr 11.

Curtis JR, Xie F, Chen L, et al. The comparative risk of **serious infections** among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis. 2011 Aug;70(8):1401-6.

Dagfi nrud H, Kvien TK, Hagen KB. Physiotherapy interventions for **ankylosing spondylitis**. Cochrane Database Syst Rev 2008; 1: CD002822.

Daïen CI, Duny Y, Barnetche T, et al. Effect of **TNF inhibitors on lipid profile** in rheumatoid arthritis: a systematic review with meta-analysis. Ann Rheum Dis. 2012 Jun;71(6):862-8.

Dalrymple JM, Stamp LK, O'Donnell JL, Chapman PT, Zhang M, Barclay ML. **Pharmacokinetics of oral methotrexate** in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Nov;58(11):3299-308.

Da Silva JA, et al. Safety of **low dose glucocorticoid** treatment in rheumatoid arthritis: published evidence and prospective trial data.Ann Rheum Dis. 2006 Mar;65(3):285-93. Epub 2005 Aug 17. (InfoPOEMs: Available data are scant, but seem to provide evidence that low-dose glucocorticoids (10 mg or less of prednisolone/equivalent) in the treatment of rheumatoid arthritis do not increase osteoporotic fractures, blood pressure, cardiovascular diseases, or peptic ulcer incidence. Weight gain is common when taking these drugs, as are skin changes. (LOE = 2b))

Davies R, Galloway JB, Watson KD, Lunt M, Symmons DP, Hyrich KL; ; BSRBR Control Centre Consortium, British Society for Rheumatology Biologics Register. **Venous thrombotic events** are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Jul 22.

De Benedetti F, Brunner H, Ruperto N, et al. Effi cacy and safety of **tocilizumab** in patients with systemic juvenile idiopathic arthritis (sJIA): 12-week data from the phase 3 tender trial. Ann Rheum Dis 2010; 69 (suppl 146): 146.

den Uyl D, van Raalte DH, Nurmohamed MT, et al. Metabolic effects of **high-dose prednisolone** treatment in early rheumatoid arthritis: Diabetogenic effects and inflammation reduction on the balance. Arthritis Rheum. 2011 Sep 27.

Diak P, Siegel J, La Grenade L, Choi L, Lemery S, McMahon A. **Tumor necrosis factor alpha blockers and malignancy in children**: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum. 2010 Aug;62(8):2517-24.

Dixon WG, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving **anti-tumor necrosis factor** therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Jul 25;54(8):2368-2376 [Epub ahead of print]

Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2009 Oct 22. [Epub ahead of print] The rate of TB in patients with RA treated with anti-TNF therapy was 3-4 fold higher in patients receiving infliximab and adalimumab compared to etanercept.

Dixon WG, Kezouh A, Bernatsky S, et al. The influence of **systemic glucocorticoid** therapy upon the risk of **non-serious infection** in older patients with rheumatoid arthritis: a nested case-control study. Ann Rheum Dis. 2011 Feb1.

Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of **oral glucocorticoid** therapy on risk of **serious infection** in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012 Jan 12.

Donahue KE, Gartlehner G, Jonas DE, et al. Systematic Review: Comparative Effectiveness and Harms of Disease-Modifying Medications for Rheumatoid Arthritis. Ann Intern Med. 2007 Nov 19; [Epub ahead of print] Limited available comparative evidence does not support one monotherapy over another for adults with rheumatoid arthritis. Although combination therapy is more effective for patients whose monotherapy fails, the evidence is insufficient to draw firm conclusions about whether one combination or treatment strategy is better than another or is the best treatment for early rheumatoid arthritis.

Dougados M, Braun J, Szanto S, et al. Efficacy of **etanercept** on rheumatic signs and pulmonary function tests in advanced **ankylosing spondylitis**: results of a randomised double-blind placebo-controlled study (SPINE). Ann Rheum Dis 2011;70:799-804 Published Online First: 13 February 2011 doi:10.1136/ard.2010.139261.

Dougados M, Baeten D. **Spondyloarthritis**. Lancet. (psoriatic arthritis, reactive arthritis, arthritis related to IBD, subgroup of JIA & ankylosing spondylitis) 2011 Jun 18;377(9783):2127-37.

Ducharme J, Pelletier C, Zacharias R. The safety of **infliximab infusions** in the community setting. Can J Gastroenterol. 2010 May;24(5):307-11.

Edwards JC, et al. Efficacy of B-cell-targeted therapy with **rituximab** in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81.

Emery P, et al. DANCER Study Group. The efficacy and safety of **rituximab** in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006 May;54(5):1390-400.

Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of **methotrexate and etanercept** in active, early, moderate to severe rheumatoid arthritis (**COMET**): a randomised, double-blind, parallel treatment trial. Lancet. 2008 Aug 2;372(9636):375-82. Epub 2008 Jul 16.

Emery P, Breedveld F, van der Heijde D, et al. Combination of **Methotrexate and Etanercept** in Early Rheumatoid Arthritis Trial Group. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: A two-year, double-blind, randomized study. Arthritis Rheum. 2010 Feb 25;62(3):674-682.

Emery P, Fleischmann R, van der Heijde D, et al. The effect of **golimumab** on radiographic progression in rheumatoid arthritis: Results of the GO-BEFORE and GO-FORWARD randomized, controlled studies. Arthritis Rheum. 2011 Jan 28.

Emery P, Kvien TK, Combe B, et al. Combination **etanercept and methotrexate provides better disease control in very early (≤4 months)** versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the COMET study. *Ann Rheum Dis* 2012; published online March 8. DOI:10.1136/annrheumdis-2011-201066.

Emery P, Smolen JS, Kavanaugh A, et al. **Maintenance of biologic-free disease control** in early rheumatoid arthritis patient after induction of low disease activity with adalimumab plus methotrexate. *Ann Rheum Dis* 2011; **70** (suppl 3)**:** 262–63.

Emery P, Kvien TK, Combe B, et al. Combination **etanercept and methotrexate** provides better disease control in very early (<=4 months) versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the **COMET** study. Ann Rheum Dis. 2012 Jun;71(6):989-92.

Ersoy A, Baran B, Ersoy C, Kahvecioglu S, Akdag I. Calcineurin inhibitors and post-transplant weight gain. Nephrology (Carlton). 2008 Mar 5; [Epub ahead of print] Only pretransplant BMI, creatinine clearance, **cyclosporine A** usage, being hypertensive and dysplipidemic were independent predictors of weight gain at the 12th month. Our results suggested that the type of immunosuppression may affect post-transplant weight gain.

Estellat C, Ravaud P. **Lack of head-to-head trials and fair control arms**: randomized controlled trials of biologic treatment for rheumatoid arthritis. Arch Intern Med. 2012;172(3):237-244.

Faber WR, et al. Treatment of recurrent **erythema nodosum leprosum** with **infliximab**. N Engl J Med. 2006 Aug 17;355(7):739.

FDA July/10 will require that the label for the rheumatoid arthritis drug **leflunomide (Arava)** carry an added warning for severe liver injury. The label already warns against the drug's use in pregnant women and those of childbearing potential. The new warning comes after the FDA received **49 reports of severe liver injury**, including 14 instances of fatal liver failure, from 2002 to 2009. Risk for liver injury was higher among patients using other drugs associated with liver injury and patients with liver disease. Clinicians should monitor liver enzymes at least monthly for 3 months after beginning the drug. After that, enzymes should be monitored every quarter. Treatment should be halted if liver enzymes rise to two times the upper limit of normal. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm218912.htm

FDA Sep/11 notified healthcare professionals that the Boxed Warning for the entire class of **Tumor Necrosis Factor-alpha (TNFα) blockers** has been updated to include the risk of infection from two bacterial pathogens, **Legionella and Listeria**. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNFα blockers have been revised so that they contain consistent information about the risk for serious infections and the associated disease-causing pathogens.

Felson David T, Smolen Josef S, Wells George, et al. American College of Rheumatology/European League Against Rheumatism Provisional **Definition of Remission** in Rheumatoid Arthritis for Clinical Trials. Ann Rheum Dis 2011;70:404-413.

Finckh A, Simard JF, Gabay C, Guerne PA; SCQM physicians. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):746-52.

Finckh A Finckh A, Bansback N, et al. Treatment of very early rheumatoid arthritis with symptomatic therapy, **disease-modifying antirheumatic drugs**, or biologic agents: a cost-effectiveness analysis. Ann Intern Med. 2009 Nov 3;151(9):612-21.

Fleischmann RM, et al. **Anakinra**, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra),in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003 Apr;48(4):927-34.

Fleischmann RM, et al. Safety of extended treatment with **anakinra** in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Aug;65(8):1006-12. Epub 2006 Jan 5.

Fleischmann R, Cutolo M, Genovese MC, et al. Phase 2B dose-ranging study of the oral JAK inhibitor **tofacitinib** (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to DMARDs. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33383.

Foell Dirk; Wulffraat Nico; Wedderburn Lucy R.; et al. for the Paediatric Rheumatology International Trials Organization (PRINTO) **Methotrexate Withdrawal at 6 vs 12 Months in Juvenile** Idiopathic Arthritis in Remission: A Randomized Clinical Trial. JAMA. 2010;303(13):1266-1273.

Fournier MR, Klein J, Minuk GY, Bernstein CN. Changes in **Liver Biochemistry** During **Methotrexate** Use for Inflammatory Bowel Disease. Am J Gastroenterol. 2010 Feb 16. Methotrexate is commonly associated with LET abnormalities, but these frequently normalize while still on therapy, and in only 5% will drug discontinuation be necessary. Liver biopsies rarely have substantive abnormalities

TOP

Furst DE, et al. Updated consensus statement on **biological agents**, specifically tumour necrosis factor {alpha} (TNF{alpha}) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2005. Ann Rheum Dis. 2005 Nov;64 Suppl 4:iv2-14.

Gabay C, Bel M, Combescure C, et al; for the **H1N1** study group. Impact of synthetic and biological disease modifying antirheumatic drugs on antibody responses to the ASO3-adjuvanted pandemic influenza vaccine. Arthritis Rheum. 2011 Mar 7. doi: 10.1002/art.30325.

Galloway JB, Hyrich KL, Mercer LK, et al. BSRBR Control Centre Consortium, Symmons DP; on behalf of the British Society for Rheumatology Biologics Register. **Anti-TNF therapy is associated with an increased risk of serious infections** in patients with rheumatoid arthritis especially in the **first 6 months** of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2010 Jul 31.

Galloway JB, Hyrich KL, Mercer LK, et al. on behalf of the BSR Biologics Register. **Risk of septic arthritis** in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Jul 21.

Galloway JB, Mercer LK, Moseley A, et al. Risk of **skin and soft tissue infections (including shingles)** in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2012 Apr 24.

Gaujoux-Viala C, Smolen JS, Landewé R, et al. Current evidence for the management of rheumatoid arthritis with **synthetic disease-modifying antirheumatic drugs**: a systematic literature review informing the **EULAR** recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9. Epub

Geborek P, Bladstrom A, et al.. **Tumour necrosis factor blockers** do not increase overall tumour risk in patients with rheumatoid arthritis, but **may** be associated with an **increased** risk of **lymphomas**. Ann Rheum Dis. 2005 May;64(5):699-703.

Gelinck LB, van der Bijl AE, Beyer WE, et al. The effect of **anti-tumor necrosis factor** alpha treatment on the antibody response to **influenza vaccination**. Ann Rheum Dis. 2007 Oct 26; [Epub ahead of print] The antibody response to influenza vaccination in patients treated with anti-TNF is only modestly impaired. The proportion of patients that achieves a protective titer is not significantly diminished by the use of TNF blocking therapies.

Genevay S, Finckh A, Zufferey P et al. **Adalimumab** in **acute sciatica** reduces the long-term need for surgery: a 3-year follow-up of a randomised double-blind placebo-controlled trial. Ann Rheum Dis. 2012 Apr;71(4):560-2.

Genovese MC, Bathon JM, et al. **Etanercept** versus **methotrexate** in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002 Jun;46(6):1443-50.

Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, Bekker P; 20000223 Study Group. **Combination** therapy with **etanercept and anakinra** in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004 May;50(5):1412-9.

Genovese MC, Becker JC, Schiff M, et al. **Abatacept** for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition (**ATTAIN**). N Engl J Med. 2005 Sep 15;353(11):1114-23.

Genovese M, Covarrubias A, Leon G, et al. **Subcutaneous abatacept** versus intravenous abatacept: A phase IIIb non-inferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011 May 25.

Gladman DD, et al. **Adalimumab** improves joint- and skin-related functional impairment in patients with **psoriatic arthritis**: Patient- reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial (**ADEPT**). Ann Rheum Dis. 2006 Oct 17; [Epub ahead of print]

Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of **four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study)**: A randomized, controlled trial. Arthritis Rheum. 2005 Nov;52(11):3381-90. CONCLUSION: In patients with early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy. (Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial (BeSt). Ann Intern Med. 2007 Mar 20;146(6):406-15. Currently available antirheumatic drugs can be highly effective in patients with early rheumatoid arthritis in a setting of tight disease control. Initial combination therapies seem to provide earlier clinical improvement and less progression of joint damage, but all treatment strategies eventually showed at 2yrs similar clinical improvements. In addition, combination therapy can be withdrawn successfully and less treatment adjustments are needed than with initial monotherapies.)

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. **Comparison of treatment strategies** in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007 Mar 20;146(6):406-15.

Goldbach-Mansky R, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. (anakinra) N Engl J Med. 2006 Aug 10;355(6):581-92.

Goldbach-Mansky R., et al. Comparison of **Tripterygium wilfordii Hook F** Versus Sulfasalazine in the Treatment of Rheumatoid Arthritis: A Randomized Trial. Ann Intern Med 2009; 229-240.

Gómez-Reino JJ, Rodríguez-Lozano C, Campos-Fernández Cet al. Change in the **discontinuation pattern of tumour necrosis factor antagonists** in rheumatoid arthritis over 10 years: data from the Spanish registry BIOBADASER 2.0. Ann Rheum Dis. 2012 Mar;71(3):382-385. (inefficacy being the main reason)

Gómez-Reino J. **Biologic monotherapy as initial treatment** in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2012 Jul;51 Suppl 5:v31-v37.

Gordon KB, et al. Clinical response to **adalimumab** in patients with moderate to severe **psoriasis**: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006 Oct;55(4):598-606. Epub 2006 Aug 10.

Gossec L, Smolen JS, Gaujoux-Viala C, et al. European League Against Rheumatism recommendations for the management of **psoriatic arthritis** with pharmacological therapies. Ann Rheum Dis. 2011 Sep 27.

Gottenberg J, Ravaud P, Bardin T, et al. on behalf of all the investigators of the AIR registry the French Society of Rheumatology.. Risk factors of severe **infections** in patients with rheumatoid arthritis treated with rituximab in the AutoImmunity And **Rituximab** (AIR) registry. Arthritis Rheum. 2010 May 6.

Gottenberg JE, Ravaud P, Cantagrel A, et al. **Positivity for anti-cyclic citrullinated peptide** is associated with a better response to **abatacept**: data from the 'Orencia and Rheumatoid Arthritis' registry. Ann Rheum Dis. 2012 May 21.

Gottlieb AB, et al. **Infliximab** induction therapy for patients with severe plaque-type **psoriasis**: a randomized, double-blind, placebo-controlled trial.J Am Acad Dermatol. 2004 Oct;51(4):534-42.

Gorman JD, Sack KE, et al. Treatment of **ankylosing spondylitis** by inhibition of tumor necrosis factor alpha **etanercept**. N Engl J Med. 2002 May 2;346(18):1349-56.

Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with **glucocorticoids**: a systematic literature review informing the **EULAR** recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1010-4. Epub 2010 May 6.

Griffiths, Christopher E.M., Strober, Bruce E., van de Kerkhof, Peter, et ak, the ACCEPT Study Group, Comparison of **Ustekinumab** and Etanercept for Moderate-to-Severe Psoriasis. N Engl J Med 2010 362: 118-128.

Grigor C, et al. Effect of a treatment strategy of **tight control** for rheumatoid arthritis (the **TICORA study**): a single-blind randomised controlled trial. Lancet. 2004 Jul 17-23;364(9430):263-9.

Graudal N, Jürgens G. Similar effects of **disease modifying anti rheumatic drugs, glucocorticoids and biologics** on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomised placebo or drug controlled studies including 112 comparisons. Arthritis Rheum. 2010 Jun 17. DMARDs, glucocorticoids, biologics and combination treatments significantly reduced radiographic progression at one year with a relative effect of 50-80%.

Greenberg Jeffrey D, Kremer Joel M, Curtis Jeffrey R, et al. , on behalf of the CORRONA Investigators. Tumour necrosis factor antagonist use and associated **risk reduction of cardiovascular events** among patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:576-582

Greenberg JD, Reed G, Decktor D, et al.on behalf of the **CORRONA** Investigators. A comparative effectiveness study of **adalimumab, etanercept and infliximab** in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. Ann Rheum Dis. 2012 Jan 30.

Greenwald MW, Shergy WJ, Kaine JL, et al. Evaluation of the safety of **rituximab in combination with a tumor necrosis factor inhibitor and methotrexate** in patients with active rheumatoid arthritis: results from a randomized controlled trial. Arthritis Rheum. 2011 Mar;63(3):622-32. doi: 10.1002/art.30194.

Gremese E, Carletto A, et al. the Gruppo Italiano di Studio sulle Early Arthritis (GISEA). **Obesity reduces** the response rate to anti TNFα in rheumatoid arthritis. an approach to a personalized medicine. Arthritis Care Res (Hoboken). 2012 Jun 21.

Grijalva CG, Chen L, Delzell E, et al. Initiation of **tumor necrosis factor-alpha antagonists** and the risk of hospitalization for **infection** in patients with autoimmune diseases. [published online November 6, 2011]. JAMA.

Hackmon, Rinat, Sakaguchi, Sachi, Koren, Gideon. Effect of **methotrexate treatment of ectopic pregnancy on subsequent pregnancy**. Can Fam Physician 2011 57: 37-39.

Hashkes PJ, Laxer RM. Medical treatment of **juvenile idiopathic arthritis**. JAMA. 2005 Oct 5;294(13):1671-84. (InfoPOEMs: Nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of corticosteroids, methotrexate, and possibly biologic-modifiers are somewhat beneficial in the management of juvenile idiopathic arthritis (JIA), particularly oligoarthritis. Patients with polyarthritis and a positive rheumatoid factor respond poorly to medications and require aggressive individual management. (LOE = 1a-))

Haraoui B, Cameron L, Ouellet M, White B. **Anti-infliximab antibodies** in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. J Rheumatol. 2006 Jan;33(1):31-6.

Harrold LR, Harrington JT, Curtis JR, et al. **Prescribing practices** in a US cohort of rheumatoid arthritis patients before and after publication of the ACR treatment recommendations. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33380.

Health Canada Aug/09 TNF blockers & risk of **cancer** in children and young adults http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_137-eng.php

Health Canada June/11 **RITUXAN (rituximab) - Fatal Infusion Related Reactions** in Patients with Rheumatoid Arthritis

Heijstek MW, Ott de Bruin LM, Bijl M, et al. EULAR recommendations for **vaccination in paediatric patients with rheumatic diseases**. Ann Rheum Dis. 2011 Oct;70(10):1704-12.

Heijstek MW, van Gageldonk PG, et al. Differences in persistence of **measles, mumps, rubella, diphtheria and tetanus antibodies** between children with **rheumatic disease** and healthy controls: a retrospective cross-sectional study. Ann Rheum Dis. 2012 Jun;71(6):948-54. (lower antibody rates in: mumps, rubella, diphtheria and tetanus)

Henes JC, Schedel J, Kanz L, Koetter I. **Rituximab** and concomitant **leflunomide** for the treatment of rheumatoid arthritis. Rheumatol Int. . [Epub ahead of print]

Hetland ML, Stengaard-Pedersen K, Junker P, et al. **CIMESTRA** study group. **Aggressive combination therapy** with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheum

TOP

arthritis: second-year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis. 2008 Jun;67(6):815-22. Epub 2007 Sep 18.
Hetland ML, Ostergaard M, Ejbjerg B, et al; **CIMESTRA** study group. Short- and long-term efficacy of **intra-articular injections with betamethasone** as part of a treat-to-target strategy in early rheumatoid arthritis: impact of joint area, repeated injections, MRI findings, anti-CCP, IgM-RF and CRP. Ann Rheum Dis. 2012 Jun;71(6):851-6.
Hider SL, et al. Comparing the long-term clinical outcome of treatment with **methotrexate or sulfasalazine** prescribed as the first disease-modifying antirheumatic drug in patients with inflammatory polyarthritis. Ann Rheum Dis. 2006 Nov;65(11):1449-55. Epub 2006 Mar 15.
Hjardem E, Ostergaard M, Podenphant J, et al.. Do rheumatoid arthritis patients in clinical practice benefit from **switching from infliximab to a second tumor necrosis factor** alpha inhibitor? Ann Rheum Dis. 2007 Sep;66(9):1184-9. Epub 2007 Mar 27. Lack of efficacy switchers had a better clinical response to the second treatment. Adverse effect switchers responded equally well to both treatments, with a low risk of discontinuing the second drug as a result of AE. Drug survival of the switchers' second biological therapy was higher than of the first, but lower than that of non-switchers. No difference between various sequences of drugs were found. Danish post-marketing data thus support that RA patients may benefit from switching biological therapy.
Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. **Bioavailability of higher dose methotrexate comparing oral and subcutaneous** administration in patients with rheumatoid arthritis. J Rheumatol. 2004 Apr;31(4):645-8.
Hoekstra M, et al. **Splitting high-dose oral methotrexate** improves bioavailability: a pharmacokinetic study in patients with rheumatoid arthritis. J Rheumatol. 2006 Mar;33(3):481-5. Epub 2006 Jan 15.
Hoes JN, Jacobs JW, Boers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis. 2007 Dec;66(12):1560-7. Epub 2007 Jul 27.
Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral **glucocorticoids** in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009 Dec;68(12):1833-8. Epub 2008 Dec 9.
Hoes JN, van der Goes MC, et al. Glucose tolerance, insulin sensitivity and {beta}-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose **glucocorticoids**. Ann Rheum Dis. 2011 Nov;70(11):1887-94.
Holle JU, Dubrau C, Herlyn K, et al. **Rituximab** for refractory **granulomatosis with polyangiitis** (**Wegener's granulomatosis**): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis. 2012 Mar;71(3):327-33.
Holvast A, et al. Safety & efficacy of influenza vaccination in systemic **lupus** erythematosus patients with quiescent disease. Ann Rheum Dis. 2006 Jul;65(7):913-8. Epub 2005 Dec1.
Horneff G, Ebert A, Fitter S, et al. Safety and effi cacy of once **weekly etanercept** 0.8 mg/kg in a multicentre 12 week trial in active polyarticular course juvenile idiopathic arthritis. Rheumatology (Oxford) 2009; 48: 916–19.
Horneff G, De Bock F, et al. Safety and efficacy of combination of **etanercept and methotrexate** compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis 2009; 68: 519–25.
Huizinga Tom W.J. Pincus Theodore **In the Clinic**: **Rheumatoid Arthritis**. *Ann Intern Med* July 6, 2010 153:ITC1-1; doi:10.1059/0003-4819-153-1-201007060-01001.
Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, et al. Dynamic **exercise programs** (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006853.
Hyrich KL, et al. Comparison of the response to **infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying** antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 May 30;54(6):1786-1794 [Epub ahead of print]
Iacono AT, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med. 2006 Jan 12;354(2):141-50.
Iannone F, Gremese E, et al. **Longterm** Retention of **Tumor Necrosis Factor-α Inhibitor** Therapy in a Large Italian Cohort of Patients with Rheumatoid Arthritis from the GISEA Registry: An Appraisal of Predictors. J Rheumatol. 2012 Apr 1.
Iking-Konert C, Aringer M, Wollenhaupt J, et al. Performance of the new 2011 ACR/EULAR remission criteria with **tocilizumab** using the phase IIIb study **TAMARA** as an example and their comparison with traditional remission criteria. Ann Rheum Dis. 2011 Nov;70(11):1986-90.
Jamnitski A et al. Patients **non-responding to etanercept obtain lower etanercept concentrations** compared with responding patients. Ann Rheum Dis. 2012 Jan;71(1):88-91.
Johnsen AK, Schiff MH, Mease PJ, et al. Comparison of 2 Doses of **Etanercept (50 vs 100 mg)** in Active Rheumatoid Arthritis: a Randomized Double Blind Study. J Rheumatol. 2006 Feb 15; [Epub ahead of print]
Kaine J et al. Evaluation of **abatacept administered subcutaneously** in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase Iiib ALLOW study). Ann Rheum Dis. 2012 Jan;71(1):38-44.
Kalden JR, Schattenkirchner M, et al. The efficacy and safety of **leflunomide** in patients with active rheumatoid arthritis: a five-year followup study. Arthritis Rheum. 2003 Jun;48(6):1513-20.
Källberg Henrik, Ding Bo, Padyukov Leonid, et al. EIRA Study Group. Concise report: **Smoking** is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis 2011;70:508-511 Published Online First: 13 December 2010 doi:10.1136/ard.2009.120899.
Kane S, Ford J, Cohen R, Wagner C. **Absence of Infliximab in Infant Sera and Breast Milk** From Nursing Mothers Receiving Therapy for Crohn's Disease Before and After Delivery. J Clin Gastroenterol. 2009 Jan 12. [Epub ahead of print]n=3. Infliximab was detected in the mothers' sera, but not in the breast milk of nursing mothers or in the sera of the breast-fed newborns. Data from this small series of patients suggest that infliximab was not transferred from mother to child, either in utero or through breast milk. These data suggest that mothers receiving infliximab should not be discouraged from nursing their children.
Kane SV, Acquah LA. **Placental transport of immunoglobulins**: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104:228-233.
Källberg H, Ding B, Padyukov L, et al. EIRA Study Group. **Smoking** is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis. 2010 Dec 13.
Kapetanovic MC, Roseman C, Jönsson G, et al. **Methotrexate but not TNF-blockers reduces antibody response following pneumococcal vaccination** using 7-valent conjugate pneumococcal vaccine in adult patients with established arthritis. Arthritis Rheum. 2011 Aug 10.
Katchamart W, Bourré-Tessier J, Donka T, Drouin J, Rohekar G, Bykerk VP. **Canadian recommendations for use of methotrexate** in patients with rheumatoid arthritis. J Rheumatol [Internet]. 2010 Jul;37(7):1422-30.
Katchamart W, Trudeau J, Phumethum V, Bombardier C. **Methotrexate monotherapy versus methotrexate combination** therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database of Syst Rev [Internet]. 2010 Apr [cited 2011 Apr 11];(4):CD008495.
Kavanaugh A, et al. The **Infliximab** Multinational **Psoriatic Arthritis** Controlled Trial (**IMPACT**): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006 Aug;65(8):1038-43. Epub 2006 Jan 26.
Kavanaugh A, van der Heijde D, McInnes I, et al. **Golimumab**, a human TNF-alpha antibody, administered every 4 weeks as a subcutaneous injection in **psoriatic arthritis**: Clinical efficacy, radiographic, and safety findings through 1year of the randomized, placebo-controlled, **GO-REVEAL**® study. Arthritis Rheum. 2012 Feb 29.
Keeling S, et al. Prospective observational analysis of the efficacy and safety of low-dose (3 mg/kg) infliximab in **ankylosing spondylitis**: 4-year followup. J Rheumatol. 2006 Mar;33(3):558-61. Epub 2006 Feb 1.
Keystone EC, Schiff MH, et al. **Once-weekly** administration of 50 mg **etanercept** in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.
Keystone EC, Genovese MC, Klareskog L, et al. GO-FORWARD Study. **Golimumab**, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the **GO-FORWARD** Study. Ann Rheum Dis. 2009 Jun;68(6):789-96. Epub 2008 Dec 9.
Keystone EC, Kremer JM, Russell A, et al. **Abatacept** in subjects who switch from intravenous to **subcutaneous** therapy: results from the phase IIIb ATTUNE study. Ann Rheum Dis. 2012 Jun;71(6):857-61.
Khanna D, Park GS, Paulus HE, et al. **Reduction of the efficacy of methotrexate** by the use of **folic acid**: post hoc analysis from two randomized controlled studies. Arthritis Rheum. 2005 Oct;52(10):3030-8.
Khanna D, McMahon M, Furst DE. **Safety of tumour necrosis factor-alpha antagonists**. (Pregnancy) Drug Saf. 2004;27(5):307-24.
Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of **glucocorticoids** on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD006356.
Klarenbeek NB, Kerstens PJ, Huizinga TW, et al. **Recent advances in the management of rheumatoid arthritis**. BMJ. 2010 Dec 21;341:c6942. doi: 10.1136/bmj.c6942.
Klarenbeek NB, van der Kooij SM, Güler-Yüksel M, et al. **Discontinuing treatment in patients with rheumatoid arthritis** in sustained clinical remission: exploratory analyses from the BeSt study. Ann Rheum Dis. 2011 Feb;70(2):315-9.
Klareskog Lars, van der Heijde Désirée, de Jager Julien P, et al. for the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the **combination** of **etanercept** and **methotrexate compared** with each treatment **alone** in patients with rheumatoid arthritis: double-blind randomised controlled trial. The Lancet Volume 363, Number 9410 28 February 2004.
Klareskog L, Catrina AI, Paget S. **Rheumatoid arthritis**. Lancet. **2009** Jan 19. [Epub ahead of print]
Klein A, Kaul I, et al. Efficacy and safety of **oral and parenteral methotrexate** therapy in children with juvenile idiopathic arthritis. An observational study with patients of the German Methotrexate Registry. Arthritis Care Res. 2012 May 30.
Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of **tocilizumab** for rheumatoid arthritis in Japan: interim analysis of 3881 patients. Ann Rheum Dis. 2011 Dec;70(12):2148-51.
Komano Y et al. Incidence and risk factors for **serious infection** in patients with rheumatoid arthritis treated with **tumor necrosis factor inhibitors**: A report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. J Rheumatol 2011 Jul; 38:1258. (about double the infection risk)
Korpela M, Laasonen L, Hannonen P, et al.; FIN-RACo Trial Group. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with **disease-modifying antirheumatic drugs**: five-year experience from the FIN-RACo study. Arthritis Rheum. 2004 Jul;50(7):2072-81.
Korswagen LA, Bartelds GM, Krieckaert CL, et al. Venous and arterial **thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies**: a case series and cohort study. Arthritis Rheum. 2011 Apr;63(4):877-83.
Kremer JM, et al. Concomitant **leflunomide** therapy in patients **with** active rheumatoid arthritis despite stable doses of **methotrexate**. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002 Nov 5;137(9):726-3
Kremer JM, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator **abatacept**: Twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Aug;52(8):22

TOP

Kremer JM, et al. Effects of **abatacept** in patients with **methotrexate-resistant** active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006 Jun 20;144(12):865-76. Summary for patients in: Ann Intern Med. 2006 Jun 20;144(12):I18. (but fair number of pts may have been partial MTX responders)
Kremer JL, Blanco R, Brzosko M, et al. **Tocilizumab** inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at 1 year: The **LITHE** study. Arthritis Rheum. 2010 Nov 19.
Kremer JM, Russell AS, Emery P, et al. Long-term safety, efficacy and inhibition of radiographic progression with **abatacept** treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis. 2011 Oct;70(10):1826-30.
Krishnan E, Lingala B, Bruce B, Fries JF. **Disability in rheumatoid arthritis in the era of biological treatments**. Ann Rheum Dis. 2012 Feb;71(2):213-8.
Kroot EJ, et al. The prognostic value of **anti-cyclic citrullinated peptide antibody** in patients with recent-onset rheumatoid arthritis.Arthritis Rheum. 2000 Aug;43(8):1831-5.
Kuriya B, Hernández-Díaz S, Liu J, Bermas BL, Daniel G, Solomon DH. **Patterns of drug use during pregnancy** in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011 Jan 4.
Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of **heart failure** after therapy with a **tumor necrosis** factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.
Lan J , Chen Y , Hsieh TC , et al. Kinetics of viral loads and risk of **HBV** reactivation in HBcAbpositive RA patients undergoing **anti-TNF-α therapy** . Ann Rheum Dis 2011 ; 70:1719–25 .
Lebwohl M, et al. **No** evidence for increased risk of **cutaneous squamous** cell carcinoma in patients with rheumatoid arthritis receiving **etanercept** for up to 5 years. Arch Dermatol. 2005 Jul;141(7):861-4.
Leffers HC, Ostergaard M, Glintborg B, et al. on behalf of all departments of rheumatology in Denmark. Efficacy of **abatacept and tocilizumab** in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish **DANBIO** registry. Ann Rheum Dis. 2011 Jul;70(7):1216-1222.
Lehman AJ, Esdaile JM, Klinkhoff AV, et al.; METGO Study Group. A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination **methotrexate and intramuscular gold** therapy in rheumatoid arthritis: results of the METGO study. Arthritis Rheum. 2005 May;52(5):1360-70.
Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB; **Etanercept Psoriasis** Study Group. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003 Nov 20;349(21):2014-22.
Lequerre T, et al. Management of **Infusion Reactions to Infliximab** in Patients with Rheumatoid Arthritis or Spondyloarthritis: Experience from an Immunotherapy Unit of Rheumatology. J Rheumatol. 2006 Jun 1; [Epub ahead of print]
Lie E, van der Heijde D, Uhlig T, et al. Treatment **strategies** in patients with rheumatoid arthritis for whom **methotrexate monotherapy has failed**: data from the NOR-DMARD register. Ann Rheum Dis. 2011 Dec;70(12):2103-10.
Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of **myocardial infarction** in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011 Jun;70(6):929-34.
Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of **atrial fibrillation** and stroke in rheumatoid arthritis: Danish nationwide cohort study. BMJ. 2012 Mar 8;344:e1257.
Lipsky PE, van der Heijde DM, et al. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. **Infliximab and methotrexate** in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000 Nov 30;343(22):1594-602.
Listing J, Strangfeld A, Kary S, et al. **Infections** in patients with rheumatoid arthritis treated with **biologic agents**. Arthritis Rheum. 2005 Nov;52(11):3403-12.
Lovell DJ, Giannini EH, et al. Pediatric Rheumatology Collaborative Study Group. Long-term efficacy and safety of **etanercept** in **children** with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum. 2003 Jan;48(1):218-26.
Lovell DJ, Giannini EH, et al. **Etanercept** in **children** with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000 Mar 16;342(11):763-9.
Lovell DJ, Reiff A, Ilowite NT, et al. Safety and efficacy of up to **eight years of continuous etanercept** therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008; 58: 1496–504.
Lovell DJ, Ruperto N, Goodman S, et al. **Adalimumab with or without methotrexate** in juvenile rheumatoid arthritis. N Engl J Med 2008; 359: 810–20.
Lukas C, Combe B, Ravaud P, et al. Favorable effect of **very early DMARD treatment** on radiographic progression in early inflammatory arthritis. The ESPOIR cohort study. Arthritis Rheum. 2011 Mar 30. doi:10.1002/art.30371.
Lunt M, Watson KD, Dixon WG, et al; The BSRBR Control Centre Consortium; on behalf of the BSR Biologics Register. **No evidence of association between anti-TNF treatment and mortality** in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2010 Jul 26.
Luqmani R, et al. British Society for Rheumatology and **British Health** Professionals in Rheumatology **Guideline** for the Management of **Rheumatoid Arthritis** (The first 2 years). Rheumatology (Oxford). 2006 Jul 13; [Epub ahead of print]
Ljung L, Simard JF, Jacobsson L, et al. ARTIS Study Group. Treatment with **tumour necrosis factor-inhibitors and the risk of acute coronary syndromes** in early rheumatoid arthritis. Arthritis Rheum. 2011 Aug 26.doi: 10.1002/art.30654.
Mahadevan U, Cucchiara S, Hyams JS, et al. The London position statement of the World Congress of Gastroenterology on **Biological Therapy for IBD with the European Crohn's and Colitis Organisation: Pregnancy and Pediatrics**. Am J Gastroenterol. 2010 Dec 14.
Maini R, St Clair EW, et al. **Infliximab** (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving **concomitant methotrexate**: a randomised phase III trial. **ATTRACT** Study Group. Lancet. 1999 Dec 4;354(9194):1932-9.
Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good Clinical Response, Remission, and Predictors of Remission in Rheumatoid Arthritis Patients Treated with **Tumor Necrosis Factor-alpha Blockers**: The GISEA Study. J Rheumatol. 2007 Aug;34(8):1670-3. Epub 2007 Jul 1. We show that **only a minority** of patients with longstanding RA achieve a good clinical response or remission at the outpatient community level. Predictors of remission identify characteristics commonly observed in subsets with less severe RA.
Mariette X, Tubach F, Bagheri H, et al. **Lymphoma** in patients treated with anti-TNF. Results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2009 Oct 14.
Mariette X, Matucci-Cerinic M, et al. **Malignancies** associated with **tumour necrosis factor inhibitors** in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis. 2011 Nov;70(11):1895-904.
Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF; American Academy of Ophthalmology. Revised recommendations on screening for **chloroquine** and **hydroxychloroquine retinopathy**. Ophthalmology. 2011 Feb;118(2):415-22.
Maxwell L, Singh JA. **Abatacept** for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007277.
McInnes IB, Schett G. The **Pathogenesis of Rheumatoid Arthritis**. N Engl J Med 2011; 365:2205-2219
Mease PJ, Goffe BS, et al. **Etanercept** in the treatment of **psoriatic arthritis** and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.
Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. **Adalimumab** for the treatment of patients with moderately to severely active **psoriatic arthritis**: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Oct;52(10):3279-89.
Mercer LK, Green AC, Galloway JB, et al; **British** Society for Rheumatology **Biologics Register** Control Centre Consortium, Symmons DP, Hyrich KL; on behalf of the British Society for Rheumatology Biologics Register. The influence of anti-TNF therapy upon incidence of **keratinocyte skin cancer** in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2012 Jun;71(6):869-874.
Mertens M, Singh JA. **Anakinra** for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD005121. Anakinra is a relatively safe and modestly efficacious biologic therapy for rheumatoid arthritis.
Micha R, Imamura F, Wyler von Ballmoos M, et al. Systematic Review and Meta-Analysis of **Methotrexate Use and Risk of Cardiovascular Disease**. Am J Cardiol. 2011 Aug 17.
Minden K, Niewerth M, Zink A, et al. **Long-term outcome of patients with JIA treated with etanercept**, results of the biologic register JuMBO. Rheumatology (Oxford). 2012 Mar 24.
Mok C, Kwok C, Ho L, et al. **Life expectancy**, standardized mortality ratios and causes of death of six rheumatic diseases in Hong Kong, China. Arthritis Rheum. 2011 Mar 9. doi: 10.1002/art.30277.
Mor A, Bingham CO 3rd, et al. **Methotrexate combined with isoniazid** treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: experience from an urban arthritis clinic. Ann Rheum Dis. 2008 Apr;67(4):462-5.
Moreland LW, Schiff MH, et al. **Etanercept** therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.
Moreland LW, Baumgartner SW, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein **etanercept**. N Engl J Med. 1997 Jul 17;337(3):141-7.
Moreland LW, et al. **Etanercept** treatment in adults with established rheumatoid arthritis: **7 years** of clinical experience. J Rheumatol. 2006 May;33(5):854-61. Epub 2006 Mar 15.
Moreland LW, O'Dell JR, Paulus HE, et al. **TEAR** Investigators. A randomized comparative effectiveness study of **oral triple therapy versus etanercept plus methotrexate** in early, aggressive rheumatoid arthritis. Arthritis Rheum. 2012 Apr 16.
Morgan SL, Baggott JE, et al. Supplementation with **folic acid during methotrexate** therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. Ann Intern Med. 1994 Dec 1;121(11):833-41.
Mottonen T, Hannonen P, et al. Comparison of **combination** therapy with **single-drug** therapy in early rheumatoid arthritis: a randomised trial. **FIN-RACo trial** group. Lancet. 1999 May 8;353(9164):1568-73.
Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. **Adalimumab** for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005113.
Neovius M, Simard JF, Klareskog L, Askling J; for the ARTIS Study Group. **Sick leave and disability pension** before and after initiation of antirheumatic therapies in clinical practice. Ann Rheum Dis. 2011 Aug;70(8):1407-1414. Obici L, Meini A,
Newton-Cheh Christopher, Lin Angela E., Baggish Aaron L., et al. Case 11-2011 — A 47-Year-Old Man with Systemic Lupus Erythematosus and Heart Failure. N Engl J Med 2011; 364:1450-1460. (Infiltrative cardiomyopathy & possible long-QT syndrome due to **hydroxychloroquine**)
NICE: Ankylosing spondylitis - adalimumab, etanercept and infliximab Adalimumab, etanercept and infliximab for ankylosing spondylitis **May 2008** http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11992
NICE Feb/09 **Rheumatoid Arthritis Guidelines** http://www.nice.org.uk/Guidance/CG79 (Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M; Guideline Development Group. Management of rheumatoid arthritis: sum

TOP

guidance. BMJ. 2009 Mar 16;338:b702. doi: 10.1136/bmj.b702.)
NICE: Rheumatoid arthritis - drugs for treatment **after failure of a TNF inhibitor** Aug/10 http://guidance.nice.org.uk/TA195.)
NICE: National Institute for Health and Clinical Excellence. **Adalimumab, etanercept, infliximab, rituximab and abatacept** for the **treatment of rheumatoid arthritis after the failure of a TNF inhibitor**. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Aug. http://www.nice.org.uk/nicemedia/live/13108/50409/50409.pdf
NICE: **Tocilizumab** for rheumatoid arthritis Aug/10 http://guidance.nice.org.uk/TA198
NICE: National Institute for Health and Clinical Excellence (NICE). Etanercept, infliximab and adalimumab for the treatment of **psoriatic arthritis**. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Aug. 35 p. (Technology appraisal guidance; no. 199). http://www.nice.org.uk/nicemedia/live/13110/50424/50424.pdf
NICE: National Institute for Health and Clinical Excellence (NICE). **Certolizumab** pegol for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Feb. (Technology appraisal guidance; no. 186). http://www.nice.org.uk/nicemedia/live/12808/47528/47528.pdf
Nigrovic PA, Mannion M, Prince FH, et al. **Anakinra** as first-line disease-modifying therapy in **systemic juvenile idiopathic arthritis**: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011 Feb;63(2):545-55. doi: 10.1002/art.30128.
Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007 Jun 5;146(11):797-808. **Anti-CCP antibodies** are more specific than RF for diagnosing rheumatoid arthritis & may better predict erosivedisease.
Nordal E, Zak M, Aalto Ket al. **Juvenile idiopathic arthritis**; Ongoing disease activity and changing categories in a long-term Nordic cohort study. Arthritis Rheum. 2011 May 10.
Nuki G, Bresnihan B, et al. European Group Of Clinical Investigators. Long-term safety and maintenance of clinical improvement following treatment with **anakinra** (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Nov;46(11):2838-46.
Obici L, Meini A, Cattalini M, et al. Favourable and sustained response to **anakinra** in **tumour necrosis factor receptor-associated periodic syndrome (TRAPS)** with or without AA amyloidosis. Ann Rheum Dis. 2011 Aug;70(8):1511-2.
O'Dell JR, Leff R, et al. Treatment of rheumatoid arthritis with **methotrexate and hydroxychloroquine**, **methotrexate and sulfasalazine**, or a **combination** of the **three** medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 May;46(5):1164-70.
O'Dell JR, Haire CE, et al. Treatment of rheumatoid arthritis with **methotrexate alone**, **sulfasalazine and hydroxychloroquine**, or a **combination** of all **three** medications. N Engl J Med. 1996 May 16;334(20):1287-91.
O'Dell JR, Blakely KW, et al. Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of **minocycline** and **hydroxychloroquine**. Arthritis Rheum. 2001 Oct;44(10):2235-41.
O'dell JR, Petersen K, Leff R, et al. **Etanercept in Combination with Sulfasalazine, Hydroxychloroquine, or Gold** in the Treatment of Rheumatoid Arthritis. J Rheumatol. 2005 Dec 15; [Epub ahead of print]
Okuyama A, Nagasawa H, Suzuki K, et al. **Fc{gamma} receptor IIIb polymorphism and use of glucocorticoids** at baseline are associated with **infusion reactions to infliximab** in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Feb;70(2):299-304.
Olivieri I, Palazzi C, Peruz G, Padula A. Management Issues with Elderly-Onset Rheumatoid Arthritis : An Update. Drugs Aging. 2005;22(10):809-822.
Ornetti P, Chevillotte H, Zerrak A, Maillefert JF. **Anti-Tumour Necrosis** Factor-alpha Therapy for Rheumatoid and Other Inflammatory Arthropathies : Update on Safety in **Older Patients**. Drugs Aging. 2006;23(11):855-60.
Ornbjerg LM, et al. Impact of **tumour necrosis factor inhibitor** treatment on **radiographic progression** in rheumatoid arthritis patients in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis. 2012 Apr 24.
Osiri M, Shea B, Welch V, Suarez-Almazor ME, Strand V, Tugwell P, et al. **Leflunomide** for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev [Internet]. 2009 [cited 2011 Apr 11];(4):CD002047.
Østergaard M, Emery P, Conaghan PG, et al. Significant improvement in synovitis, osteitis, and bone erosion following **golimumab and methotrexate** combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. Arthritis Rheum. 2011 Dec;63(12):3712-22.
Otten Marieke H., Prince Femke H. M., Armbrust Wineke, et al. Original Contribution Factors Associated With Treatment Response to **Etanercept** in **Juvenile Idiopathic Arthritis**. JAMA. 2011;Published online November 6, 2011.
Paller AS, Siegfried EC, Langley RG, et al.; **Etanercept Pediatric Psoriasis** Study Group. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008 Jan 17;358(3):241-51.
Papp KA, Tyring S, Lahfa M, et al.; **Etanercept Psoriasis** Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005 Jun;152(6):1304-12.
Pavelka K, Jarosova K, et al. Increasing the **infliximab dose** in rheumatoid arthritis patients: a randomized, double blind study failed to confirm its efficacy. Ann Rheum Dis. 2009 Apr 6. [Epub ahead of print]
Peters MJ, Symmons DP, McCarey D et al. EULAR evidence-based recommendations for **cardiovascular risk** management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2009 Sep 22.
Pharmacist's Letter. Selected Issues in the Effective and Safe Use of **Live Vaccines**. Oct 2007.
Pikwer M, Bergström U, et al. **Breast-feeding**, but not oral contraceptives, is associated with a reduced risk of rheumatoid arthritis. Ann Rheum Dis. 2008 May 14. [Epub ahead of print]
Pikwer M, Bergström U, Nilsson JÅ et al. **Early menopause** is an independent predictor of rheumatoid arthritis. Ann Rheum Dis. 2012 Mar;71(3):378-81.
Plant D, Prajapati R, Hyrich KL, et al. Investigation of established rheumatoid-arthritis (RA) susceptibility genetic markers as predictors of response to **anti-TNF therapy** in a large UK cohort replicates association with the **PTPRC gene**. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33381.
Plosker GL, Croom KF. **Sulfasalazine**: a review of its use in the management of rheumatoid arthritis. Drugs. 2005;65(13):1825-49.
Poor G, Strand V. Efficacy and safety of **leflunomide 10 mg versus 20 mg** once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. Rheumatology (Oxford). 2004 Mar 16 [Epub ahead of print]
Prakken B, Albani S, Martini A. **Juvenile idiopathic arthritis (JIA)**. Lancet 2011; 377: 2138–49.
Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation --- United States, 2003—2005 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5540a2.htm?s_cid=mm5540a2_x
Prey S, Paul C. Effect of **folic or folinic acid** supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br J Dermatol. 2008 Oct 20. [Epub ahead of print] Supplementation with folic acid is an effective measure to reduce hepatic adverse effects associated with methotrexate treatment. There is no difference between folinic acid and folic acid, but the lower cost of the latter promotes its use.
Prince FH, Otten MH, van Suijlekom-Smit LW. Diagnosis and management of **juvenile idiopathic arthritis**. BMJ. 2010 Dec 3;341:c6434. doi: 10.1136/bmj.c6434.
Quartier Pierre, Allantaz Florence, Cimaz Rolando, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist **anakinra** in patients with **systemic-onset juvenile** idiopathic arthritis (**ANAJIS** trial). Ann Rheum Dis 2011;70:747-754 Published Online First: 20 December 2010 doi:10.1136/ard.2010.134254.
Raaschou P, Simard JF, Neovius M, Askling J; Anti-Rheumatic Therapy in Sweden Study Group (ARTIS). Does **cancer** that occurs during or after **anti-tumor necrosis factor therapy** have a worse prognosis? A national assessment of overall and site-specific cancer survival in rheumatoid arthritis patients treated with biologic agents. Arthritis Rheum. 2011 Jul;63(7):1812-22.
Rahman MU, Buchanan J, et al. Changes in **patient characteristics in anti-tumour necrosis factor clinical trials** for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis. 2011 Sep;70(9):1631-40.
Ravindran V, Rachapalli S, Choy EH. Safety of medium- to long-term **glucocorticoid therapy** in rheumatoid arthritis: a meta-analysis. Rheumatology (Oxford). 2009 Jul;48(7):807-11. Epub 2009 May 15.
Reich K, Nestle FO, Papp K, et al.; **EXPRESS** study investigators. Infliximab induction and maintenance therapy for moderate-to-severe **psoriasis**: a phase III, multicentre, double-blind trial. Lancet. 2005 Oct 15-21;366(9494):1367-74.
Rezaei H, Saevarsdottir S, Forslind K et al. In early rheumatoid arthritis, patients with a good initial response to **methotrexate** have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial. Ann Rheum Dis. 2012 Feb;71(2):186-91.
Ribeiro AC, Guedes LK, Moraes JC, et al. **Reduced seroprotection after pandemic H1N1 influenza** adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis. 2011 Dec;70(12):2144-7.
Richards BL, Whittle SL, Buchbinder R. **Antidepressants for pain management** in rheumatoid arthritis. Cochrane Database Syst Rev. 2011 Nov 9;11:CD008920. There is currently insufficient evidence to support the routine prescription of antidepressants as analgesics in patients with RA as no reliable conclusions about their efficacy can be drawn from eight placebo RCTs.
Richards BL, Whittle SL, Buchbinder R. **Muscle relaxants for pain** management in rheumatoid arthritis. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008922. DOI: 10.1002/14651858.CD008922
Richards BL, Whittle SL, Buchbinder R. **Neuromodulators for pain** management in rheumatoid arthritis. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008921. DOI: 10.1002/14651858.CD008921.
Rigby W, Ferraccioli G, Greenwald M, et al. **Rituximab** improved physical function and quality of life in patients with rheumatoid arthritis naïve to methotrexate (**IMAGE** study). Arthritis Care Res (Hoboken). 2010 Dec 8.
Robert N, Wong GW, Wright JM. Effect of **cyclosporine on blood pressure**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007893. There appears to be a dose-related effect with lower doses (1-4 mg/kg/d) increasing mean BP by an average of 5 mmHg and higher doses (>10 mg/kg/d) increasing mean BP by 11 mmHg on average.
Rudwaleit M, van der Heijde D, et al. The development of **Assessment of SpondyloArthritis international Society** classifi cation criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68:
Ruperto N, Murray KJ, Gerloni V, et al. A randomized trial of parenteral **methotrexate** comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of meth

TOP

Arthritis Rheum 2004; 50: 2191–201.
Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of **infliximab plus methotrexate** for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56: 3096–106.
Ruperto N, Lovell DJ, Quartier P, et al. **Abatacept** in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008; 372: 383–91.
Ruperto N, Lovell DJ, et al. Long-term efficacy and safety of **infliximab plus methotrexate** for the treatment of polyarticular-course juvenile rheumatoid arthritis: fi ndings from an open-label treatment extension. Ann Rheum Dis 2010; 69: 718–22.
Ruperto N, Lovell DJ, Quartier P, et al. Long-term safety and efficacy of **abatacept** in children with juvenile idiopathic arthritis. Arthritis Rheum 2010; 62: 1792–802.
Ruperto N, Quartier P, Wulffraat N, et al. for the Paediatric Rheumatology International Clinical Trials Organisation (**PRINTO**). A phase II study to evaluate dosing and preliminary safety and efficacy of **canakinumab** in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33342.
Ryu YS, Park SH, Kim JM, et al. A case of **leukoencephalopathy associated with adalimumab**-treated rheumatoid arthritis and a review of literature. Rheumatol Int. 2011 Nov 8.
Saad AA, Symmons DP, Noyce PR, et al. Risks and benefits of 12 tumor necrosis factor-alpha inhibitors in the management of **psoriatic arthritis**: systematic review and meta-analysis of randomized controlled trials. J Rheumatol 2008;35:883-90.
Saag KG, Teng GG, et al. American College of Rheumatology-**ACR 2008** recommendations for the use of **nonbiologic and biologic disease-modifying antirheumatic drugs** in rheumatoid arthritis. Arthritis Rheum 2008 Jun 15;59(6):762-84.
Salliot C, van der Heijde D. **Long-term safety of methotrexate** monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009 Jul;68(7):1100-4. Epub 2008 Dec 5.
Salmon-Ceron D, Tubach F, Lortholary O, for RATIO group. Drug-specific risk of non-tuberculosis **opportunistic infections** in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Dec 21. Various and severe OIs, especially those with intracellular micro-organisms, may develop in patients receiving anti-TNF treatment. Monoclonal anti-TNF antibody rather than soluble TNF receptor therapy and steroid use >10 mg/day are independently associated with OI.
Sarnes E, Crofford L, Watson M, et al. Incidence and US Costs of **Corticosteroid-Associated Adverse Events**: A Systematic Literature Review. Clin Ther. 2011 Oct 12.
Savage RL. **Leflunomide in combination** therapy for rheumatoid arthritis. Drug Saf. 2010 Jun 1;33(6):523-6.
Schanz S, Schmalzing M, Guenova E, et al. **Interstitial granulomatous dermatitis** with arthritis responding to **tocilizumab**. Arch Dermatol. 2012 Jan;148(1):17-20
Schiff MH, et al. Safety Analyses of **Adalimumab** (HUMIRA(R)) in Global Clinical Trials and US Postmarketing Surveillance of Patients With Rheumatoid Arthritis. Ann Rheum Dis. 2006 Feb 13; [Epub ahead of print]
Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of **abatacept** in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis. 2009 Nov;68(11):1708-14. Epub 2008 Dec 15.
Schiff M. **Abatacept** treatment for rheumatoid arthritis. Rheumatology (Oxford). 2011 Mar;50(3):437-49.
Schiff M, Keiserman M, et al. Clinical response & tolerability to **abatacept** in patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the **ATTEST** Study. Ann Rheum Dis. 2011 Nov;70(11):2003-7.
Schipper LG, Vermeer M, Kuper HH, et al. A **tight control** treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis. 2012 Jun;71(6):845-50.
Schmajuk G, Trivedi AN., Solomon DH., et al. Receipt of **Disease-Modifying Antirheumatic Drugs** Among Patients With Rheumatoid Arthritis in **Medicare Managed** Care Plans. *JAMA*. 2011;305(5):480-486.doi:10.1001/jama.2011.67
Schmitz S, Adams R, Walsh CD, et al. A **mixed treatment comparison of the efficacy of anti-TNF agents** in rheumatoid arthritis for methotrexate non-responders demonstrates differences between treatments: a Bayesian approach. Ann Rheum Dis. 2012 Feb;71(2):225-30.
Schoels M, Wong J, Scott DL, et al. **Economic aspects of treatment options in rheumatoid arthritis**: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):995-1003.
Schumacher HR, Chen LX. **Injectable corticosteroids** in treatment of arthritis of the knee. Am J Med. 2005 Nov;118(11):1208-14.
Schuna AA. **Rituximab** for the treatment of rheumatoid arthritis. Pharmacotherapy. 2007 Dec;27(12):1702-10.
Scott DL, et al. European Leflunomide Study Group. Treatment of active rheumatoid arthritis with **leflunomide**: two year follow up of a double blind, placebo controlled trial **versus sulfasalazine**. Ann Rheum Dis. 2001 Oct;60(10):913-23.
Scott DL, Wolfe F, Huizinga TW. **Rheumatoid arthritis**. Lancet. 2010 Sep 25;376(9746):1094-108.
Scott DL, Kingsley GH. **Tumor necrosis factor inhibitors** for rheumatoid arthritis. N Engl J Med. 2006 Aug 17;355(7):704-12.
Semb AG, Kvien TK, Demicco D, et al. Effect of **intensive lipid lowering** on cardiovascular outcome in patients with and without inflammatory joint disease. Arthritis Rheum. 2012 May 10.
Setoguchi S, et al. **Tumor necrosis factor** alpha antagonist use and **cancer** in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2757-64. Comparing biologic DMARD users with MTX users, the propensity score-adjusted pooled hazard ratio was 1.37 (95% confidence interval 0.71-2.65) for hematologic malignancies and 0.91 (95% confidence interval 0.65-1.26) for solid tumors. Our results indicate that users of biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with MTX users.
Silva F, Seo P, Schroeder DR, et al; for the **Wegener's Granulomatosis Etanercept Trial Research Group. Solid malignancies** among patients with Wegener's granulomatosis treated with etanercept: Long-term follow-up of a multicenter longitudinal cohort. Arthritis Rheum. 2011 Apr 11.
Silverman E. et al. **Leflunomide or Methotrexate** for **Juvenile Rheumatoid Arthritis**. N Engl J Med 2005;352:1655-66.
Silverman E, Spiegel L, Hawkins D, et al. Long-term open-label preliminary study of the safety and efficacy of **leflunomide** in patients with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2005; 52: 554–62.
Simard JF, Neovius M, Hagelberg S, Askling J. **Juvenile idiopathic arthritis and risk of cancer**: a nationwide cohort study. Arthritis Rheum 2010; 62: 3776–82.
Simsek I, Erdem H, Pay S, Sobaci G, Dinc A. **Optic neuritis occurring with anti-tumour necrosis factor alpha** therapy.Ann Rheum Dis. 2007 Sep;66(9):1255-8. Epub 2007 Apr 24.
Singh JA, Christensen R, Wells GA, et al. **Biologics for rheumatoid arthritis**: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848.
Singh, Jasvinder A, Christensen, Robin, Wells, George A, et al. A network meta-analysis of randomized controlled trials of **biologics for rheumatoid arthritis**: a Cochrane overview. CMAJ 2009 0: cmaj.091391.
Singh JA, Noorbaloochi S, Singh G. **Golimumab** for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341.
Singh JA, Beg S, Lopez-Olivo MA. **Tocilizumab** for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jul 7;7:CD008331. Tocilizumab is beneficial in decreasing RA disease activity and improving function. Tocilizumab treatment was associated with significant increase in cholesterol levels and in total adverse events. Larger safety studies are needed to address these safety concerns.
Singh JA, Wells GA, Christensen R, et al. **Adverse effects of biologics**: a network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD008794. DOI: 10.1002/14651858.CD008794.pub2. Overall, in the short term biologics were associated with significantly higher rates of total adverse events, withdrawals due to adverse events and TB reactivation. Some biologics had a statistically higher association with certain adverse outcomes compared to control, but there was no consistency across the outcomes so caution is needed in interpreting these results.
Singh JA, Furst DE, Bharat A, et al. **2012 update** of the 2008 American College of Rheumatology recommendations for the use of **disease-modifying antirheumatic drugs and biologic agents** in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39.
Smolen JS, Kalden JR, Scott DL, et al.. Efficacy and safety of **leflunomide** compared with placebo and **sulphasalazine** in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet. 1999 Jan 23;353(9149):259-66.
Smolen JS, Emery P, Keystone EC, et al. Consensus Statement on the Use of **Rituximab** in Patients With Rheumatoid Arthritis. Ann Rheum Dis. 2006 Nov 15; [Epub ahead of print]
Smolen JS, Kay J, Doyle MK, et al. GO-AFTER study investigators. **Golimumab** in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (**GO-AFTER** study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21. Epub 2009 Jun 26.
Smolen JS, Landewé R, Breedveld FC, et al. **EULAR** recommendations for the management of rheumatoid arthritis with **synthetic and biological disease-modifying antirheumatic drugs**. Ann Rheum Dis. 2010 May 5. [Epub ahead of print]
Snijders GF, van den Ende CH, van Riel PL, et al. on behalf of NOAC study group. The effects of **doxycycline** on reducing symptoms in knee osteoarthritis: results from a triple-blinded randomised controlled trial. Ann Rheum Dis. 2011 Jul;70(7):1191-1196.
Soliman Moetaza M, Ashcroft Darren M, Watson Kath D, et al. , on behalf of the British Society for Rheumatology Biologics Register. Impact of **concomitant use of DMARDs on the persistence with anti-TNF therapies** in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:583-589
Solomon DH, Avorn J, Katz JN, et al. **Immunosuppressive medications** and hospitalization for **cardiovascular events** in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Nov 29;54(12):3790-3798. Monotherapy with oral glucocorticoids was associated with an increased risk of cardiovascular events (OR 1.5, 95% CI 1.1 - 2.1), and a similar trend in the direction of risk was seen with glucocorticoid combination therapy (OR 1.3, 95% CI 0.8-2.0). Cytotoxic immunosuppressive agents other than MTX (azathioprine, cyclosporine, and leflunomide) were also associated with an increased risk of cardiovascular events (with both monotherapy and combination treatment, OR 1.8, 95% CI 1.1-3.0). When compared with RA patients receiving MTX monotherapy, those receiving biologic immunosuppressive agents had neither an increased nor decreased risk of experiencing a cardiovascular event, whereas use of oral glucocorticoids and cytotoxic immunosuppressive agents was associated with significant increases in the risk of cardiovascular events.
Solomon Daniel H., Massarotti Elena, Garg Rajesh, et al. Association Between **Disease-Modifying Antirheumatic Drugs and Diabetes Risk** in Patients With Rheumatoid Arthritis and Psoriasis. JAMA. 2011;305(24):2525-2531.
Solomon DH, Mercer E, Kavanaugh A. Observational studies on the risk of **cancer associated with TNF-Inhibitors** in RA: A review of their methodologies and results. Arthritis Rheum. 2011 Aug 26. doi: 10.1002/art.30653.

TOP

Song I-H, Hermann KG, Haibel H, et al. Effects of **etanercept versus sulfasalazine** in early axial **spondyloarthritis** on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 2011;70:590-596 doi:10.1136/ard.2010.139667

Song IH, Althoff CE, Haibel H, et al. Frequency and duration of drug-free remission after 1 year of treatment with **etanercept versus sulfasalazine** in early **axial spondyloarthritis**: 2 year data of the ESTHER trial. Ann Rheum Dis. 2012 Mar 22.

Sterry W, Ortonne JP, Kikham B, Brocq O, Robertson D, Pederson RD, et al. 1 Comparison of two **etanercept** regimens for treatment of psoriasis and **psoriatic arthritis**: **PRESTA** randomised double blind multicentre trial. BMJ 2010;340:c147.

St Clair EW, van der Heijde DM, Smolen JS, et al.; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of **Early Onset** Study Group. Combination of **infliximab and methotrexate** therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43.

Strand V, Cohen S, et al. Treatment of active rheumatoid arthritis with **leflunomide** compared with placebo and **methotrexate**. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med. 1999 Nov 22;159(21):2542-50.

Strand V, Smolen JS, van Vollenhoven RF, et al. **Certolizumab pegol plus methotrexate** provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. Ann Rheum Dis. 2011 Mar 17.

Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A. Risk of **herpes zoster** in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009 Feb 18;301(7):737-44. Treatment with monoclonal anti-**TNF-alpha antibodies** may be associated with increased risk of herpes zoster, but this requires further study.

Strangfeld A, Eveslage M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011 Nov;70(11):1914-20.

Summers KM, Kockler DR. **Rituximab** Treatment of Refractory Rheumatoid Arthritis (December). Ann Pharmacother. 2005 Oct 25; [Epub ahead of print]

Suter Lisa G.; Fraenkel Liana; Braithwaite R. Scott. Cost-effectiveness of Adding **Magnetic Resonance Imaging** (MRI) to Rheumatoid Arthritis Management. Arch Intern Med. 2011;171(7):657-667.

Svensson B, Boonen A, Albertsson K, et al. **Low-dose prednisolone** in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum. 2005 Nov;52(11):3360-70.

Symmons D, et al. Patients with stable long-standing rheumatoid arthritis **continue to deteriorate** despite intensified treatment with traditional disease modifying anti-rheumatic drugs--results of the British Rheumatoid Outcome Study Group Randomized controlled clinical trial.
Rheumatology (Oxford). 2006 May;45(5):558-65. Epub 2005 Nov 1.

Rituximab (Rituxan) for Rheumatoid Arthritis. Pharmacist's Letter Aug, 2006. (Roche patient Assisance program 1-888-748-8926)

Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with **rituximab plus methotrexate** in early active rheumatoid arthritis: the **IMAGE** trial. Ann Rheum Dis. 2011 Jan;70(1):39-46.

Tan CS, Koralnik IJ. **Progressive multifocal leukoencephalopathy** (PML) and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010 Apr;9(4):425-37.

Tanaka Y, et al. for the RRR study investigators. **Discontinuation of infliximab** after attaining **low disease activity** in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. Ann Rheum Dis. 2010 Apr 1.

Ter Wee MM, Lems WF, Usan H et al. The effect of **biological agents on work participation** in rheumatoid arthritis patients: a systematic review. Ann Rheum Dis. 2012 Feb;71(2):161-71.

Tesfa1 D, Ajeganova S, Hägglund1 H, et al. **Late-onset neutropenia following rituximab** therapy in rheumatic diseases: Association with B-lymphocyte depletion and infections. Arthritis Rheum. 2011 May 10. doi: 10.1002/art.30427.

Thompson AE, Rieder SW, Pope JE. **TNF therapy and the risk of serious infection** and malignancy in patients with early rheumatoid arthritis: A meta-analysis of randomized controlled trials. Arthritis Rheum. 2011 Feb 25. doi: 10.1002/art.30310.

Tubach F, Salmon D, Ravaud P, et al. Research Axed on Tolerance of Biotherapies Group. **Risk of tuberculosis** is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective french research axed on tolerance of biotherapies registry. Arthritis Rheum. 2009 Jun 29;60(7):1884-1894.

Tugwell P, Pincus T, et al. Combination therapy with **cyclosporine and methotrexate** in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. N Engl J Med. 1995 Jul 20;333(3):137-41.

Tugwell P, Singh JA, Wells GA. **Biologicals for rheumatoid arthritis**. BMJ. 2011 Jul 28;343:d4027.

Tynjälä P, Vähäsalo P, Tarkiainen M, et al. Aggressive Combination Drug Therapy in **Very Early Polyarticular Juvenile Idiopathic** Arthritis (**ACUTE-JIA**): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 May 28.

Tyring S, Gottlieb A, Papp K, Gordon K, et al. **Etanercept** and clinical outcomes, fatigue, and depression in **psoriasis**: double-blind placebo-controlled randomised phase III trial. Lancet. 2006 Jan 7;367(9504):29-35.

van Assen S, et al. Humoral responses after **influenza vaccination** are severely reduced in patients with rheumatoid arthritis treated with **rituximab**. Arthritis Rheum. 2009 Dec 28;62(1):75-81.

van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for **vaccination in adult patients** with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;**70**:414-422. Online: 3 Dec 2010 doi:10.1136/ard.2010.137216

van den Broek M, Klarenbeek NB, Dirven L, et al. **Discontinuation of infliximab** and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the **BeSt** study. Ann Rheum Dis. 2011 Aug;70(8):1389-94.

van den Broek M, Dirven L, Klarenbeek N, et al. The association of **treatment response and joint damage with ACPA-status** in recent-onset RA: a subanalysis of the 8-year follow-up of the **BeSt study**. Ann Rheum Dis. 2012 Feb;71(2):245-8.

van der Heijde D, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: **Two-year** clinical and radiographic results from the **TEMPO** study, a double-blind, randomized trial. Arthritis Rheum. 2006 Mar 29;54(4):1063-1074 [Epub ahead of print]

van der Heijde D, et al. **Once-weekly** 50-mg dosing of **Etanercept** (Enbrel(R)) is as effective as 25-mg twice-weekly dosing in patients with **ankylosing spondylitis**. Ann Rheum Dis. 2006 Sep 12; [Epub ahead of print]

van der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease Activity, Physical Function, and Radiographic Progression After Longterm Therapy with **Adalimumab** Plus Methotrexate: 5-Year Results of **PREMIER**. J Rheumatol. 2010 Oct 1.

van der Heijde Désirée, Sieper Joachim, Maksymowych Walter P, et al. for the Assessment of SpondyloArthritis international Society. **2010 Update of the international ASAS recommendations** for the use of **anti-TNF agents** in patients with **axial spondyloarthritis**. Ann Rheum Dis 2011;70:905-908 doi:10.1136/ard.2011.151563.

van der Linden MP, van der Woude D, Ioan-Facsinay A, et al. Value of **anti-modified citrullinated vimentin** and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2232-41.

van der Linden MP, le Cessie S, Raza K, et al. Long-term **impact of delay in assessment of patients with early arthritis**. Arthritis Rheum. 2010 Dec;62(12):3537-46. doi: 10.1002/art.27692.

van der Woude D, Young A, Jayakumar K,et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free **remission** in rheumatoid arthritis: Results from two large early arthritis cohorts. Arthritis Rheum. 2009 Aug;60(8):2262-71. Sustained DMARD-free remission in RA patients treated with conventional therapy is not uncommon (15%). Symptom duration at presentation and the absence of autoantibodies are associated with sustained DMARD-free remission.

van Everdingen AA, Jacobs JW, et al. **Low-dose prednisone** therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med. 2002 Jan 1;136(1):1-12.

van Lümig PPM et al. Relevance of laboratory investigations in **monitoring patients with psoriasis on etanercept or adalimumab**. Br J Dermatol 2011 Mar 24

van Riel PL, et al. Add **Enbrel or Replace Methotrexate** Study Investigators. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis. 2006 Nov;65(11):1478-83. Epub 2006 Feb 7.

van Rossum MA, et al. **Sulfasalazine** in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch **Juvenile** Chronic Arthritis Study Group. Arthritis Rheum. 1998 May;41(5):808-16.

van Sijl AM, van den Oever IA, Peters MJ, et al. Subclinical **renal dysfunction** is independently associated with cardiovascular events in rheumatoid arthritis: **the CARRE Study**. Ann Rheum Dis. 2012 Mar;71(3):341-4.

van Vollenhoven RF et al. Addition of **infliximab** compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (**Swefot** trial): 1-year results of a randomised trial. *Lancet* 2009 Aug 8; 374:459.

van Vollenhoven RF, Geborek P, Forslind K, et al, for the **Swefot** study group. **Conventional combination treatment versus biological** treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012; online March 29.

Vermeer M, Kuper HH, Hoekstra M et al. Implementation of a **treat-to-target strategy in very early** rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study **(DREAM Study).** Arthritis Rheum. 2011 Oct;63(10):2865-72.

Verstappen SM, Bakker MF, et al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with **methotrexate** tight control therapy (the CAMERA study). Ann Rheum Dis. 2009 Jul 5.

Verstappen SM, McCoy MJ, Roberts C, et al. The beneficial effects of a **3 week** course of **intramuscular glucocorticoid** injections in patients with very early inflammatory polyarthritis: Results of the STIVEA trial. Ann Rheum Dis. 2009 Oct 12.

Verstappen Suzanne M M, King Yvonne, Watson Kath D, et al. BSRBR Control Centre Consortium, BSR Biologics Register. **Anti-TNF therapies and pregnancy**: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:823-826 Published Online First: 28 February 2011 doi:10.1136/ard.2010.140822.

Verstappen SM, Lunt M, Bunn DK, Scott DG, Symmons DP. In patients with **early inflammatory polyarthritis**, ACPA positivity, younger age and inefficacy of the first non-biological DMARD are predictors for receiving biologic
results from the Norfolk Arthritis Register. Ann Rheum Dis. 2011 Aug;70(8):1428-32.

TOP

Welsh P, Peters MJ, Sattar N. **Vitamin D** in rheumatoid arthritis: A magic bullet or a mirage? The need to improve the evidence base prior to calls for supplementation. Arthritis Rheum. 2011 Mar 11. doi: 10.1002/art.30341.
Vinet E, Pineau C, Gordon C, Clarke AE, Bernatsky S. **Biologic therapy and pregnancy** outcomes in women with rheumatic diseases. Arthritis Rheum. 2009 May 15;61(5):587-92.
Visser K, Katchamart W, Loza E, et al. Multinational **evidence-based recommendations for the use of methotrexate** in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis. 2008 Nov 25. [Epub ahead of print]
Visser K, van der Heijde D. Optimal dosage and route of administration of **methotrexate** in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009 Jul;68(7):1094-9. Epub 2008 Nov 25. Starting on methotrexate 15 mg/week orally, escalating with 5 mg/month to 25-30 mg/week, or the highest tolerable dose, with a subsequent switch to subcutaneous administration in the case of an insufficient response, seems to be the optimal evidence-based dosing and routing recommendation for methotrexate in RA.
Vo Kevin H, Waddell James Aubrey, Suda Katie J. Rapid Development of Infusion-Related Severe **Hypotension During Rituximab** Therapy. Articles Ahead of Print published on 1 May 2011, DOI 10.1345/aph.1P733. Ann Pharmacother ;45:e29.
Vriezekolk JE, van Lankveld WG, Geenen R, et al. Longitudinal association between **coping and psychological distress** in rheumatoid arthritis: a systematic review. Ann Rheum Dis. 2011 Jul;70(7):1243-50.
Vroom F, et al. Disease-modifying antirheumatic drugs in **pregnancy**: current status and implications for the future. Drug Saf. 2006;29(10):845-63.
Wasko MC, Hubert HB, Lingala VB, et al. **Hydroxychloroquine and risk of diabetes** in patients with rheumatoid arthritis. JAMA. 2007 Jul 11;298(2):187-93.
Wassenberg S, Rau R, Steinfeld P, et al. Very **low-dose prednisolone** in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2005 Nov;52(11):3371-80.
Wasserman AM. **Diagnosis and management of rheumatoid arthritis**. Am Fam Physician. 2011 Dec 1;84(11):1245-52.
Weiss-Smith S, Deshpande G, Chung S, et al. The **FDA drug safety surveillance program: adverse event reporting** trends. Arch Intern Med 2011;171:591-3. The drugs most frequently cited were biologic agents etanercept, adalimumab and infliximab (the first, third and fourth most frequently reported suspect drugs).
Wegener's Granulomatosis Etanercept Trial (**WGET**) Research Group. **Etanercept** plus standard therapy for **Wegener's** granulomatosis. N Engl J Med. 2005 Jan 27;352(4):351-61. (Stone JH, et al. Solid malignancies among patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 2006 May;54(5):1608-18.)
Weinblatt ME, Kremer JM, et al. A trial of **etanercept**, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis **receiving methotrexate**. N Engl J Med. 1999 Jan 28;340(4):253-9.
Weinblatt ME, et al. Long term efficacy and safety of **adalimumab plus methotrexate** in patients with rheumatoid arthritis: **ARMADA** 4 year extended study. Ann Rheum Dis. 2006 Jun;65(6):753-9. Epub 2005 Nov 24.
Weinblatt ME, et al.. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45. Erratum in: Arthritis Rheum. 2003 Mar;48(3):855. Arthritis Rheum. 2004 Mar-Apr;22(2):144.
Weinblatt ME, et al. Selective co-stimulation modulation using **abatacept** in patients with active rheumatoid arthritis while receiving etanercept: a randomized clinical trial. Ann Rheum Dis. 2006 Aug 25; [Epub ahead of print]
Weinblatt M, et al. Safety of the selective costimulation modulator **abatacept** in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006 Aug 31;54(9):2807-2816 [Epub ahead of print] Abatacept in combination with synthetic DMARDs was well tolerated and improved physical function and physician- and patient-reported disease outcomes. However, abatacept in combination with biologic background therapies was associated with an increase in the rate of serious adverse events. Therefore, abatacept is not recommended for use in combination with biologic therapy.
Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. An **oral spleen tyrosine kinase (Syk) inhibitor** for rheumatoid arthritis. N Engl J Med. 2010 Sep 30;363(14):1303-12.
Welsh P, Peters MJ, Sattar N. **Vitamin D** in rheumatoid arthritis: A magic bullet or a mirage? The need to improve the evidence base prior to calls for supplementation. Arthritis Rheum. 2011 Mar 11. doi: 10.1002/art.30341.
Westhovens R, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: A large, randomized,placebo-controlled trial. Arthritis Rheum. 2006 Mar 29;54(4):1075-1086 [Epub ahead of print] CONCLUSION: The risk of serious infections in patients receiving the approved infliximab dose of 3 mg/kg plus MTX was similar to that in patients receiving MTX alone. Patients receiving the unapproved induction regimen of 10 mg/kg infliximab plus MTX followed by a 10 mg/kg maintenance regimen had an increased risk of serious infections through week 22.
Westlake SL, Colebatch AN, Baird J, et al.. The effect of **methotrexate on cardiovascular disease** in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford). 2009 Nov 27. [Epub ahead of print]
Whiting Penny F., Smidt Nynke, Sterne Jonathan A.C., Et al. Systematic Review: Accuracy of **Anti–Citrullinated Peptide Antibodies** for Diagnosing Rheumatoid Arthritis. *Ann Intern Med* April 6, 2010 152:456-464.
Whittle SL, Richards BL, Husni E, et al. **Opioid therapy** for treating rheumatoid arthritis pain. Cochrane Database Syst Rev. 2011 Nov 9;11:CD003113. There is limited evidence that weak oral opioids may be effective analgesics for some patients with RA, but adverse effects are common and may offset the benefits of this class of medications.
Wolbink GJ, et al. Development of **antiinfliximab antibodies** and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):711-5.
Woo P, Southwood TR, et al. Randomized, placebo-controlled, crossover trial of low-dose oral **methotrexate** in **children** with extended oligoarticular or systemic arthritis. Arthritis Rheum. 2000 Aug;43(8):1849-57.
Wong SP, Chu CM, Kan CH, Tsui HS, Ng WL. Successful treatment of leflunomide-induced acute pneumonitis with **cholestyramine** wash-out therapy. J Clin Rheumatol. 2009 Dec;15(8):389-92.
Yazici Y, Curtis JR, Ince A, et al. Efficacy of **tocilizumab** in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012 Feb;71(2):198-205.
Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of **tocilizumab** in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008; 371: 998–1006.
Young JD, McGwire BS. **Infliximab** and reactivation of **cerebral toxoplasmosis**. N Engl J Med. 2005 Oct 6;353(14):1530-1; discussion 1530-1.
Zink A, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: Comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006 Oct 30;54(11):3399-3407 [Epub ahead of print] Only 21-33% of the patients in the RABBIT register would have been eligible for the major trials.
Zochling J, van der Heijde D, Burgos-Vargas R, et al. ASAS/EULAR recommendations for the management of **ankylosing spondylitis**. Ann Rheum Dis 2006; 65: 442–52.
Zulian F, Martini G, Vallongo C, et al. **Methotrexate in juvenile localized scleroderma**: A randomised, double-blind, placebo-controlled trial. Arthritis Rheum. 2011 Jan 28.

TOP

See also: Sexual Dysfunction Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Sexual-Dysfx-Drugs-Overview.pdf

Erectile Dysfunction Comparison Chart (ED) Treatment Chart

[1] Fazio L, Brock G. Erectile dysfunction: management update. CMAJ. **2004** Apr 27;170(9):1429-37.
[2] Therapeutic Choices 5rd Edition, 2007
[3] Micromedex 2011
[4] Basu A, Ryder RE. New treatment options for erectile dysfunction in patients with diabetes mellitus. Drugs. 2004;64(23):2667-88.
[5] Anderson PC, Gommersall L, Hayne D, Arya M, Patel HR. New phosphodiesterase inhibitors in the treatment of erectile dysfunction. Expert Opin Pharmacother. 2004 Nov;5(11):2241-9.
[6] Viera AJ, Clenney TL, et al. Newer pharmacologic alternatives for erectile dysfunction. Am Fam Physician. 1999 Sep 15;60(4):1159-66, 1169, 1172. Review. Erratum in: Am Fam Physician 2000 Apr 15;61(8):2344.
[7] Montague DK, Barada JH, Belker AM, Levine LA, Nadig PW, Roehrborn CG, Sharlip ID, Bennett AH. Clinical guidelines panel on erectile dysfunction: summary report on the treatment of organic erectile dysfunction. The American Urological Association. J Urol. 1996 Dec;156(6):2007-11.
[8] **Canadian** Urological Association Guidelines Committee. Erectile dysfunction practice guidelines. Can J Urol. **2002** Aug;9(4):1583-7. **2006 Guidelines**: http://www.cua.org/guidelines/ed_2006_en.asp
[9] Briggs GG, Freeman RK, Sumner JY. Drugs in **Pregnancy** and Lactation **9th Edition**. Williams & Wilkins, Baltimore, 2011.
[10] Fink HA, Mac Donald R, Rutks IR, Nelson DB, Wilt TJ. Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2002 Jun 24;162(12):1349-60.
[11] Carson CC, et al. Erectile response with vardenafil in sildenafil nonresponders: a multicentre, double-blind, 12-week, flexible-dose, placebo-controlled erectile dysfunction clinical trial. BJU Int. 2004 Dec;94(9):1301-9.
[12] Raina R, Lakin MM, Agarwal A, Sharma R, et a.. Long-term effect of sildenafil citrate on erectile dysfunction after radical **prostatectomy**: 3-year follow-up. Urology. 2003 Jul;62(1):110-5.
[13] Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate Therapy for Pulmonary Arterial Hypertension. N Engl J Med 2005;353:2148-57.(InfoPOEMs: Sildenafil improves the 6-minute walking distance by approximately 15% & leads to an improvement in functional status for between 28% & 42% of patients with pulmonary arterial hypertension (number needed to treat = 2.5 - 4). It is reasonable to begin with 20 mg TID & only increase that dose if the drug is well tolerated & there is no clear response. (LOE = 1b))
[14] Fries R, Shariat K, von Wilmowsky H, Bohm M. Sildenafil in the treatment of **Raynaud's phenomenon** resistant to vasodilatory therapy. Circulation. 2005 Nov 8;112(19):2980-5.
[15] Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol. 2002 Oct;168(4 Pt 1):1332-6.
[16] Tadalafil (cialis) for erectile dysfunction. Med Lett Drugs Ther. 2003 Dec 22;45(1172):101-2.
Arif SA, Poon H. Tadalafil: A Long-Acting Phosphodiesterase-5 Inhibitor for the Treatment of **Pulmonary Arterial Hypertension**. Clin Ther. 2011 Jul 13
[17] Crowe SM, Streetman DS. Vardenafil treatment for erectile dysfunction. Ann Pharmacother. 2004 Jan;38(1):77-85.
[18] Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. Drugs. 2003;63(23):2673-703.
[19] Hellstrom WJ, Gittelman M, et al. Vardenafil Study Group. Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. Urology. 2003 Apr;61(4 Suppl 1):8-14.
[20] Stark S, Sachse R, Liedl T, Hensen J, et al. Vardenafil increases penile rigidity and tumescence in men with erectile dysfunction after a single oral dose. Eur Urol. 2001 Aug;40(2):181-8; discussion 189-90.
[21] Goldstein I, Young JM, et al. Vardenafil Diabetes Study Group. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care. 2003 Mar;26(3):777-83.
[22] Brock G, Nehra A, Lipshultz LI, Karlin GS, et al. Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic **prostatectomy**. J Urol. 2003 Oct;170(4 Pt 1):1278-83.
[23] Markou S, Perimenis P, Gyftopoulos K, Athanasopoulos A, Barbalias G. Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports. Int J Impot Res. 2004 Dec;16(6):470-8.
[24] Vardenafil (Levitra) for erectile dysfunction. Med Lett Drugs Ther. 2003 Sep 29;45(1166):77-8.
[25] Valiquette L, et al.; Vardenafil Study Group. Sustained efficacy and safety of vardenafil for treatment of erectile dysfunction: a randomized, double-blind, placebo-controlled study. Mayo Clin Proc. 2005 Oct;80(10):1291-7.
[26] van Ahlen H, Wahle K, Kupper W, Yassin A, Reblin T, Neureither M. Safety and efficacy of vardenafil, a selective phosphodiesterase 5 inhibitor, in patients with erectile dysfunction and arterial hypertension treated with multiple antihypertensives. J Sex Med. 2005;2:856-864.
[27] Viagra and Loss of Vision. Medical Lett Drugs Ther. 2005 June 20;47(1211):49. FDA July/05 http://www.fda.gov/bbs/topics/NEWS/2005/NEW01201.html ; Health Canada July/05 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_83_e.html June/06 (**5CDN cases as of Oct/05**) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/cialis_levitra_viagra_hpc-cps_e.html
[28] Raina R, Agarwal A, Ausmundson S, et al. Long-term efficacy and compliance of MUSE for erectile dysfunction following radical **prostatectomy**: SHIM (IIEF-5) analysis. Int J Impot Res. 2005 Feb;17(1):86-90.
[29] Steidle C, Padma-Nathan H, Salem S, Tayse N, et al. Topical alprostadil cream for the treatment of erectile dysfunction: a combined analysis of the phase II program. Urology. 2002 Dec;60(6):1077-82.
[30] Sommer F, Engelmann U. Future options for combination therapy in the management of erectile dysfunction in older men. Drugs Aging. 2004;21(9):555-64.
[31] Jaffe JS, Antell MR, Greenstein M, Ginsberg PC, Mydlo JH, Harkaway RC. Use of intraurethral alprostadil in patients not responding to sildenafil citrate. Urology. 2004 May;63(5):951-4.
[32] Urciuoli R, Cantisani TA, CarliniI M, Giuglietti M, Botti FM. Prostaglandin E1 for treatment of erectile dysfunction. Cochrane Database Syst Rev. 2004;(2):CD001784.
[33] Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. J Urol. 2000 Aug;164(2):371-5.
[34] Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. J Urol. 1998 Feb;159(2):433-6.
[35] Milbank AJ, Montague DK. Surgical management of erectile dysfunction. Endocrine. 2004 Mar-Apr;23(2-3):161-5.
[36] Erectile Dysfuntion Guideline Update Panel. The management of ED: an Update. **American** Urological Association, **2005**. (Updated **2006**) http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=ed
[37] Barada James. Clinical Perspectives on ED. Medscape Conference Coverage – International Society for Sexual and Impotence Research 11th World Congress, 2005
[38] Basson R. Chapter 78: Male Sexual Dysfunction. Therapeutic Choices. CPhA; 2003.
[39] Wespes E et al. Guidelines on Erectile Dysfunction. European Urology 2002; 41:1-5.
[40] Brock GB et al. Efficacy and safety of tadalafil for treatment of erectile dysfunction: results of integrated analysis. J Urol 2002;168:1332-36.
[41] Anderson P et al. New phosphodiesterases inhibitors in the treatment of erectile dysfunction. Expert Opin Pharmacother 2004;5(11):2241-49.
[42]

Apomorphine (CR sublingual tabs) **ApoKyn** (USA)	Centrally acting agent stimulates dopamine sites in the hypothalamus C	SE: nausea (↓with time, CR SL tabs);headache, dizziness, sedation, yawning Not affected by food or alcohol	Onset <30min Peak ~1h Duration ~1-2h Safe with nitrates so may be preferred in select cardiac patients Can be used in combination with PDE5 inhibitors for increased effect Limited efficacy compared to PDE5 inhibitors generally [39]	2-3mg 6mg	

[43] Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? Drugs. 2005;65(12):1621-50.

TOP

Additional sources:

Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function **following treatment for prostate cancer**. JAMA. 2011;306(11):1205-1214.

Archer, Stephen L., Michelakis, Evangelos D. Phosphodiesterase Type 5 Inhibitors for **Pulmonary Arterial Hypertension**. N Engl J Med 2009 361: 1864-1871.

Arif SA, Poon H. Tadalafil: A Long-Acting Phosphodiesterase-5 Inhibitor for the Treatment of **Pulmonary Arterial Hypertension**. Clin Ther. 2011 Jul 13

Badesch DB, Hill NS, Burgess G, et al. SUPER Study Group. Sildenafil for **pulmonary arterial hypertension** associated with connective tissue disease. J Rheumatol. 2007 Dec;34(12):2417-22. Epub 2007 Nov 1.

Barst RJ, et al. A randomized, double-blind,placebo-controlled, dose-ranging study of oral **sildenafil** citrate in treatment-naive children with **pulmonary arterial hypertension**. Circulation. 2012 Jan 17;125(2):324-34.

Basson R. Clinical practice. Sexual desire and arousal disorders in **women**. N Engl J Med. 2006 Apr 6;354(14):1497-506.

Baumhakel M, Schlimmer N, Kratz M, et al. **Cardiovascular risk, drugs and erectile function** - a systematic analysis. Int J Clin Pract. 2011 Mar;65(3):289-98. doi: 10.1111/j.1742-1241.2010.02563.x.

Blum A. Treating **heart failure** with sildenafil. Congest Heart Fail. 2009 Jul-Aug;15(4):181-5.

Böhm M, Baumhäkel M, Teo K, et al. for the **ONTARGET/TRANSCEND** Erectile Dysfunction Substudy Investigators. Erectile Dysfunction Predicts Cardiovascular Events in High-Risk Patients Receiving Telmisartan, Ramipril, or Both. The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. Circulation. 2010 Mar 15.

Burton TD, Liday C. The comparison of combination **SSRI and PDE-5 inhibitor** therapy to SSRI monotherapy in men with **premature ejaculation**. Ann Pharmacother. 2011 Jul;45(7-8):1000-4.

Carson CC 3rd. **Cardiac safety** in clinical trials of phosphodiesterase 5 inhibitors. Am J Cardiol. 2005 Dec 26;96(12B):37M-41M. Epub 2005 Dec 5.

Chiurlia E, D'Amico R, Ratti C, et al. Subclinical coronary artery **atherosclerosis** in patients with erectile dysfunction. J Am Coll Cardiol. 2005 Oct 18;46(8):1503-6. Epub 2005 Sep 28.

Chong J, Poole P, Leung B, Black PN. Phosphodiesterase 4 inhibitors for **chronic obstructive pulmonary disease**. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002309. DOI: 10.1002/14651858.CD002309.pub3. In people with COPD, PDE4 inhibitors offered benefit over placebo in improving lung function and reducing likelihood of exacerbations, however, they had little impact on quality of life or symptoms. Gastrointestinal adverse effects and weight loss were common.

Cordell WH, Maturi RK, et al.; ERG Testing During Chronic PDE5 Inhibitor Administration (ERG-PDE5i) Consortium. **Retinal effects** of 6 months of daily use of tadalafil or sildenafil. Arch Ophthalmol. 2009 Apr;127(4):367-73. No abnormalities in ERG or visual function and no treatment-related findings suggestive of drug toxicity are associated with daily administration of tadalafil or sildenafil for 6 months.

De Rose AF, et al. Combined oral therapy with **sildenafil and doxazosin** for the treatment of non-organic erectile dysfunction refractory to sildenafil monotherapy. Int J Impot Res. 2002 Feb;14(1):50-3.

Dimitriadis F, Tsambalas S, Tsounapi P, et al. Effects of **phosphodiesterase-5 inhibitors** on **Leydig cell secretory** function in oligoasthenospermic infertile men: a randomized trial. BJU Int. 2010 Feb 22.

Do C, Huyghe E, Lapeyre-Mestre M, et al. **Statins** and Erectile Dysfunction: Results of a Case/Non-Case Study using the French Pharmacovigilance System Database. Drug Saf. 2009;32(7):591-7. doi: 10.2165/00002018-200932070-00005. Despite some methodological limitations, the present study suggests that statins may induce or worsen ED in accordance with other data.

Doggrell SA. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. Expert Opin Pharmacother. 2005 Jan;6(1):75-84.

Dowswell G, Ismail T, Greenfield S, Clifford S, Hancock B, Wilson S. Men's experience of **erectile dysfunction after treatment for colorectal cancer**: qualitative interview study. BMJ 2011;343:d5824.

Drug-induced Male Sexual Dysfunction. Pharmacist's Letter Sept 2006.

Fava M, et al. Efficacy and safety of sildenafil in men with **serotonergic antidepressant-associated erectile dysfunction**: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2006 Feb;67(2):240-6.

FDA May 2007 FDA chemical analysis revealed that **Energy Max** contains thione analog of sildenafil, a substance with a structure similar to sildenafil, the active ingredient in Viagra, an FDA-approved drug for ED.Substances like this are called analogs because they have a structure similar to another drug and may cause similar side effects and drug interactions. **True Man** contains a thione analog of sildenafil or piperadino vardenafil, an analog of vardenafil, the active ingredient in Levitra, another FDA-approved prescription drug for ED. Neither the thione analog of sildenafil nor piperadino vardenafil are components of approved drug products.

FDA: Sept 21, 2007 -- TWC Global LLC, Inc., issued nationwide recall of **Axcil** and **Desirin**, both marketed as dietary supplements, because they contain potentially harmful, undeclared ingredients. FDA laboratory analysis of **Axcil and Desirin** found that the lot of 02B07 contained 3mg/g of sildenafil, the active ingredient of a FDA approved drug used for erectile dysfunction (ED).

FDA Feb/08 Palo Alto Labs and FDA notified consumers and healthcare professionals of a voluntary nationwide recall of two dietary supplements, **Aspire36** and **Aspire Lite**. The products were recalled because they were found to contain Aildenafil in trace amounts and Dimethyl sildenafil thione, an analog of Sildenafil, a drug used to treat erectile dysfunction.

FDA May/08 The U.S. Food and Drug Administration is advising consumers not to purchase or use "**Blue Steel**" or "**Hero**" products, marketed nationally as dietary supplements, because these products contain undeclared ingredients similar to sildenafil.

FDA May/08 is requesting that the manufacturer of **Xiadafil** — an "all natural" dietary supplement sold to treat erectile dysfunction — recall all its stock from natural food stores & discontinue marketing it on the Web since it contains an analog of sildenafil.

FDA May/08 notified consumers and healthcare professionals that supplement products sold under the brand name of **Viril-ity Power** (VIP) Tablets is being recalled because one lot was found to contain a potentially harmful undeclared ingredient, hydroxyhomosildenafil, an analog of sildenafil.

FDA July/08 Jack Distribution, LLC issued a voluntary nationwide recall of selected lots of **Rize 2 The Occasion Capsules** and **Rose 4 Her Capsules**, marketed as dietary supplements. The products were recalled because certain lots contained thiomethisosildenafil, an undeclared analog of sildenafil, a FDA-approved drug used for Erectile Dysfunction.

FDA July/08 not to buy or use **Viapro** 375mg Capsules because one lot of the product was found to contain a potentially harmful undeclared ingredient, thio-methisosildenafil, an analog of sildenafil.

FDA Aug/08 chemical analysis of **Xiadafil VIP** tablet lots 6K029 and 6K029-SEI found that the product contained an undeclared ingredient, hydroxyhomosildenafil

FDA Mar/09- Bodee LLC and FDA notified consumers and healthcare professionals of a nationwide recall of all the company's supplement product sold under the name **Zencore Plus**. FDA lab analysis of Zencore Plus samples found the product contains benzamidenafil, an undeclared drug product and a PDE5 inhibitor.

FDA Apr/09 Nature & Health Co. and FDA notified healthcare professionals of a recall of a supplement product, **Libimax**. FDA analysis found the product contains tadalafil.

FDA July/09 and Haloteco notified healthcare professionals and consumers of a nationwide voluntary recall of Libipower Plus. Lab analysis of **Libipower Plus** samples were found to contain undeclared Tadalalafil.

FDA July/09 found **Steam** (Nutracoastal Trading LLC's dietary supplement) product contains sulfoaildenafil, an analog of sildenafil.

FDA Nov/09 notified consumers that **Stiff Nights**, a product sold as a dietary supplement, contains sulfoaildenafil, a chemical similar to sildenafil (Viagra).

FDA Nov/09 & RockHard Laboratories notified consumers that **RockHard Weekend**, a product sold as a dietary supplement, contains sulfoaildenafil, an analogue of sildenafil.

FDA Dec/09 warned that **Atlas Operations, Inc**. notified consumers of a nationwide recall of the company's dietary supplements for sexual enhancement. These products are sold as dietary supplements throughout the USA. FDA lab analyses found that the products tested from certain batches contain Sulfoaildenafil.

FDA Mar/10 & Natural Wellness notified consumers that **MasXtreme**, a product sold as a dietary supplement contains aildenafil close in structure to sildenafil and is expected to possess a similar pharmacological and adverse event profile as well as the drug phentolamine which is an alpha-adrenergic blocker.

FDA Apr/10 & Kanec USA notified healthcare professionals of a nationwide recall of **Stud Capsule For Men** [Lot #060607-01/060108-01, Exp 6-2013], after being informed by FDA that laboratory analysis of a sample found the product to be adulterated with sildenafil, an FDA approved drug.

FDA June/10 **Magic Power Coffee**: Product marketed as a dietary supplement for sexual enhancement contains the drug ingredient hydroxythiohomosildenafil.

FDA Aug/10 lab analysis of **Revivexxx Extra Strength** was found to contain undeclared tadalafil.

FDA Aug/10 notified Novacare LLC that certain products appear to contain sulfoaildenafil: **Stiff Nights, Aziffa, Size Matters, Erex, Mojo, Hard Drive, Eyeful, Red Magic, Straight Up, Zotrex, Monster Excyte, WOW, Xaitrex, Verect, Prolatis, Xytamax, Maxyte, Libidinal, OMG, OMG45, and Zilex (with Golden Spear) summers.**

FDA July/10 & Good Health, Inc. is conducting a voluntary recall after FDA lab analyses found that the product tested from certain batches of **Vialipro** contain Sulfoaildenafil.

FDA July/10 notified consumers that lab analysis of lots of ejaculoid **XXTREME** and **stimuloid II** found that the products, sold as dietary supplements, contain sulfoaildenafil

FDA Aug/10 had Lab analysis of **Mr. Magic** to contain hydroxythiohomosildenafil and sulfoaildenafil.

FDA Aug/10 analyzed **TimeOut** and determined that it contains hydroxythiohomosildenafil.

FDA Nov/10 ISSUE: Lab analysis has found **Duro Extend Capsules for Men** to contain Sulfoaidenafil, an analogue of Sildenafil

FDA Dec/10 warned consumers not to use **Man Up Now** capsules, marketed as a dietary supplement for sexual enhancement, because FDA analysis determined that the product contains sulfoaildenafil

FDA Dec/10 notified the public that testing determined that **RockHard Weekend** Lot Numbers 100159 and 100260 sold as blister packs, 3ct bottles and 8ct bottles & **Pandora** Lot Numbers 100378 sold as blister packs & **Passion Coffee**

TOP

analogue of sildenafil.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analysis confirmed that **Black Ant** contains sildenafil.

FDA Mar/11 ISSUE: FDA lab analysis of **X-Hero** found the product contains sulfosildenafil, the analogue of the active ingredient of an FDA-approved drug. In addition, FDA analysis of **Male Enhancer** sample found the product contains tadalafil.

FDA Apr/11 Lab analyses of **Best Enhancer** found that the products to contain Sulfoaildenafil.

FDA May/11 **Regenerect**: Recall - Undeclared Drug Ingredient of lab confirmed the presence of Sulfoaildenafil.

FDA June/11 lab analyses found Via **Xtreme Ultimate Sexual Enhancer Dietary** Supplement for Men to contain sulfoaildenafil methanesulfonate.

FDA Nov/11 lab analysis for Lot 10090571 found **Virility Max** to contain sulfoaildenafil.

FDA Feb/12 Healthy People Co. notified the public of a recall of the company's dietary supplements sold under the brand names Healthy People Co. FDA lab confirmed presence of Sibutramine & Tadalafil, making these products unapproved new drugs. (Mince Belle Dietary Supplement, PERFECT Men Dietary Supplement , EVERLAX Dietary Supplement, EVER Slim Dietary Supplement, Herbal Drink Acai-man Mangosteen Dietary Supplement, EVER SLIM Shake Mix Dietary Supplement)

FDA Feb/12 Regeneca, Inc. notifed the public of a nationwide recall of **RegenArouse**, Lot Number 130100. FDA lab analysis confirmed the presence of Tadalafil.

FDA Feb/12 is advising consumers not to purchase or use "**Hard Ten Days**," & "**Man King**" a product for sexual enhancement sold on various websites. FDA laboratory analysis confirmed that "Hard Ten Days" contains sildenafil

FDA Apr/12 laboratory analysis confirmed that "**France T253**" contains sildenafil.

FDA Apr/12 is advising consumers not to purchase or use "**X-Rock**," a product for sexual enhancement manufactured by CRM Laboratories and sold on various websites, including www.xrockme.com. FDA laboratory analysis confirmed that "X-Rock" contains sildenafil and hydroxythiohomosildenafil.

FDA Apr/12 laboratory analysis confirmed that "**Instant Hard Rod**" contains aminotadalafil. FDA laboratory analysis confirmed that "**ZenMaxx**" contains aminotadalafil. FDA laboratory analysis confirmed that "**RigiRx Plus**" contains aminotadalafil.

FDA May/12 is advising consumers not to purchase or use "**VMaxx Rx**," a product for sexual enhancement sold on various websites, including www.vmaxxrx.com. FDA laboratory analysis confirmed that "VMaxx Rx" contains the undeclared ingredient sulfoaildenafil. FDA is also advising consumers not to purchase or use "**Boost — Ultra Sexual Enhancement Formula**." This product is promoted and sold on various websites, includingwww.boostultra.biz. FDA laboratory analysis confirmed that "Boost—Ultra Sexual Enhancement Formula" contains sildenafil. FDA is also advising consumers not to purchase or use "**Firminite**," a product for sexual enhancement sold on various websites, including **www.firminite.com.** FDA laboratory analysis confirmed that "Firminite" contains tadalafil.

FDA May/12 West Coast Nutritionals, Ltd. is conducting a recall of all lots of their dietary supplements **Firminite, Extra Strength Instant Hot Rod, & Libidron** to the consumer. FDA lab analysis of Firminite was found to contain undeclared Tadalafil.

FDA May/12 is advising consumers not to purchase or use "**EreXite**," a product for sexual enhancement sold on various websites, including www.amazon.com. FDA laboratory analysis confirmed that "EreXite" contains tadalafil.

Galiè N, Ghofrani HA, Torbicki A, Barst RJ, et al.; Sildenafil Use in Pulmonary Arterial Hypertension (**SUPER**) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005 Nov 17;353(20):2148-57.

Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, et al.; on behalf of the Pulmonary Arterial Hypertension and Response to Tadalafil (**PHIRST**) Study Group. Tadalafil Therapy for Pulmonary Arterial Hypertension. Circulation. 2009 May 26. [Epub ahead of print]. In patients with **pulmonary arterial hypertension, tadalafil 40 mg** was well tolerated and improved exercise capacity and quality of life measures and reduced clinical worsening.

Gazzaruso C, Solerte SB, Pujia A, et al. Erectile dysfunction as a **predictor of cardiovascular events** and death in diabetic patients with angiographically proven asymptomatic coronary artery disease a potential protective role for statins and 5-phosphodiesterase inhibitors. J Am Coll Cardiol. 2008 May 27;51(21):2040-4.

Giannetta E, et al. Chronic Inhibition of Cyclic GMP Phosphodiesterase 5A **Improves Diabetic Cardiomyopathy**: A Randomized, Controlled Clinical Trial using Magnetic Resonance Imaging with Myocardial Tagging. Circulation. 2012 Apr 11.

Gleason JM, Slezak JM, Jung H, et al. Regular Nonsteroidal Anti-Inflammatory Drug (**NSAIDs**) Use and Erectile Dysfunction. J Urol. 2011 Feb 18.

Gopalakrishnan R, et al. **Sildenafil** in the treatment of antipsychotic-induced erectile dysfunction: a randomized, double-blind, placebo-controlled, flexible-dose,two-way crossover trial.Am J Psychiatry.2006Mar;163(3):494-9.

Grover SA, Lowensteyn I, Kaouache M, et al. The prevalence of erectile dysfunction in the primary care setting. Importance of risk factors for diabetes and vascular disease. Arch Intern Med 2006; 166:213-219.

Giuliano F, et al.; Vardenafil Study Group. Efficacy and safety of vardenafil in men with erectile dysfunction caused by **spinal cord injury**. Neurology. 2006 Jan 24;66(2):210-6.

Giuliano F, Sanchez-Ramos A, Lochner-Ernst D, et al. Efficacy and Safety of Tadalafil in Men With Erectile Dysfunction Following **Spinal Cord Injury**. Arch Neurol. 2007 Sep 10; [Epub ahead of print] Tadalafil (10 mg and 20 mg) improved erectile function and was well tolerated by men with ED secondary to traumatic SCI.

Goldstein I, Lue TF, Padma-Nathan H, et al.; Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998;338:1397-404. (**low 25mg dose effective**)

Guazzi M, Vicenzi M, Arena R, et al. **Pulmonary hypertension** in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition (sildenafil) in a 1-year study. Circulation. 2011 Jul 12;124(2):164-74.

Gupta BP, Murad MH, Clifton MM, et al. The effect of **lifestyle modification and cardiovascular risk factor reduction** on erectile dysfunction: a systematic review and meta-analysis [Sept 12, 2011]. Arch Intern Med. 2011

Health Canada Jan/06 Natural health product **Libidfit** may pose health risks (promoted for sexual enhancement and erectile dysfunction, but contains an undeclared amount of a pharmaceutical ingredient similar to sildenafil) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_02_e.html

Health Canada May/06 is warning consumers not to use the product **Nasutra** because it has been found to contain the undeclared ingredient sildenafil (chemical name for Viagra) that could lead to serious health risks, especially for patients with existing medical conditions such as heart problems, those who may be taking heart medications, or those who may be at risk for strokes.

Health Canada Feb/07 is advising consumers not to use the following product listed in the table below due to concerns about possible side-effects. More info **Power 58; Platinum Power 58; Ehanix; Jolex; Onyo; Deguozonghengtianxia** because they contained acetildenafil. Acetildenafil is an analogue of sildenafil, a prescription medication indicated for treatment of erectile dysfunction.

Health Canada Mar/07 is warning consumers not to use the unauthorized natural health product **XOX For Men**, because it contains an undeclared pharmaceutical ingredient, tadalafil, an ingredient found in the prescription drug Cialis. The use of XOX For Men could pose serious health risks, especially for patients with existing medical conditions such as heart problems, those taking heart medication, or those at risk of stroke.

Health Canada Mar/07 is warning consumers not to use the unauthorized product **Vigorect** Oral Gel Shooter, because it contains an undeclared drug substance tadalafil, which should only be available by prescription.

Health Canada Apr/07 is warning consumers from the United States FDA found **V.MAX and Rhino Max (Rhino V Max) to contain undeclared amounts of aminotadalafil**, an analogue of tadalafil, used to treat erectile dysfunction.

Health Canada May/07 is warning consumers **Urat Madu** capsules are marketed for the treatment of erectile dysfunction. The product is adulterated with **sildenafil**, a prescription drug that has been associated with serious side effects including sudden vision loss, penile tissue damage and urinary tract infection.

Health Canada May/07 is advising consumers that **HS Joy of Love** product is marketed as a dietary supplement and was found to contain piperadino **vardenafil**.

Health Canada May/07 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: **Power 58 Extra, Platinum Power 58 Extra, Enhanix New Extra Men's Formula, Valentino, King Power Oral Solution, and Stretch Up** Capsules are marketed as treatments for erectile dysfunction. The products contain analogues of **sildenafil** and **vardenafil**, which are prescription drugs used for the treatment of erectile dysfunction.

Health Canada June/07 is warning consumers not to use the product **Encore Tabs for Men**, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.

Health Canada July/07 is warning consumers not to use **Zencore** Tabs, a product advertised as a dietary supplement for sexual enhancement, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.

Health Canada July/07 & the US Food and Drug Administration (FDA) found ***Liviro3*** to contain tadalafil, a prescription drug that should only be taken under the guidance of a health professional.

Health Canada Aug/07 via Medsafe, the New Zealand health regulatory authority, advised the public not to use the products **Darling Capsules, Dali Capsules, Spanish Fly** Capsules, and an unnamed product, because they were found to contain sildenafil.

Health Canada Aug/07 Consumers who use **Excite for women or Ultimates for men** may be at risk of serious side effects similar to those associated with sildenafil.

Health Canada Sept/07 is advising consumers not to use **Satis 60 Hours Ever Lasting Formula** is used for the treatment of erectile dysfunction/sexual enhancement. It was found to contain piperidenafil an analogue of vardenafil.. **True Man** and **Energy Max** are used as sexual enhancement/ erectile dysfunction products and were found to contain an analogue of sildenafil or vardenafil.

Health Canada Sept/07 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: **Top Gun for Men Herbal Extracts** has been found to contain a substance similar to tadalafil. **Oyster Plus** has been found to contain tadalafil. **Deguozhanjiang** contains sildenafil and tadalafil, prescription drugs used for the treatment of erectile dysfunction. **Chongcaoliubian Jiaonang** and **Santi Scalper Penis Erection** Capsule contain sildenafil.

Health Canada Nov/07 is advising consumers not to use **Axcil** and **Desirin**, are promoted as natural sexual enhancement/ erectile dysfunction products. Consumers are warned not to use Axcil and Desirin because both products were found to contain the prescription drug sildenafil.

Health Canada Mar/08 is warning consumers not to use **ADAM**, an unauthorized product that contains an undeclared pharmaceutical ingredient similar to the prescription drug sildenafil.

Health Canada Mar/08 is warning consumers not to use **Libidus**, an unauthorized product promoted on the web site of the manufacturer for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the undeclared prescription drug sildenafil.

TOP

Health Canada April//08 warns that Singapore's Health Sciences Authority (HSA) advised the public not to use the product **Power 1 Walnut**, because it was found to contain the prescription drugs sildenafil and glibenclamide

Health Canada April//08 is advising consumers not to use 2 foreign health products, **Aspire 36** and **Aspire Lite**, because they were found to contain undeclared sildenafil analogues.

Health Canada April/08 is warning consumers not to use **Vigoureux**, an unauthorized product promoted for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the prescription drug sildenafil

Health Canada April/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **Tian Li** was found to contain tadalafil and hydroxyhomosildenafil. Xian Zhi Wei II was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.

Health Canada May/08 is advising consumers not to use **vpxl No1** Dietary Supplement for Men was found to contain tadalafil

Health Canada May/08 is warning consumers not to use **Desire**, an unauthorized product promoted to enhance male sexual performance as this product may pose serious health risks in certain patients. Lot 0070263 of the product was found to contain the prescription drug phentolamine.

Health Canada June/08 **Nangen Zengzhangsu** (may also be known as Nangen or Nangeng), Sanbianwan, Jiu Bian Wang, Tian Huang Gu Shen Dan, Zui Xian Dan Gong Shi Zi, and Power Up. The Hong Kong Department of Health has warned consumers not to use these herbal/proprietary Chinese medicine products promoted for erectile dysfunction because they have been found to contain sildenafil and/or glibenclamide.

Health Canada June/08 **Zhong Hua Niu Bian**. Zhong Hua Niu Bian is an herbal/proprietary Chinese medicine product promoted for erectile dysfunction. Singapore's Health Sciences Authority has warned against the use of this product because it has been found to contain sildenafil, glibenclamide, tadalafil and sibutramine

Health Canada July/08 Foreign Product Alerts: **Super Shangai,Strong Testis, Shangai Ultra, Shangai Ultra X, Lady Shangai, Shangai Regular (also known as Shangai Chaojimengnan), Actra-Sx, An unknown product containing the plant Lycium barbarum L., Adam Free, NaturalUp, Erextra, Yilishen, Blue Steel, Hero, & Naturalē Super Plus.** These products have been found to contain sildenafil or an unapproved substance similar to sildenafil.

Health Canada July/08 is advising consumers not to use foreign health products due to concerns about possible side-effects: Wodibo. **Wodibo** is promoted as an all-natural Chinese potency-enhancing product for the treatment of erectile dysfunction. The Danish Medicines Agency has warned against the use of Wodibo because it was found to contain sildenafil and tadalafil, prescription drugs authorized for treatment of erectile dysfunction. **Viril-Ity-Power** (VIP) Tabs. The U.S. Food and Drug Administration has warned consumers not to use Viril-Ity-Power (VIP) Tabs because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil.

Health Canada Aug/08 is warning consumers not to use **Rize 2 The Occasion** capsules (Rize2), an unauthorized product promoted for the treatment of erectile dysfunction, because it may pose serious health risks. Rize 2 contains an undeclared pharmaceutical ingredient similar to the prescription drug sildenafil.

Health Canada Aug/08 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: **Oyster Extract** Caps. The Hong Kong Department of Health has recalled Oyster Extract Caps because they were found to contain an undeclared ingredient similar to the prescription drug sildenafil. **Xiadafil** VIP Tabs. At the request of the U.S. Food and Drug Administration, U.S. federal authorities seized all Xiadafil VIP Tabs sold in 8 tablet bottles (Lot #6K029) and blister cards of 2 tablets (Lot #6K029-SEI) because they were found to contain an undeclared ingredient similar to the prescription drug sildenafil. **Herb Vigour, Natural Vigour and China Vigour**. The Netherlands Health Care Inspectorate, the U.K. Medicines and Healthcare Products Regulatory Agency, and the Danish Medicines Agency has warned against the use of Herb Vigour, Natural Vigour and China Vigour because they were found to contain undeclared pharmaceutical ingredients used for the treatment of erectile dysfunction that should only be taken under the supervision of a health care professional.

Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Armstrong Natural Herbal Supplement, Enhanix New Extra Men's Formula, Power 58 Extra, and Platinum Power 58 Extra** were adulterated with tadalafil or unapproved substances with structures similar to tadalafil and vardenafil.

Health Canada Sep/08 is advising consumers not to use 3 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lover Liquid Nutriment Herbal Supplement and Onyo** because they were found to contain undeclared pharmaceutical ingredients. Lover Liquid Nutriment Herbal Supplement was found to contain sildenafil while Onyo was found to contain sildenafil, as well as unapproved substances with structures similar to sildenafil and vardenafil. The U.S. Food and Drug Administration warned consumers not to use the product **Rose 4 Her** because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil.

Health Canada Sep/08 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Dr. Life or Chong Cao Ju Wang** because they were found to contain undeclared pharmaceutical ingredients. Dr. Life contains an unauthorised substance similar in structure to tadalafil while Chong Cao Ju Wang contains sildenafil.

Health Canada Oct/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: Swissmedic warned consumers not to buy or use the product **Powertabs** because it contains an unauthorised substance similar in structure to sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Sweet Energizer Vitality** Candy because it was found to contain an unauthorised substance similar in structure to tadalafil.

Health Canada Oct/08 is warning consumers not to use **Eros Fire**, a product promoted to enhance sexual performance, as this product may pose serious health risks. The product was found to contain xanthoanthrafil (also known as benzamidenafil), which is not indicated on the label.

Health Canada Nov/08 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lu Quan** because it contains undeclared glibenclamide and sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine, and **Zhuang Yao Gu Shen** Capsule because it contains sildenafil.

Health Canada Nov/08 is warning consumers not to use **Firm Dose** and **Granite Rooster**, two products promoted to enhance male sexual performance, as these products may pose serious health risks. Firm Dose was found to contain an undeclared pharmaceutical ingredient similar to sildenafil, while the product Granite Rooster was found to contain an undeclared pharmaceutical ingredient similar to tadalafil.

Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains the undeclared prescription drug sibutramine.

Health Canada Mar/09 Foreign Product Alerts: 68 Weight Loss Products; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien; Relacore
http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php

Health Canada June/09 Foreign Product Alerts: **Jia Yi Jian** (undeclared sibutramine & tadalafil); **Zencore Plus** (undeclared benzamidenafil) & **Zhong Guo Shen Fang** (undeclared med like sildenafil).

Health Canada July/09 is warning that the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **XP Tongkat Ali Supreme** after it was found to contain undeclared tadalafil.

Health Canada Oct/09: **Dynasty Worldwide Jinglida So Young Formula**- The Singapore Health Sciences Authority (HSA) warned consumers to not buy or use since contained undeclared aminotadalafil.

STEAM lot#80214, 90260 -The U.S. FDA informed consumers of a voluntary manufacturer recall of two lots of STEAM after FDA testing found these lots to contain undeclared sulfoaildenafil (lot# 80214) & undeclared tadalafil (lot# 90260).

Syntrax Fyre (contained Yohimbine), **Kam Yuen Brand Wan Ying Yang Gan Wan (contained sildenafil)** - The Hong Kong Department of Health warned consumers not to buy or use these products.

Health Canada Nov/09 is warning consumers not to use Herblex "**Once More**"since it was found to contain sildenafil.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products advertised for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is advising consumers not to use the following foreign health products: 1. **Power-Plus P**: The Singapore Health Sciences Authority issued a recall notice for Power-Plus P (expiry date 03/03/2011) after it was found to contain undeclared tadalafil. 2. **Zeng Da Yan Shi Wan**: The Hong Kong Department of Health warned consumers not to buy or use after it was found to contain undeclared sildenafil.

Health Canada Jan/10 informs that Finish Food Safety Authority: **Full Contact Max Potency** contains thio-sildenafil and thio-homosildenafil; Singapore Health Sciences Authority: **M-Action** contains desmethylacetildenafil and acetilacid. U.S. FDA: **RockHard Weekend** contains sulfoaildenafil.

Health Canada Jan/10 is advising consumers not to use the unauthorized product "**Stiff Nights**" after the U.S Food and Drug Administration (FDA) found that this product contains an undeclared substance similar to the prescription drug sildenafil.

TOP

Health Canada Feb/10: **2H & 2D-** Hong Kong Department of Health (HKDH) warned consumers not to buy or use 2H & 2Dafter it was found to contain undeclared tadalafil. Products distributed by **Atlas Operations Inc**. The FDA informed consumers of a voluntary recall by Atlas Operations Inc. of certain lots of some products that were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil. **STRO Emperor** Capsules The Irish Medicines Board warned consumers not to buy or use STRO Emperor Capsules after it was found to contain undeclared tadalafil.

Health Canada Mar/10 is warning Canadians that an unapproved health product, **POWER-MAX** that contains sildenafil.

Health Canada May/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Man Power** The Hong Kong Department of Health warned consumers not to buy or use Man Power product after it was found to contain undeclared tadalafil.

Health Canada June/10 is warning Canadians that the unauthorized health products "**Vigofit**" and "**Once More**," which are promoted to enhance male sexual performance, have been seized by Health Canada inspectors from retail stores in Abbotsford and Surrey, British Columbia. These two products contain sildenafil.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) due to concerns about possible adverse reactions: 1. **Stud Capsule For Men** The U.S. FDA informed consumers of a voluntary recall of one lot (Lot #060607-01/060108-01 Exp 6-2013) after it was found to contain undeclared Sildenafil.

Health Canada July/10 is advising Canadians about "**UP Ultimate Performance for Men**", an unauthorized health product containing undeclared sildenafil.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume 1. **Atlas Operations Inc. expands its U.S. recall of over 30 sexual enhancement supplements** The U.S. FDA informed consumers of an expanded recall of certain lots of products after some were found to contain undeclared sulfoaildenafil. The products are being voluntarily recalled nationwide in the U.S. by the company Atlas Operations Inc. 2. **Stallion, SZM Formula for Men, Tomcat Ali and Volcanic** New Zealand's Medsafe warned consumers not to buy or use these four products after they were found to contain undeclared tadalafil. 3. **Vitalex for men and Vitalex for women** The U.S. FDA informed consumers that the *Vitalex*products were found to contain acetildenafil, which is an unauthorized substance similar to sildenafil.

Health Canada Aug/10 is advising **Magic Power Coffee** The U.S. FDA warned consumers not to buy or use Magic Power Coffee after it was found to contain undeclared hydroxythiohomosildenafil.

Health Canada Aug/10: "**SeXXX DRIVE**", promoted as a herbal supplement to enhance male sexual performance, was tested by Health Canada and found to contain undeclared hydroxyhomosildenafil.

Health Canada Aug/10 has seized the unauthorized sexual enhancement supplements "**Male Enhancement ExtenZe**" and "**Women ExtenZe**" imported and sold by the Happy Paradise Adult Store in Burnaby, British Columbia. The labels of each of these unauthorized products list the prescription ingredient pregnenolone and the controlled drug, DHEA dehydroepiandrosterone). The labels of the unauthorized "Male Enhancement ExtenZe Nutritional Supplements" list the ingredient yohimbe extract (bark).

Health Canada Sep/10 **E.O.D. Erection on Demand**" being promoted as a herbal to enhance male sexual performance, the product was tested by Health Canada and found to contain tadalafil.

Health Canada Sep/10 is advising consumers not to use : 1. **Golden aryuru, Baisheng wei ge, Zhonghua niubian, Ten ka dai 1 bou, Kuai gan bei zeng chao yue zi wo (Happy felling doubly increase [sic]), Ling tou lang, SkyFruit, Chu bi ho ken, Jinbolang, Suika Koso, Lov, I ka ou (2009 nen sin hoso) and/or I ka ou (saisinsui shutsu hoso)** The Japanese Ministry of Health, Labour and Welfare warned consumers not to buy or use the 12 products listed above because they were found to contain undeclared sildenafil and/or other unauthorized substances similar to sildenafil that may pose similar health risks (norhongdenafil, acetil acid, and tioqinapiperifil). 2. **Vialipro** The U.S. FDA informed consumers of a recall of certain lots of Vialipro after FDA tests found product samples to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. MasXtreme** contains undeclared aminotadalafil while the other (#911035) contains undeclared aildenafil and phentolamine **2. Mr. Magic Male Enhancer from Don Wands** contained hydroxythiohomosildenafil and sulfoaildenafil **3. So Hard for Men - Pulse8 for Women - The Rock - Tonic 66** contained the undeclared pharmaceutical substances tadalafil, sildenafil, and/or hydroxyhomosildenafil **4. TimeOut** contained undeclared hydroxythiohomosildenafil.

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 "**Durazest**" and "**Once More**": Certain lots of two male sex enhancement products recalled as they may pose serious health risks. Certain lots (listed below) of two health products promoted for male sexual enhancement, "Durazest for Men" and "Once More," have been voluntarily recalled by Natural Performance Products Ltd. Health Canada laboratory tests identified the presence of a chemical similar to tadalafil (nortadalafil) in one lot of each product.

Health Canada Dec/10 is informing Canadians that NorthRegentRx has begun to voluntarily recall its product, **ResurreXX** from the Canadian market. NorthRegentRx is requesting that wholesalers, distributors and retailers stop sale of this product since contained an undeclared substance "hydroxyhomosildenafil".

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Shaguar, Signature Signergy, VIGRX (green capsule), VIGRX (white capsule), VigRx, VigRX Plus** New Zealand's MedSafe warned consumers to not buy or use these products after they were found to contain undeclared sildenafil, hydroxyhomosildenafil, thiosildenafil, and/or tadalafil. .

Health Canada Feb/11 is advising consumers not to use the following foreign health products promoted for sexual enhancement due to the presence of unauthorized substances (PDE5 derivatives eg. sildenafil): **1. Aziffa, Erex, Eyeful, Hard Drive, Libidinal, Maxyte, Mojo, Monster Excyte, OMG, OMG45, Prolatis, Red Magic, Size Matters, Stiff Nights, Straight Up, Verect, WOW, Xaitrex, Xytamax, Zilex (with Golden Spear), Zotrex 2. Prolatis' Duro Extend Capsules For Men 3. Tiger King 4. Vigor-25, Man Up Now**

Health Canada Feb/11 is advising consumers not to use the following foreign health product **RockHard Weekend (lots 100159 and 100260 sold as blister packs, 3-count bottles and 8-count bottles)** The U.S. FDA informed consumers of a nationwide voluntary recall of certain lots (see above) of RockHard Weekend and Pandora after lab tests confirmed the products contain an unauthorized substance similar to sildenafil.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Nite Rider Maximum Sexual Enhancer for Men - STUD Capsule for Men:** The U.S. FDA informed consumers of a company recall of these products after they were found to contain undeclared sildenafil.

Health Canada May/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Gold Seagull Long Zhi Wan, Venergy** The Hong Kong Department of Health advised consumers not to buy or use these products after Gold Seagull Long Zhi Wan was found to contain undeclared glibenclamide, while Venergy was found to contain undeclared sildenafil. **2. Rock Hard Extreme, Passion Coffee** The U.S. FDA advised consumers not to buy or use these products after they were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada July/11 "**Man Up Now**" Removed From Sale at Delta and Surrey Stores: May Pose Serious Health Risks to Canadians, was removed from sale at "O! Behave" retail stores in Delta and Surrey, B.C. after Health Canada's testing identified undeclared sildenafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products. These products were also removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. {**Sildenafil: in BAOLONG Switzerland Rolex 168 Prolong Time, BAOLONG Yilishen, Black Gold, Herbal Viagra, "Jin Chong Chao – Golden Cordyceps", Lubiangaowansu, MAGNA-RX, MAXMAN II capsules, Shenrong dabuwan, Traditional Chinese Medicine Viagra, V100, VIGER, VigRX for Men, VINIX capsules, Wolf, "XiongBaTian", Zang Gong Mi Lian Nan Bao} & Zeng Bei Jiu Zhan-Tadalafil.**

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Black Ant** The U.S. Food and Drug Administration warned consumers to immediately stop using *Black Ant* after it was found to contain undeclared sildenafil at an amount three times the starting dosage for the approved prescription drug product. **2. Natural Vigra VIAGRA Tablets and Satibo Capsules** The Australian Therapeutic Goods Administration (TGA) advised consumers to stop using *Natural Vigra VIAGRA Tablets* after it was found to contain undeclared sildenafil, and *Satibo Capsules* after it was found to contain undeclared tadalafil and hydroxyhomosildenafil. **3. X-Hero and Male Enhancer** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *X-Hero* was found to contain undeclared sulfosildenafil while *Male Enhancer* was found to contain undeclared tadalafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products to include a new product, **Tibet Babao**, which was found to contain undeclared sildenafil, a prescription

TOP

dysfunction drug. This product and several others have been removed from sale at the **Happy Paradise Adult Store in Burnaby, B.C**.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **SXL Sexcellence sachets**- The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains an unauthorized drug (sulfosildenafil).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Maxidus capsules, Chao Jimengnan SuperPowerful Man tablets, Fu Yuan Chun capsules, and Qing Tian Zhu tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain prescription drugs (sildenafil, tadalafil) and/or unauthorized drugs (sulfohydroxyhomosildenafil, sulfosildenafil).

Health Canada Nov/11: An unauthorized health product, "**Stiff One Hard 169**" is being voluntarily recalled from the Canadian market after Health Canada's testing identified an undeclared prescription medication in the product (thiodimethylsildenafil, an undeclared substance similar to the prescription medication sildenafil).

Health Canada Dec/11 is advising "**Yanshiwang**", "**Jin Kong Fu**" and "**Chong Cao She Bian Zhuang Yang Dan**". These products were removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. These contained sildenafil.

Health Canada Jan/12 advises: **1. Get Stiff, Maxi Mize** New Zealand's Medsafe warned that these sexual enhancement products contain prescription drugs (tadalafil, vardenafil, yohimbine) and/or unauthorized drugs (hydroxyhomosildenafil, hydroxythiohomosildenafil). **2. Ying Da Wang tablets** The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains sildenafil.

Health Canada seized a variety of **Stiff4Ever** and **PurePillz** products from The Love Shop retail outlets located in Ontario. These products are unauthorized drugs and are considered potentially dangerous to the health and safety of Canadians. Health Canada tested the Stiff4Ever products, advertised as male sexual stimulants, and identified sildenafil. The labels of the PurePillz products (see below) state that they contain BZP and TFMPP.

Health Canada Mar/12 **Power-X**" has been removed from a Canadian retail location after Health Canada's testing identified undeclared thiodimethylsildenafil which is similar to the prescription medication sildenafil.

Health Canada May/12: Unauthorized health products, **"X-Rock", "Kaboom" and "One For Her"** have been removed from sale from various retail outlets in British Columbia and Saskatchewan. Health Canada's testing identified undeclared prescription drugs sildenafil and tadalafil, and an undeclared substance, hydroxythiohomosildenafil, which is similar to sildenafil.

Health Canada May/12 **1. AdvanceMen capsules; Miraculous Evil Root tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain either a prescription drug (sildenafil) or an unauthorized drug (sulfoaildenafil).

Health Canada June/12 **1. African Black Ant; France T253; Hard Ten Days; Man King; Stree Overlord** : The U.S. Food and Drug Administration warned that these sexual enhancement products contain prescription drugs (sildenafil. One product also contains tadalafil). **2. RegenArouse; RegenErect:** The U.S. Food and Drug Administration informed of a recall because these sexual enhancement products contain a prescription drug (tadalafil). **3. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil).

Hedelin H, Stroberg P. Treatment for Erectile Dysfunction Based on Patient-Reported Outcomes: To Every Man the PDE5 Inhibitor that He Finds Superior. **Drugs. 2005**;65(16):2245-51.

Heidelbaugh JJ. Management of **erectile** dysfunction. Am Fam Physician. 2010 Feb 1;81(3):305-12.

Herrick AL, van den Hoogen F, Gabrielli A, et al. Modified-release **sildenafil** reduces Raynaud's phenomenon attack frequency in limited **cutaneous systemic sclerosis**. Arthritis Rheum. 2011 Mar;63(3):775-82.

Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, Anstrom KJ, et al. A controlled trial of **sildenafil** in advanced **idiopathic pulmonary fibrosis**. N Engl J Med. 2010 Aug 12;363(7):620-8.

Jena, Anupam B. Goldman, Dana P. Kamdar, Amee et al. **Sexually Transmitted Diseases** Among Users of Erectile Dysfunction Drugs: Analysis of Claims Data. *Ann Intern Med* July 6, 2010 153:1-7; doi:10.1059/0003-4819-153-1-201007060-00003

Kao SL, Chan CL, Tan B, Lim CC, Dalan R, Gardner D, Pratt E, Lee M, Lee KO. An unusual outbreak of hypoglycemia. N Engl J Med. 2009 Feb 12;360(7):734-6. No abstract available. Hypoglycaemia outbreak linked to contamination of illegal **sexual-enhancement drugs with glyburide**.

Katz A, Katz A. **Erectile** dysfunction. CMAJ. 2010 Feb 8.

Kloner RA. Pharmacology and **Drug Interaction** Effects of the Phosphodiesterase 5 Inhibitors: Focus on alpha-Blocker Interactions. Am J Cardiol. 2005 Dec 26;96(12 Suppl 2):42-6. Epub 2005 Dec 5.

Köhler TS, Kim J, Feia K, et al. Prevalence of **androgen deficiency** in men with erectile dysfunction. Urology. 2008 Apr;71(4):693-7. Epub 2008 Mar 3. Androgen deficiency was quite common in men presenting with ED and correlated significantly with age, uncontrolled diabetes, hypercholesteremia, and anemia. Although additional prospective studies evaluating the effect of testosterone supplementation in this population are needed, clinicians, including urologists, should be keenly aware of the large overlap of patients with ED who might also have the entity, androgen deficiency in the aging male.

Kostis JB, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol. 2005 Jul 15;96(2):313-21.

Ledda A, Belcaro G, Cesarone MR, et al. Investigation of a complex plant extract for mild to moderate erectile dysfunction in a randomized, double-blind, placebo-controlled, parallel-arm study. BJU Int. 2010 Feb 22. Prelox, contains pine bark extract and the amino acid L-arginine aspartate; was given as two tablets of Prelox twice daily.

Levine GN, Steinke EE, Bakaeen FG, et al. **Sexual activity and cardiovascular disease**. A scientific statement from the American Heart Association (**AHA**). Circulation 2012. http://circ.ahajournals.org/content/early/2012/01/19/CIR.0b013e3182447787.full.pdf?sid=8d962f06-2506-473d-aaaf-5761032aed2b

Lindman BR et al. Effects of Phosphodiesterase Type 5 Inhibition on Systemic and Pulmonary Hemodynamics and Ventricular Function in Patients with Severe Symptomatic **Aortic Stenosis**. Circulation. 2012 Mar 25.

Ma RC, So WY, Yang X, et al.Erectile dysfunction **predicts coronary heart disease** in type 2 diabetes.J Am Coll Cardiol. 2008 May 27;51(21):2045-50.

Maggiorini M, et al. Both **tadalafil and dexamethasone** may reduce the incidence of **high-altitude pulmonary edema**: a randomized trial. Ann Intern Med. 2006 Oct 3;145(7):497-506.

McGwin G Jr, Vaphiades MS, Hall TA, Owsley C. **Non-arteritic anterior ischaemic optic neuropathy** and the treatment of erectile dysfunction. Br J Ophthalmol. 2006 Feb;90(2):154-7.

McGwin G Jr. Phosphodiesterase type 5 inhibitor use and **hearing impairment**. Arch Otolaryngol Head Neck Surg. 2010 May;136(5):488-92.

McLaughlin VV, Archer SL, Badesch DB, et al.; ACCF/AHA. ACCF/**AHA 2009** expert consensus document on **pulmonary hypertension**: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. 2009 Apr 28;119(16):2250-94. Epub 2009 Mar 30. Review. Erratum in: Circulation. 2009 Jul 14;120(2):e13.

McMahon CN, Smith CJ, Shabsigh R. Treating erectile dysfunction when **PDE5 inhibitors fail**. BMJ. 2006 Mar 11;332(7541):589-92.

McVary KT. **Erectile dysfunction**. N Engl J Med. **2007** Dec 13;357(24):2472-81.

Medical Letter, Sildenafil (Revatio) for **Pulmonary Arterial Hypertension**. Vol 47 (Issue 1215/1216) Aug 15/29,2005. p.65-67.

Melnik T, Soares B, Nasselo A. **Psychosocial interventions** for erectile dysfunction. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004825. There was evidence that group psychotherapy may improve erectile function. Treatment response varied between patient subgroups, but focused sex-group therapy showed greater efficacy than control group (no treatment). In a meta-analysis that compared group therapy plus sildenafil citrate versus sildenafil, men randomised to receive group therapy plus sildenafil showed significant improvement of successful intercourse, and were less likely than those receiving only sildenafil to drop out. Group psychotherapy also significantly improved ED compared to sildenafil citrate alone. Regarding the effectiveness of psychosocial interventions for the treatment of ED compared to local injection, vacuum devices and other psychosocial techniques, no differences were found.

MHRA Feb/12 has received advice from AGES PharmMed in Austria and the Danish Medicines Agency, warning that these unlicensed products have been tested and found to contain Tadalafil and/or Sildenafil: **AH Free/Reflexit, Stree Overlord, Man King, VigRX, Maxman, Maxman III, Viriya, & Imbiza for Men.**

Min JK, Williams KA, Okwuosa TM, et al. Prediction of **coronary heart disease** by erectile dysfunction in men referred for nuclear stress testing. *Arch Intern Med* 2006; 166:201-206.

TOP

Mittleman MA, Maclure M, Glasser DB. Evaluation of acute risk for myocardial infarction in men treated with sildenafil citrate. Am J Cardiol. 2005 Aug 1;96(3):443-6.
Morrison Deborah, Aitchison Michael, Connelly Derek T, et al. **10-Minute Consultation: Sexual dysfunction in cardiovascular disease**. BMJ 2011;343:doi:10.1136/bmj.d4437 (Published 26 July 2011)
Muller A, Smith L, Parker M, Mulhall JP. Analysis of the efficacy and safety of sildenafil citrate in the **geriatric population**. BJU Int. 2007 Jul;100(1):117-21. From these data, sildenafil is an effective agent in elderly men, but had a lower efficacy rate with increasing age, especially in men aged >80 years.
Namachivayam P, et al. Sildenafil **prevents** rebound **pulmonary hypertension** after withdrawal of nitric oxide in children. Am J Respir Crit Care Med. 2006 Nov 1;174(9):1042-7. Epub 2006 Aug 17.
Nickel M, et al. **Cabergoline** treatment in men with psychogenic erectile dysfunction: a randomized, double-blind, placebo-controlled study. Int J Impot Res. 2006 May 18; [Epub ahead of print]
Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial.JAMA. 2008 Jul 23;300(4):395-404. In this study population, **sildenafil treatment of sexual dysfunction in women** taking SRIs was associated with a reduction in adverse sexual effects.
Padma-Nathan H, Yeager JL. An integrated analysis of **alprostadil topical cream** for the treatment of erectile dysfunction in 1732 patients. Urology. 2006 Aug;68(2):386-91.
Park K, Ku JH, Kim SW, Paick JS. Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction. BJU Int. 2005 Feb;95(3):366-70.
Pennisi G, Vacante M, Russo C, Malaguarnera M. Rhabdomyolysis Induced by **Rosuvastatin and Sildenafil**. South Med J. 2010 Sep 2.
Penson DF, McLerran D, Feng Z, Li L, et al. 5-year urinary and sexual outcomes **after radical prostatectomy**: results from the Prostate Cancer Outcomes Study. J Urol. 2008 May;179(5 Suppl):S40-4. Urinary and sexual dysfunction were common 5 years following radical prostatectomy in this large, community based cohort of prostate cancer survivors. While a small minority of subjects experienced changes in urinary or sexual function between years 2 and 5 after prostatectomy, functional outcomes remained relatively stable in the majority of participants.
Pharmacist's Letter Oct 2006. **Alternative or Off-label** Routes of Drug Administration. (**Vaginal & sublingual** administration of: sildenafil)
Philip A, Ramchandani S, Dorrance K, Dorrance C. **Sildenafil-induced thrombocytopenia**. Ann Intern Med. 2008 Sep 16;149(6):437-9.
Piazza G, Goldhaber SZ. Chronic **Thromboembolic Pulmonary Hypertension**. N Engl J Med. 2011 Jan 27;364(4):351-360.
Porst H, et al. Evaluation of the Efficacy and Safety of **Once-a-Day** Dosing of Tadalafil 5mg and 10mg in the Treatment of Erectile Dysfunction: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Eur Urol. 2006 Aug;50(2):351-9. Epub 2006 Mar 20. 12-week study enrolled 268 men
Pryor JL, et al.; Dapoxetine Study Group. Efficacy and tolerability of **dapoxetine** in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. Lancet. 2006 Sep 9;368(9539):929-37. (InfoPOEMs: In this study, dapoxetine (an investigational new short-acting selective serotonin reuptake inhibitor) taken 1 to 3 hours before sexual activity delayed ejaculation in men with moderate-to-severe premature ejaculation. The net improvement due to medication was less than 2 minutes compared with baseline, but patients and partners were satisfied with this small amount of improvement. (LOE = 2b))
Qaseem A., Snow V., Denberg T. D., et al and for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians. **Hormonal Testing and Pharmacologic Treatment of Erectile Dysfunction**: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med* 2009; 60520-151.
Recommendation 1: The American College of Physicians recommends that clinicians initiate therapy with a PDE-5 inhibitor in men who seek treatment for erectile dysfunction and who do not have a contraindication to PDE-5 inhibitor use (Grade: strong recommendation; high-quality evidence).
Recommendation 2: The American College of Physicians recommends that clinicians base the choice of a specific PDE-5 inhibitor on the individual preferences of men with erectile dysfunction, including ease of use, cost of medication, and adverse effects profile (Grade: weak recommendation; low-quality evidence).
Recommendation 3: The American College of Physicians does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction (Grade: insufficient evidence to determine net benefits and harms).
Raina R, Pahlajani G, Agarwal A, Zippe CD. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. BJU Int. 2007 Dec;100(6):1317-21. Epub 2007 Sep 11. Initiating **MUSE** shortly after RP is safe and tolerable, and appears to shorten the recovery time to reagin erectile function.
Rees J, Patel B. **Erectile dysfunction**. BMJ. 2006 Mar 11;332(7541):593.
Reffelmann T, Kloner RA. Pharmacotherapy of erectile dysfunction: focus on cardiovascular safety. Expert Opin Drug Saf. 2005 May;4(3):531-40.
Roizenblatt S, et al. A double-blind, placebo-controlled, crossover study of sildenafil in **obstructive sleep apnea**. Arch Intern Med. 2006 Sep 18;166(16):1763-7. In patients with severe obstructive sleep apnea, a single 50-mg dose of sildenafil at bedtime worsens respiratory and desaturation events.
Rosen R, et al.; Vardenafil Study Site Investigators. Efficacy and tolerability of vardenafil in men with mild **depression** and erectile dysfunction: the depression-related improvement with vardenafil for erectile response study. Am J Psychiatry. 2006 Jan;163(1):79-87.
Rosenthal BD, et al.Adjunctive use of AndroGel(testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone.Urology.2006Mar;67(3):571-4.
Rubin LJ, Badesch DB, Fleming TR, et al; the **SUPER-2** Study Group. Long-term Treatment With **Sildenafil** Citrate in **Pulmonary Arterial Hypertension**: The SUPER-2 Study. Chest. 2011 Nov;140(5):1274-1283.
Saigal CS, Wessells H, Pace J, et al. **Predictors and prevalence** of erectile dysfunction in a racially diverse population. *Arch Intern Med* 2006; 166:207-212.
Schwartz Bryan G., Kloner Robert A.. **Cardiovascular Implications** of Erectile Dysfunction. **Patient Page**. Circulation 123: e609-611e, doi:10.1161/CIRCULATIONAHA.110.017681
Setter SM, Iltz JL, Fincham JE, Campbell RK, Baker DE. Phosphodiesterase 5 inhibitors for erectile dysfunction. Ann Pharmacother. 2005 Jul;39(7):1286-95.
Sharma RK, Prasad N, Gupta A, Kapoor R. Treatment of erectile dysfunction with sildenafil citrate in **renal allograft** recipients: a randomized, double-blind, placebo-controlled, crossover trial. Am J Kidney Dis. 2006 Jul;48(1):128-33.
Sheets NC, Goldin GH, Meyer AM, et al. **Intensity-modulated radiation therapy**, **proton therapy, or conformal radiation therapy** and morbidity and disease control in localized **prostate cancer**. JAMA. 2012 Apr 18;307(15):1611-20. (more erectile dysfunction)
Simonneau G, Rubin LJ, Galiè N, et al. PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with **pulmonary arterial hypertension**: a randomized trial. Ann Intern Med. 2008 Oct 21;149(8):521-30. Summary for patients in: Ann Intern Med. 2008 Oct 21;149(8):I-38.
Schwartz BG, Kloner RA. **Drug interactions with phosphodiesterase-5 inhibitors** used for the treatment of erectile dysfunction or pulmonary hypertension. Circulation. 2010 Jul 6;122(1):88-95.
Striano P, Zara F, Minetti C, Striano S. **Epileptic seizures** can follow high doses of oral vardenafil. BMJ. 2006 Oct 14;333(7572):785.
Stringham R, Shah NR. **Pulmonary arterial hypertension**: an update on diagnosis and treatment. Am Fam Physician. 2010 Aug 15;82(4):370-7.
Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and **subsequent cardiovascular disease**. JAMA. 2005 Dec 21;294(23):2996-3002.
Tsertsvadze A, Yazdi F, Fink HA, et al. Oral **Sildenafil** Citrate (Viagra) for Erectile Dysfunction: A Systematic Review and Meta-analysis of Harms. Urology. 2009 Jul 8. [Epub ahead of print]
Oral PDE-5 inhibitors improved erectile functioning and had similar efficacy and safety profiles. Results on the efficacy of hormonal treatments and the value of hormone testing in men with ED were inconclusive.
Tsertsvadze A., Fink H. A., Yazdi F., et al. **Oral Phosphodiesterase-5 Inhibitors** and **Hormonal Treatments** for Erectile Dysfunction: A Systematic Review and Meta-analysis. Ann Intern Med 2009; 60520-150.
Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. Am J Respir Crit Care Med 2005;171:1292-97. (InfoPOEMs: Is sildenafil (Viagra) more effective than bosentan (Tracleer) in patients with class III pulmonary hypertension? In this small study, sildenafil and bosentan had similar effects on patients with moderately severe pulmonary hypertension. (LOE = 1b))
Wirostko BM, Tressler C, Hwang LJ et al. **Ocular safety of sildenafil** citrate when administered chronically for pulmonary arterial hypertension: results from phase III, randomised, double masked, placebo controlled trial and open label extension. BMJ. 2012 Feb 21;344:e554.

Web Links:

TOP

American Academy of Family Physicians Web site: http://familydoctor.org
American Urological Association Foundation Web site: http://www.urologyhealthorg/adult/index.cfm?cat=11&topic=174
National Institutes of Health Web site: http://www.nlm.nih.gov/medlineplus/erectiledysfunction.html

TOP

Reviewers: Dr. K. Knox (SHR Rehabilitation), C Bell (UofS-SDIS), A Kuntz (SK Health), M Jin (PharmD, Hamilton), & the RxFiles Advisory Committee.

Extras:
in Europe dapoxetine *Priligy* has official indication for Premature Ejaculation

Additional references:

American College of Obstetricians and Gynecologists (ACOG). **Female sexual dysfunction**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2011 Apr. 12 p. (ACOG practice bulletin; no. 119).
Burton TD, Liday C. The comparison of combination **SSRI and PDE-5 inhibitor** therapy to SSRI monotherapy in men with **premature ejaculation**. Ann Pharmacother. 2011 Jul;45(7-8):1000-4.
FDA: Apr/12 The labels of the alopecia drug Propecia (**finasteride** 1 mg) and the benign prostatic hyperplasia drug Proscar (finasteride 5 mg) are being updated with an expanded list of adverse **sexual effects**, the FDA has announced. Propecia label will include libido, ejaculation, and orgasm disorders that persist after treatment ends; Proscar label will include decreased libido that persists posttreatment & both labels will note reports of male infertility or poor semen quality that improved after drug discontinuation.
Foran T. Managing Postmenopausal Symptoms in Australian Prescriber Nov 2010. Accessed at: http://www.australianprescriber.com/magazine/33/6/171/5 . Link to RxFiles Postmenopausal chts: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Postmenopausal-RxandHerbal.pdf
Gregston M. Teen survival in a sex crazed culture. Parenting Today's Teens. Accessed online 04 Aug 2011 at: http://www.heartlightministries.org/blogs/markgregston/2011/07/29/teen-sexual-promiscuity/
Gupta BP, Murad MH, Clifton MM, et al. The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction: A Systematic Review and Meta-analysis. Arch Intern Med. 2011 Nov 14;171(20):1797-803. Epub 2011 Sep 12.
Kellogg ND. **Sexual behaviors in children**: evaluation and management. Am Fam Physician. 2010 Nov 15;82(10):1233-8.
Levine GN, Steinke EE, Bakaeen FG, et al. **Sexual activity and cardiovascular disease**. A scientific statement from the American Heart Association (AHA). Circulation 2012. http://circ.ahajournals.org/content/early/2012/01/19/CIR.0b013e3182447787.full.pdf?sid=8d962f06-2506-473d-aaaf-5761032aed2b
Lindau, Stacy Tessler, Schumm, L. Philip, Laumann, Edward O., et al. A Study of Sexuality and Health among Older Adults in the United States. N Engl J Med 2007 357: 762-774.
Lindau Stacy Tessler, Gavrilova Natalia.Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. BMJ 2010;340:c810, doi: 10.1136/bmj.c810 (Published 9 March 2010)
Melnik T, Althof S, Atallah ÁN, Puga MEDS, Glina S, Riera R. **Psychosocial interventions for premature ejaculation**. Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD008195. DOI: 10.1002/14651858.CD008195.pub2.
Mitchell KJ et al. Use of social networking sites in online sex crimes against minors: An examination of national incidence and means of utilization. J Adolesc Health 2010 Apr 25
Morrison Deborah, Aitchison Michael, Connelly Derek T, et al. **10-Minute Consultation: Sexual dysfunction in cardiovascular disease**. BMJ 2011;343:doi:10.1136/bmj.d4437 (Published 26 July 2011)
Reed SD, Guthrie KA, Joffe H, et al. **Sexual function in nondepressed women using escitalopram** for vasomotor symptoms: a randomized controlled trial. Obstet Gynecol. 2012 Mar;119(3):527-38.
Wespes E, Amar E, Eardley F, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Arnhem, The Netherlands: European Association of Urology (EAU); 2009 Mar.
Wylie K, Rees M, Hackett G, et al. Androgens, health and sexuality in women and men. Hum Fertil (Camb). 2010 Dec;13(4):277-97.

References: Sexual Dysfunction: Overview & Drug Considerations (www.RxFiles.ca)

[1] Shifren J. UpToDate: Sexual dysfunction in women. Sept 30, 2009.
[2] Frank JE, Mistretta P, Will J. Diagnosis and treatment of female sexual dysfunction. Am Fam Physician. 2008 Mar 1;77(5):635-42. Review. Erratum in: Am Fam Physician. 2009 Feb 1;79(3):180.
[3] Stimmel GL, Gutierrez MA. Sexual dysfunction and psychotropic medications. CNS Spectr. 2006 Aug;11(8 Suppl 9):24-30.
[4] Gray, J. Editor. Therapeutic choices – 5th Edition. Canadian Pharmacists Association. 2007.
[5] Labbate LA. Psychotropics and sexual dysfunction: the evidence and treatments. Adv Psychosom Med. 2008;29:107-30.
[6] Hordern A. Intimacy and sexuality after cancer: a critical review of the literature. Cancer Nurs. 2008 Mar-Apr;31(2):E9-17.
[7] Stilos K, Doyle C, Daines P. Addressing the sexual health needs of patients with gynecologic cancers. Clin J Oncol Nurs. 2008 Jun;12(3):457-63.
[8] Ayaz S, Kubilay G. Effectiveness of the PLISSIT model for solving the sexual problems of patients with stoma. J Clin Nurs. 2009 Jan;18(1):89-98.
[9] Drugs for female sexual dysfunction. Med Lett Drugs Ther. 2007 Apr 23;49(1259):33-5. PubMed PMID: 17450112.
[10] Goldstein I. Current management strategies of the postmenopausal patient with sexual health problems. J Sex Med. 2007 Mar;4 Suppl 3:235-53.
[11] RxFiles Postmenopausal Chart. http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Postmenopausal-RxandHerbal.pdf
[12] RxFiles Androgen Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Androgens.pdf
[13] RxFiles Q&A: Can *Zyban*® (bupropion / *Wellbutrin*®) be given with SSRIs Accessed online 19 Mar, 2010 at http://www.rxfiles.ca/rxfiles/uploads/documents/zyban-ssri-QandA.pdf
[14] Segraves RT, Clayton A, Croft H, Wolf A, Warnock J. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. J Clin Psychopharmacol. 2004 Jun;24(3):339-42.
[15] RxFiles Erectile Dysfunction Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-erectile-dysfx.pdf
[16] Sprunk E, Alteneder RR. The impact of an ostomy on sexuality. Clin J Oncol Nurs. 2000 Mar-Apr;4(2):85-8.
[17] Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, Vardi Y, Wespes E. Guidelines on Male Sexual Dysfunction: Erectile Dysfunction and Premature Ejaculation. Eur Urol. 2010 Feb 20.
[18] Stimmel GL, Gutierrez MA. Counseling patients about sexual issues. Pharmacotherapy. 2006 Nov;26(11):1608-15.
[19] Albright JM. Sex in America online: an exploration of sex, marital status, and sexual identity in internet sex seeking and its impacts. J Sex Res. 2008. Apr-Jun;45(2):175-86. Other (AU-ABC): http://www.abc.net.au/religion/articles/2011/06/14/3243186.htm?topic1=home&t
[20] Giuliano F, Hellstrom WJ. The pharmacological treatment of premature ejaculation. BJU Int. 2008 Sep;102(6):668-75. Epub 2008 May 15.
[21] Palmer B, Henrich W, Snyder P. Sexual dysfunction in uremic men. UpToDate. Sep 30, 2009.
[22] Higgins A. Impact of psychotropic medication on sexuality: literature review. Br J Nurs. 2007 May 10-23;16(9):545-50.
[23] Tessler S, Gavrilova N. Sex, health, and years of sexually active life gained due to good health: evidence form two population based cross sectional surveys of ageing. BMJ 2010;340c810. Accessed online 11 Mar, 2010 at http://www.bmj.com/cgi/content/full/340/mar09_2/c810 .
[24] Willhite LA, O'Connell MB. Urogenital atrophy: prevention and treatment. Pharmacotherapy. 2001 Apr;21(4):464-80. Accessed online 11 Mar 2010 at http://www.medscape.com/viewarticle/409697_4
[25] Harden CL. Sexuality in men and women with epilepsy. CNS Spectr. 2006 Aug;11(8 Suppl 9):13-8.
[26] Gil-Nagel A, López-Muñoz F, Serratosa JM, Moncada I, García-García P, Alamo C. Effect of lamotrigine on sexual function in patients with epilepsy. Seizure. 2006 Apr;15(3):142-9.
[27] RxFiles Q&A. Updated Sep 2006. Can bupropion (Zyban) be added to SSRIs? http://www.rxfiles.ca/rxfiles/uploads/documents/zyban-ssri-QandA.pdf
Sayuk GS, Gott BM, Nix BD, Lustman PJ. Improvement in sexual functioning in patients with type 2 diabetes and depression treated with **bupropion**. Diabetes Care. 2011 Feb;34(2):332-4.
[28] Segraves RT. Sexual dysfunction associated with antidepressant therapy. Urol Clin North Am. 2007 Nov;34(4):575-9, vii.
[29] RxFiles Antidepressant Chart. http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Psyc-Antidepressant.pdf

TOP

[30] Clayton A, Kornstein S, Prakash A, Mallinckrodt C, Wohlreich M. Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. J Sex Med. 2007 Jul;4(4 Pt 1):917-29.
[31] Herzog AG, Drislane FW, Schomer DL, Pennell PB, Bromfield EB, Dworetzky BA,Farina EL, Frye CA. Differential effects of antiepileptic drugs on sexual function and hormones in men with epilepsy. Neurology. 2005 Oct 11;65(7):1016-20.
[32] Berner MM, Hagen M, Kriston L. Management of sexual dysfunction due to antipsychotic drug therapy. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD003546.
[33] RxFiles Antipsychotics Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-Psyc-Neuroleptics.pdf
[34] Mortimer JE. Managing the toxicities of the aromatase inhibitors. Curr OpinObstet Gynecol. 2010 Feb;22(1):56-60.
[35] Palha AP, Esteves M. Drugs of abuse and sexual functioning. Adv Psychosom Med.2008;29:131-49.
[36] Bang-Ping J. Sexual dysfunction in men who abuse illicit drugs: a preliminary report. J Sex Med. 2009 Apr;6(4):1072-80.
[37] Gades NM, Nehra A, Jacobson DJ, McGree ME, Girman CJ, Rhodes T, Roberts RO, Lieber MM, Jacobsen SJ. Association between smoking and erectile dysfunction: a population-based study. Am J Epidemiol. 2005 Feb 15;161(4):346-51.
[38] Natural Medicines Comprehensive Database 2010. (www.naturaldatabase.com)

TOP

Extras:

1) ACs, Other: **propantheline** -less effective & ↑ SE than flavoxate & oxybutynin.[11] NICE states not to use[1]; Adult: 7.5mg tid, 7.5-30mg 3-5x/day, 60mg qid; Geriatric: 7.5mg tid; Peds: 7.5-15mg q4-6h;
2) Adrenoreceptor agonists (**phenylpropanolamine** predominantly studied but use extended to **ephedrine**, **pseudoephedrine**): studied for SUI. But cardiac arrhythmias & HTN outweigh benefits [31].
3) **Belladonna & opium suppositories**-used to relieve **pain of uretal spasms** & pain associated with bladder tenesmus that can occur post-op[32]. Some report use in nocturnal diuresis[11]
dicyclomine -insufficient data to recommend over other agents, dose 20-40mg qid.[11]
4) **Flavoxate**: Not used for OAB currently[1] but may be used in discomfort associated with BPH. Efficacy might be comparable to propantheline according to older, short-term studies[11].
Dose: Adult: 100-200mg tid-qid. May reduce dose with Sx improvement. One trial found 1200mg to be superior to 600mg/day. May be effective in children from 6-12 y/o experiencing nocturnal enuresis (33% vs 17% response in placebo)[11]. Pediatrics > 12y/o: 100-200mg tid-qid. May reduce dose with Sx improvement[11].
5) **Phenazopyridine**[11]: used strictly as a **urinary analgesic**. The necessity of this medication would suggest pathology different from UI. Dose: Adult: 200mg tid after meals. If renal GFR > 50ml/min 200mg q8-16h. Avoid if GFR < 50ml/min. Geriatrics: ↑risk of accumulation & toxicity. SE: discolor urine
6) **Propiverine** [53]: tertiary amine with anticholinergic & calcium channel antagonist activity; has active metabolites; dose: 15mg IR bid or 30mg ER daily; available United Kingdom [2006].

Oxybutynin (Oxy) vs Tolterodine in OAB

- OBJECT: Oxy ER 10mg daily vs Tolt IR 2mg BID; 12 week; ♂ & ♀; Oxy ER slightly more effective (e.g. Total incontinence episodes/wk: NNT=45); no difference in overall AEs (dry mouth, CNS effects).[52]
- OPERA: Oxy ER 10mg vs Tolt ER 4mg daily; 12 week; ♀ only with severe symptoms; Oxy ER somewhat more effective (e.g. 23 vs 16.8% no UI; NNT=16); but also more dry mouth (Any 29.7% vs 22.3%; NNH=13; mod-severe 7.4% vs 5.0% , NS).[50]
- ACET: Oxy ER 5 or 10mg vs Tolt ER 2 or 4mg daily; 8 week; ♂ & ♀; Tolt 4mg more effective than Oxy 10 70 vs 60% improvement; but lower doses efficacy still ~60% & less dry mouth but similar for Tolt 4 vs Oxy 5 ; open label trial & subjective assessments subject to bias.[51]

Acknowledgements: Contributors & Reviewers: Dr. A. Epp (SHR Obs/Gyne), Dr. C. Jabs (RQHR Obs/Gyne), Dr. S. Gonor (SHR-Urol), Dr. L. Rudachak (SHR-Rehab), Dr. R. Li Pi Shan (SHR-Rehab), Dr. J. Yelland (Parkridge LTC), S. Knezacek (Pharmacist, Parkridge LTC), Juliet Sarjeant (SHR-Physio), Eliza Meggs (RN, NCA, Nurse Continence Advisor; Saskatoon), Ann Burton (SHR-RN-Specialist, Parkridge Centre) & the RxFiles Advisory Committee.

Prepared by: *K Mulherin* PharmD Cand *L. Regier* BSP, BA, B. *Jensen* BSP

References – RxFiles Urinary Incontinence Treatment Chart - www.RxFiles.ca

1. Urinary Incontinence: The management of urinary incontinence in women. www.nice.org.uk/nicemedia/pdf/CG40fullguideline.pdf National Institute for Health and Clinical Excellence (**NICE**) clinical guideline 40; October 2006:1-14.
Hashim H, Abrams P. How should patients with an overactive bladder manipulate their fluid intake? BJU Int. 2008 Feb 18; [Epub ahead of print] Fluid manipulation is a cheap, noninvasive and easy way to help control the symptoms of OAB. Patients have difficulty in either decreasing or increasing their fluid input by 50%. Patients can now be told to expect a significant improvement in urgency, frequency and nocturia episodes if they reduce their fluid input by 25%.
Glazener C, Boachie C, Buckley B, et al. Urinary incontinence in men after formal one-to-one pelvic-fl oor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. Lancet 2011; published online July 12. DOI:10.1016/S0140-6736(11)60751-4.
Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Systematic Review: **Benefits and Harms of Pharmacologic Treatment for Urinary Incontinence** in Women. Ann Intern Med. 2012 Apr 9.
2. Ouslander JG. Management of Overactive Bladder. NEJM 2004;350:786-99.
Nygaard I, Barber MD, Burgio KL, et al. Pelvic Floor Disorders Network. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008 Sep 17;300(11):1311-6.
Nygaard Ingrid. Idiopathic Urgency Urinary Incontinence. N Engl J Med 2010; 363:1156-1162.
3. Kilicarlslan H, Ayan S, et al. Treatment of detrusor sphincter dyssynergia with baclofen and doxazosin. Int Urol Nephrol 2006;38:537-541.
4. Hay-Smith EJC, Dumoulin C. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database of Systematic Reviews* 2006, Issue 1.
5. Corcos J, Gajewski J, Heritz D, Patrick A, Reid I, Schick E, Stothers L; Canadian Urological Association. **Canadian Urological Association guidelines** on urinary incontinence. Can J Urol. 2006 Jun;13(3):3127-38.
6. Thüroff, J et al. Guidelines on urinary incontinence. European Association of Urology 2006: 1-12. www.uroweb.org/fileadmin/user_upload/Guidelines/16%20Urinary%20Incontinence.pdf
7. Ancelin, ML et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergics drugs: Longitudinal cohort study. BMJ 2006;332:455-459. www.bmj.com/cgi/content/full/332/7539/455
8. Siegler, EL et al. Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia. Clin Pharmacol Ther 2004;75:484-8.
9. Edwards, KR et al. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. Editorial Letter. JAGS 2002;50:1165-1166.
10. Donnellan, CA et al. Oxybutynin and cognitive dysfunction. BMJ 1997;315:1363-1364.
11. McDonagh, MS et al. Drug class review on agents for overactive bladder. **Oregon Evidence-based Practice** Center 2005: 1-215. www.ohsu.edu/drugeffectiveness/reports/documents/OAB%20Final%20Report%20Update%203.pdf
12. Kay G, Crook T, Rekeda L, Lima R, et al. Darifenacin has theoretical cognitive advantages. Some preliminary placebo controlled trials have results supporting this claim. At first glance this trial by Key et al. appears to support these advantages based on the *name-face association test*. However when trial design issues (e.g. high oxybutinin dose for elderly, early drop outs), discussion bias, adverse event rates and overall limitations are considered, this study does not prove a definite advantage for darifenacin over oxybutynin. Further study is needed (especially with a more rational dose comparator) in elderly with urinary incontinence and at high risk for cognitive impairment. Darifenacin may offer a relative advantage or disadvantage to other anticholinergics depending on dose used and individual patient response. Currently, darifenacin offers a cost advantage over some comparators. {Cost/month[SK]: Enablex 7.5-15mg/day= $59; Ditropan XL 5-10mg/day= $84,15-20mg/day=$159; Uromax10-15mg/day=$50-53; Detrol LA 2-4mg/day= $72.} See http://www.rxfiles.ca/acrobat/UI-Darifenacin-Kay-Trial-Q&A.pdf }
13. CPS 2008 online edition
14. Briggs GG et al. Drugs in Pregnancy and lactation, 9th ed, 2011.
15. CEDAC final recommendation and reasons for recommendation: Trospium Chloride. (Trosec -Oryx Pharm) CADTH 24/8/2006. http://cadth.ca/media/cdr/complete/cdr_complete_Trosec_August24-06.pdf
16. CEDAC final recommendation Darifenacin. (Enablex –Novartis) CADTH 16/04/2009. http://cadth.ca/media/cdr/complete/cdr_complete_Enablex_Oct-19-06.pdf http://www.cadth.ca/media/cdr/complete/cdr_complete_Enablex%20Resubmission-1_April-17-2009.pdf
17. CEDAC final recommendation and reasons for recommendation: Solifenacin. (Vesicare –Astellas) CADTH 24/1/2006. http://cadth.ca/media/cdr/complete/cdr_complete_Vesicare_Jan-24-2007.pdf
CADTH Resubmission June/09 http://www.cadth.ca/media/cdr/complete/cdr_complete_Vesicare-Resubmisson_1_June-17-2009.pdf
18. Micromedex 2008. Thompson Healthcare.
19. Hay-Smith J et al. Which anticholinergics drug for overactive bladder symptoms in adults. Cochrane Database of Systematic Reviews 2005, Issue 3.
20. Nabi G, Cody JD, Ellis G, Herbison P, Hay-Smith J. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. **Cochrane** Database Syst Rev. 2006 Oct 18;(4):CD003781. {Also: Herbison P et al. Effectiveness of anticholinergics drugs compared with placebo in the treatment of overactive bladder: systematic review. BMJ 2003;326:841-844.}
21. Chapple CR et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: Results of the **STAR** trial. European Urology 2005;48:464-470.
22. Lipton RB et al. Assessment of cognitive function of the elderly population: Effects of darifenacin. J of Urology 2005;173:493-498.
23. Abrams P et al. Muscarinic receptor antagonists for overactive bladder. BJU int 2007;100:987-1006.
24. Hendrix SL et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005;293:935-948.
25. Moehrer B et al. Oestrogens for urinary incontinence in women. **Cochrane** database of systematic reviews 2003, Issue 2.
Cody JD, Richardson K, Moehrer B, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD001405. Local oestrogen treatment for incontinence may improve or cure it, but there was little evidence from the trials on the period after oestrogen treatment had finished and none about long-term effects. However, systemic hormone replacement therapy, using conjugated equine oestrogen, may make incontinence worse. There were too few data to reliably address other aspects of oestrogen therapy, such as oestrogen type and dose, and no direct evidence on route of administration. The risk of endometrial and breast cancer after long-term use suggests that oestrogen treatment should be for limited periods, especially in those women with an intact uterus.
26. Bélisle S et al. **Canadian Consensus** conference on **menopause** 2006 update. JOGC 2006;171:S7-S10. **SOGC 2009 Menopause and Osteoporosis** Update 2009-SOGC Jan 2009. http://www.sogc.org/media/pdf/advisories/Meno-Osteo-Update_JOGC-Jan_09.pdf
27. Scottish Intercollegiate Guidelines Network. Management of urinary incontinence in primary care. 2004;December. www.sign.ac.uk/pdf/sign79.pdf
28. Haueusler G et al. Drug therapy of urinary urge incontinence: A systematic review. Obstet Gynecol 2002;100:1003-16.
29. Zinner NR et al. Pharmacotherapy for stress urinary incontinence: Present and future options. Drugs 2004;64:1503-1519.
30. Hashim H et al. Pharmacological management of women with mixed urinary incontinence. Drugs 2006;66:591-606.
31. Alhasso A et al. Adrenergic drugs for urinary incontinence in adults. **Cochrane** Database of Systematic Reviews 2005, Issue 3.
32. University of Maryland medical center website. Accessed 14/11/07. www.umm.edu/altmed/drugs/belladonna-opium-012800.htm#Use.
33. Johnson TM 2nd, Burgio KL, Redden DT, Wright KC, Goode PS. Effects of behavioral and drug therapy on nocturia in older incontinent women. J Am Geriatr Soc. 2005 May;53(5):846-50.

(**Physiotherapy**- especially if pt can't isolate or exercising wrong muscles, or if stops breathing during Kegels;
Saskatoon Health Region: **Pelvic Floor Rehab Program** 655-8208, typically sees females q1-2weeks x 8 times, waiting list ~6months; **Private Clinics** in Saskatoon also treat, quicker access, 3rd party coverage?: Bourassa & Daniels Kimber)
Nurse Continence Advisor: Eliza Meggs RN,NCA (Nightingale Nursing Group) Phone: 306-652-3314

Braekken IH, Majida M, Engh ME, et al. Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. Am J Obstet Gynecol. 2010 Aug;203(2):170.e1-7. Epub 2010 May 1.
Glazener C, Boachie C, Buckley B, et al. Urinary incontinence in men after formal one-to-one pelvic-fl oor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. Lancet 2011; published online July 12. DOI:10.1016/S0140

CADTH= Canadian Agency for Drugs and Technology in Health (www.CADTH.ca)
CDR=Common Drug Review (http://cadth.ca//index.php/en/cdr)
CEDAC= Canadian Expert Drug Advisory Committee

TOP

34. Schurch B, de Sèze M, Denys P, et al.; Botox Detrusor Hyperreflexia Study Team. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005 Jul;174(1):196-200.
35. Karsenty G, Denys P, Amarenco G, et al. Botulinum Toxin A (Botox((R))) Intradetrusor Injections in Adults with Neurogenic Detrusor Overactivity/Neurogenic Overactive Bladder: A Systematic Literature Review. Eur Urol. 2007 Oct 16; [Epub ahead of print]
36. Schurch B. **Botulinum** toxin for the management of bladder dysfunction.Drugs. 2006;66(10):1301-18.
Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 May 6;70(19):1707-14. Botulinum neurotoxin (BoNT) should be offered as a treatment option for the treatment of axillary hyperhidrosis and detrusor overactivity (Level A), should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia after spinal cord injury (Level B), and may be considered for gustatory sweating and low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B). There is presently no consistent or strong evidence to permit drawing conclusions on the efficacy of BoNT in chronic daily headache (mainly transformed migraine) (Level U). While clinicians' practice may suggest stronger recommendations in some of these indications, evidence-based conclusions are limited by the availability of data.
Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and Safety of **OnabotulinumtoxinA** for Idiopathic Overactive Bladder: A Double-Blind, Placebo Controlled, Randomized, Dose Ranging Trial. J Urol. 2010 Dec;184(6):2416-22.
Duthie JB, Vincent M, Herbison GP, et al. **Botulinum toxin injections** for adults with overactive bladder syndrome. Cochrane Database Syst Rev. 2011 Dec 7;12:CD005493. Intravesical botulinum toxin appears to be an effective therapy for refractory OAB symptoms, but as yet little controlled trial data exist on benefits and safety compared with other interventions, or with placebo.
37. Ayan S, Topsakal K, Gokce G, Gultekin EY. Efficacy of combined anticholinergic treatment and behavioral modification as a first line treatment for nonneurogenic and nonanatomical voiding dysfunction in children: a randomized controlled trial. J Urol. 2007 Jun;177(6):2325-8; discussion 2328-9.
38. Kilic N, Balkan E, Akgoz S, Sen N, Dogruyol H. Comparison of the effectiveness and side-effects of tolterodine and oxybutynin in children with detrusor instability. Int J Urol. 2006 Feb;13(2):105-8.
39. Nijman RJ, Borgstein NG, et al. Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. J Urol. 2005 Apr;173(4):1334-9.
40. Siami P, Seidman LS, Lama D. A multicenter, prospective, open-label study of tolterodine extended-release 4 mg for overactive bladder: the speed of onset of therapeutic assessment trial (STAT). Clin Ther. 2002 Apr;24(4):616-28.
41. Sand PK, Goldberg RP, Dmochowski RR, McIlwain M, Dahl NV. The impact of the overactive bladder syndrome on sexual function: a preliminary report from the Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin trial. Am J Obstet Gynecol. 2006 Dec;195(6):1730-5.
42. Feinberg M. The problems of anticholinergic adverse effects in older patients.Drugs Aging. 1993 Jul-Aug;3(4):335-48.
43. Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry. 2001;62 Suppl 21:11-4.
Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008 Mar 10;168(5):508-13.
Sink KM, Thomas J 3rd, Xu H, Craig B, et al. Dual Use of Bladder Anticholinergics and Cholinesterase Inhibitors: Long-Term Functional and Cognitive Outcomes. J Am Geriatr Soc. 2008 Apr 1. [Epub ahead of print] In higher-functioning NH residents, dual use of ChIs and bladder anticholinergics may result in greater rates of functional decline than use of ChIs alone. The MDS-COGS may not be sensitive enough to detect differences in cognition due to dual use.
Lackner TE, Wyman JF, McCarthy TC, Monigold M, Davey C. Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin 5mg/day in cognitively impaired nursing home residents with urge urinary incontinence. J Am Geriatr Soc. 2008 May;56(5):862-70. Epub 2008 Apr 9. n=50. 4 weeks. Short-term treatment using oral extended-release oxybutynin 5 mg once daily was safe and well tolerated, with no delirium, in older female nursing home participants with mild to severe dementia. Future research should investigate different dosages and long-term treatment.
Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc. 2008 Dec;56(12):2203-10. Cumulative anticholinergic exposure across multiple medications over 1 year may negatively affect verbal memory and executive function in older men. Prescription of drugs with anticholinergic effects in older persons deserves continued attention to avoid deleterious adverse effects.
Carrière I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009 Jul 27;169(14):1317-24.
Campbell NL, Boustani MA, Lane KA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. Neurology. 2010 Jul 13;75(2):152-9.
Teramura-Grönblad Mariko, Muurinen Seija, Soini Helena, et al. Use of Anticholinergic Drugs and Cholinesterase Inhibitors and Their Association with Psychological Well-Being Among Frail Older Adults in Residential Care Facilities. Ann Pharmacother ;45:596-602.
Stephenson Anne; Seitz Dallas; Bell Chaim M.; et al. Inhaled Anticholinergic Drug Therapy and the Risk of Acute Urinary Retention in Chronic Obstructive Pulmonary Disease: A Population-Based Study. Arch Intern Med. 2011;171(10):914-920.
Anticholinergic Cognitive Burden (ACB) scale http://www.indydiscoverynetwork.org/AnticholinergicCognitiveBurdenScale.html
Fox C, Richardson K, Maidment ID, et al. **Anticholinergic Medication Use** and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study. J Am Geriatr Soc. 2011 Jun 24
Torjesen I. Anticholinergic effects of common drugs are associated with increased **mortality** in over 65s. BMJ. 2011 Jun 28;342:d4037.
44. Abrams P, Andersson KE. **Muscarinic** receptor antagonists for overactive bladder. BJU Int. **2007** Nov;100(5):987-1006.
45. Waine E, Hashim H, Abrams P. **Management of the overactive bladder: a review** of pharmacological therapies and methods used by the urological specialist. Can J Urol. **2007** Apr;14(2):3478-88.
46. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, Coyne K, Kelleher C, Hampel C, Artibani W, Abrams P. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries (Canada, Germany, Italy, Sweden, and the United Kingdom): results of the EPIC study. Eur Urol. 2006 Dec;50(6):1306-14; discussion 1314-5. Epub 2006 Oct 2.
47. Dmochowski RR, Sanders SW, Appell RA, Nitti VW, Davila GW. Bladder-health diaries: an assessment of 3-day vs 7-day entries. BJU Int. 2005 Nov;96(7):1049-54.
48. Anderson RU, Mobley D, Blank B, Saltzstein D, Susset J, Brown JS. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. **OROS** Oxybutynin Study Group. J Urol. 1999 Jun;161(6):1809-12.
49. Diokno A, Sand P, Labasky R, et al. Long-term safety of extended-release oxybutynin chloride in a community-dwelling population of participants with overactive bladder: a one-year study. Int Urol Nephrol. 2002;34(1):43-9.
50. Diokno AC, Appell RA, Sand PK, Dmochowski RR, et al.; **OPERA** Study Group. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc. 2003 Jun;78(6):687-95.
51. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (**ACET**). Curr Med Res Opin. 2002;18(4):177-84.
52. Appell RA, Sand P, et al. Overactive Bladder: Judging Effective Control and Treatment Study Group. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the **OBJECT** Study.Mayo Clin Proc. 2001 Apr;76(4):358-63.
53. Jünemann KP, Halaska M, Rittstein T, et al. Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder. Eur Urol. 2005 Sep;48(3):478-82.
54. Albo ME, Richter HE, Brubaker L, et al; Urinary Incontinence Treatment Network. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007 May 24;356(21):2143-55. Epub 2007 May 21.
Schulz JA, Chan MC, Farrell SA, Sub-Committee on Urogynaecology (**SGOC**) . Midurethral minimally invasive sling procedures for stress urinary incontinence. J Obstet Gynaecol Can 2008 Aug;30(8):728-33. http://www.sogc.org/guidelines/documents/gui213TU0808.pdf
AUA –American Urological Association, **Surgical Management of Female Stress Urinary Incontinence** Update 2009 http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/stress2009/chapter1.pdf
De Vocht TF, Chrzan R, Dik P, et al. Long-Term Results of Bulking Agent Injection for Persistent Incontinence in Cases of Neurogenic Bladder Dysfunction. J Urol. 2009 Dec 16.
Richter, Holly E., Albo, Michael E., Zyczynski, Halina M. et al, the Urinary Incontinence Treatment Network, **Retropubic versus Transobturator Midurethral Slings for Stress Incontinence** N Engl J Med 2010 0: NEJMoa0912658
SOGC: **Transvaginal Mesh procedures for Pelvic Organ Prolapse** Feb 2011. http://www.sogc.org/guidelines/documents/gui254TU1102E.pdf
Lovatsis D, Easton W, Wilkie D, Urogynaecology Committee. **SOGC** Guidelines for the evaluation and **treatment of recurrent urinary incontinence following pelvic floor surgery**. J Obstet Gynaecol Can 2010 Sep;32(9):894-99. http://www.sogc.org/guidelines/documents/gui248CPG1009E_000.pdf
Altman Daniel, Väyrynen Tapio, Engh Marie Ellström, et al. for the Nordic Transvaginal Mesh Group. Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse. N Engl J Med 2011; 364:1826-1836.
Walter JE, Lovatsis D, Easton W, Epp A, Farrell SA, Girouard L, Gupta CK, Harvey MA, Larochelle A, et al. **SOGC**: Transvaginal mesh procedures for pelvic organ prolapse. J Obstet Gynaecol Can 2011 Feb;33(2):168-74.
55. Chapple C, Khullar V, Gabriel Z, et al. The effects of antimuscarinic treatments in overactive bladder: a **systematic review** & meta-analysis. Eur Urol. 2005 Jul;48(1):5-26. Epub 2005 Mar 22. Review. Erratum: Eur Urol. 2005 Nov;48(5):875.
56. Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. Eur Urol. 2004 Apr;45(4):420-9; discussion 429.
57. Cardozo L, Chapple CR, Toozs-Hobson P, et al. Efficacy of trospium chloride in patients with detrusor instability: a placebo-controlled, randomized, double-blind, multicentre clinical trial. BJU Int. 2000 Apr;85(6):659-64.
58. Zinner N, Gittelman M, Harris R, et al; Trospium Study Group. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. J Urol. 2004 Jun;171(6 Pt 1):2311-5, quiz 2435.
59. Staskin D, et al.; Trospium Study Group. Once daily 60mg trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. J Urol. 2007 Sep;178(3 Pt 1):978-83.
60. Cardozo L, Lisec M, Millard R, et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. J Urol. 2004 Nov;172(5 Pt 1):1919-24.
61. Layton D, Pearce GL, Shakir SA. Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. Drug Saf. 2001;24(9):703-13.
62. a) Hussain RM, Hartigan-Go K, Thomas SH, Ford GA. Effect of oxybutynin on the QTc interval in elderly patients with urinary incontinence. Br J Clin Pharmacol. 1996 Jan;41(1):73-5. b) Layton D, Pearce GL, Shakir SA. Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. Drug Saf. 2001;24(9):703-13. {See also www.torsades.org }
63. Kaplan SA, Roehrborn CG, Rovner ES, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA. 2006 Nov 15;296(19):2319-28. Erratum in: JAMA. 2007 Mar 21:297(11):1195. JAMA. 2007 Oct 24;298(16):1864.
64. Tsao JW, Heilman KM. Transient memory impairment and hallucinations associated with tolterodine use. N Engl J Med. 2003 Dec 4;349(23):2274-5.
65. Womack KB, Heilman KM. Tolterodine and memory: dry but forgetful. Arch Neurol. 2003 May;60(5):771-3.
66. **3rd International Consultation on Incontinence**. Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Faecal Incontinence. 2005 http://www.icsoffice.org/documents/ici_pdfs_3/v2.pdf/summary.pdf
67. Mitterberger M, Marksteiner R, et al. Autologous myoblasts and fibroblasts for female stress incontinence: a 1-year follow-up in 123 patients. BJU Int. 2007 Nov;100(5):1081-5. Epub 2007 Aug 30.
68. Robinson D, Cardozo L, Terpstra G, Bolodeoku J; Tamsulosin Study Group. A randomized double-blind placebo-controlled multicentre study to explore the efficacy and safety of tamsulosin and **tolterodine** in women with overactive bladder syndrome. BJU Int. 2007 Oct;100(4):840-5.
Pharmacist's Letter. Alpha-Blockers for Urinary Problems in Women. Oct 2010.
69. FDA Dec/07 Certain patients taking desmopressin are at risk for developing severe hyponatremia that can result in seizures and death. Children treated with desmopressin intranasal formulations for primary nocturnal enuresis (PNE) are particularly susceptible to severe hyponatremia and seizures. As such, **desmopressin intranasal formulations** are **no longer indicated** for the **treatment** of **primary nocturnal enuresis** and should not be used in hyponatremic patients or patients with a history of hyponatremia. PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia. http://www.fda.gov/cder/drug/infopage/desmopressin/default.htm Health Canada July 2008 http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/desmopressin_hpc-cps-eng.php
70. Steers WD, Herschorn S, Kreder KJ, et al. Duloxetine OAB Study Group. Duloxetine compared with placebo for treating women with symptoms of overactive bladder. BJU Int. 2007 Aug;100(2):337-45. Epub 2007 May 19.
71. Ghoniem GM, Van Leeuwen JS, et al. Duloxetine/Pelvic Floor Muscle Training Clinical Trial Group. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. J Urol. 2005 May;173(5):1647-53.
72. van Kerrebroeck P, Abrams P, Lange R, et al. Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. BJOG. 2004 Mar;111(3):249-57.
73. Millard RJ, Moore K, Rencken R, et al. Duloxetine UI Study Group. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. BJU Int. 2004 Feb;93(3):311-8.
74. Norton PA, Zinner NR, Yalcin I, Bump RC; Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol. 2002 Jul;187(1):40-8.
75. Dmochowski RR, Miklos JR, Norton PA, et al. Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. J Urol. 2003 Oct;170(4 Pt 1):1259-63.
76. Pharmacotherapy of BPH with overactive bladder. Pharmacist's Letter/Prescriber's Letter Feb 2007;23 (2): 230205.
77. Athanasopoulos A, Perimenis P. Efficacy of the combination of an alpha1-blocker with an anticholinergic agent in the treatment of lower urinary tract symptoms associated with bladder outlet obstruction. Expert Opin Pharmacother. 2005 Nov;6(14):2429-33.
78. Athanasopoulos AA, Perimenis PS. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int. 2005 May;95(7):1117-8.
79. Athanasopoulos A, Gyftopoulos K, Giannitsas K, et al. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. J Urol. 2003 Jun;169(6):2253-6.
80. Wagg AS, Cardozo L, Chapple C, De Ridder D, Kelleher C, Kirby M, Milsom I, Vierhout M. Overactive bladder syndrome in older people. BJU Int. 2007 Mar;99(3):502-9.
81. Chapple C, Khullar V, Gabriel Z, Dooley JA. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. Eur Urol. 2005 Jul;48(1):5-26. Epub 2005 Mar 22. Review. Erratum in: Eur Urol. 2005 Nov;48(5):875.
82. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction (**BOO**). J Urol. 2006 Mar;175(3 Pt 1):999-1004.
83. Gill SS, Mamdani M, Naglie G, Streiner DL, Bronskill SE, Kopp A, Shulman KI, Lee PE, Rochon PA. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. Arch Intern Med. 2005 Apr 11;165(7):808-13.

TOP

84. Hashimoto M, Imamura T, Tanimukai S, Kazui H, Mori E. Urinary incontinence: an unrecognised adverse effect with donepezil. Lancet. 2000 Aug 12;356(9229):568.
Hogan DB, Bailey P, Carswell A, et al. Management of mild to moderate Alzheimer's disease and dementia. Alzheimer's & Dementia 3 (2007) 355-384.
85. DeBeau K. American Geriatrics: Urinary Incontinence (Ch 20). Accessed at: http://www.americangeriatrics.org/staging/products/ui/incon5.m.htm
86. Alhasso AA, McKinlay J, Patrick K, Stewart L. Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD003193.
87. Armitage J, Emberton M. The role of anticholinergic drugs in men with lower urinary tract symptoms. Curr Opin Urol. 2008 Jan;18(1):11-5.
CAU (Canadian Urological Association) 2010 Update: Guidelines for the management of benign prostatic Hyperplasia http://www.cua.org/guidelines/bph_2009_en__v2a.pdf
Nickel JC, Méndez-Probst CE, Whelan TF, Paterson RF, Razvi H. 2010 Update: Guidelines for the management of **benign prostatic hyperplasia**. **Canadian** Urol Assoc J. 2010 Oct;4(5):310-6.
Goode PS, Burgio KL, Johnson TM 2nd, et al. **Behavioral therapy** with or without biofeedback and pelvic floor electrical stimulation for persistent **postprostatectomy incontinence**: a randomized controlled trial. JAMA. 2011 Jan 12;305(2):151-9.
Benign prostatic hyperplasia (BPH): **American** Urological Association (**AUA**) Guidelines **2011**. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chap_1_GuidelineManagementof(BPH).pdf
88. Roehrborn CG, Siami P, et al; on behalf of the **CombAT** Study Group. The Effects of Dutasteride, Tamsulosin and Combination Therapy on Lower Urinary Tract Symptoms in Men With Benign Prostatic Hyperplasia & Prostatic Enlargement: **2-Year** Results From the **CombAT** Study. J Urol. 2007 Dec 12; [Epub ahead of print]
Roehrborn CG, Siami P, Barkin J, et al. on behalf of the CombAT Study Group. The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: **4-Year** Results from the **CombAT** Study. Eur Urol. 2010 Jan;57(1):123-131.
Keam SJ, Scott LJ. Dutasteride: a review of its use in the management of prostate disorders. Drugs. 2008;68(4):463-85. (Dutasteride is being investigated for its efficacy in reducing the risk of prostate cancer in at-risk men in the 4-year REDUCE study and as treatment to extend the time to progression in men with low-risk localized prostate cancer who would otherwise undergo watchful waiting in the 3-year REDEEM study)
Kramer BS, Hagerty KL, Justman S, et al. Use of 5alpha-Reductase Inhibitors for **Prostate Cancer Chemoprevention**: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. J Urol. 2009 Feb 24. [Epub ahead of print] Asymptomatic men with a prostate-specific antigen (PSA) </=3.0 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of both the benefits of 5-ARIs for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer). Men who are taking 5-ARIs for benign conditions such as lower urinary tract [obstructive] symptoms (LUTS) may benefit from a similar discussion, understanding that the improvement of LUTS relief should be weighed with the potential risks of high-grade prostate cancer from 5-ARIs (although the majority of the Panel members judged the latter risk to be unlikely). A reduction of approximately 50% in PSA by 12 months is expected in men taking a 5-ARI; however, because these changes in PSA may vary across men, and within individual men over time, the Panel cannot recommend a specific cut point to trigger a biopsy for men taking a 5-ARI. No specific cut point or change in PSA has been prospectively validated in men taking a 5-ARI. http://jco.ascopubs.org/cgi/reprint/27/9/1502
Redman MW, Tangen CM, Goodman PJ, Lucia MS, Coltman CA Jr, Thompson IM. Finasteride does not increase the risk of high-grade prostate cancer: a bias-adjusted modeling approach. Cancer Prev Res (Phila Pa). 2008 Aug;1(3):174-81. Epub 2008 May 18.
Elliott CS, Shinghal R, Presti JC Jr. The Influence of Prostate Volume on Prostate-Specific Antigen Performance: Implications for the Prostate Cancer Prevention Trial Outcomes. Clin Cancer Res. 2009 Jul 7. [Epub ahead of print]
Pharmacist's Letter. Controversies in Prostate Cancer: Role of PSA Testing and 5-Alpha-Reductase Inhibitors. July, 2009.
Lebdai S, Bigot P, Azzouzi AR. High-grade prostate cancer and finasteride. BJU Int. 2009 Nov 20. [Epub ahead of print]
Vickers AJ, Savage CJ, Lilja H. Finasteride to Prevent Prostate Cancer: Should All Men or Only a High-Risk Subgroup Be Treated? J Clin Oncol. 2010 Feb 16.
Andriole, Gerald L., Bostwick, David G., Brawley, Otis W., et al. the **REDUCE** Study Group, Effect of Dutasteride on the Risk of Prostate Cancer. N Engl J Med 2010 362: 1192-1202.
Tacklind J, Fink HA, MacDonald R, Rutks I, Wilt TJ. **Finasteride** for benign prostatic hyperplasia. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006015. DOI: 10.1002/14651858.CD006015.pub3.
Wilt TJ, Macdonald R, Hagerty K, Schellhammer P, Tacklind J, Somerfield MR, Kramer BS. 5-α-Reductase inhibitors for prostate cancer chemoprevention: an updated Cochrane systematic review. BJU Int. 2010 Nov;106(10):1444-51. doi: 10.1111/j.1464-410X.2010.09714.x.
CAU (Canadian Urological Association) 2010 Update: Guidelines for the management of benign prostatic Hyperplasia http://www.cua.org/guidelines/bph_2009_en__v2a.pdf
Nickel JC, Méndez-Probst CE, Whelan TF, Paterson RF, Razvi H. 2010 Update: **Guidelines** for the management of **benign prostatic hyperplasia**. **Can** Urol Assoc J. 2010 Oct;4(5):310-6.
Andriole GL, Bostwick D, Brawley OW, et al. REDUCE Study Group. The Effect of **Dutasteride** on the Usefulness of Prostate Specific Antigen for the Diagnosis of High Grade and Clinically Relevant Prostate Cancer in Men With a Previous Negative Biopsy: Results From the REDUCE Study. J Urol. 2011 Jan;185(1):126-31.
FDA June/11 notified that the Warnings and Precautions section of the labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs has been revised to include new safety information about the **increased** risk of being diagnosed with a more serious form of prostate cancer **(high-grade prostate cancer)**. {PCPT & Reduce
FDA reviewed data from two prostate cancer prevention trials. In one, finasteride (given daily for 7 years) was associated with a higher frequency of prostate cancers with Gleason scores between 8 and 10, compared with placebo (1.8% vs. 1.1%). In the other, dutasteride (given daily for 4 years) was also associated with more high-grade cancers relative to placebo (1% vs. 0.5%)}.
Theoret Marc R., Ning Yang-Min, Zhang Jenny J., et al. The **Risks and Benefits of 5α-Reductase Inhibitors** for Prostate-Cancer Prevention. June 15, 2011 (10.1056/NEJMp1106783)
Fleshner NE, Lucia MS, Egerdie B, et al. **Dutasteride** in localised prostate cancer management: the **REDEEM** randomised, double-blind, placebo-controlled trial. Lancet 2012; published online January 25.
89. Carson CC. Combination of phosphodiesterase-5 inhibitors and alpha-blockers in patients with benign prostatic hyperplasia: treatments of lower urinary tract symptoms, erectile dysfunction, or both?BJU Int. 2006 Apr;97 Suppl 2:39-43; discussion 44-5.
90. Klausner AP, Steers WD. Antimuscarinics for the treatment of overactive bladder: a review of central nervous system effects.Curr Urol Rep. 2007 Nov;8(6):441-7.
91. Sahai A, Mallina R, Dowson C, Larner T, Khan MS. Evolution of transdermal oxybutynin in the treatment of overactive bladder. Int J Clin Pract. 2008 Jan;62(1):167-70.
92. Farrell SA, Baydock S, Amir B, Fanning C. Effectiveness of a new self-positioning pessary for the management of urinary incontinence in women. Am J Obstet Gynecol. 2007 May;196(5):474.e1-8.
93. Wallace SA, Roe B, Williams K, Palmer M. **Bladder training** for urinary incontinence in adults. **Cochrane** Database Syst Rev. 2004;(1):CD001308.
94. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, et al; Medical Therapy of Prostatic Symptoms (**MTOPS**) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med. 2003 Dec 18;349(25):2387-98.
95. Wilt TJ, N'Dow J. Benign prostatic hyperplasia. Part 2-Management. BMJ. 2008 Jan 26;336(7637):206-10.
Nix JW, Carson CC. Medical management of benign prostatic hypertrophy. Can J Urol. 2007 Dec;14 Suppl 1:53-7.
American Urological Assoc 2006 Kaplan et al. www.auanet.org/guidelines/bph.cfm ;
European 2004 Madersbacher et al. http://www.uroweb.org/fileadmin/user_upload/Guidelines/11%20BPH.pdf
96a. Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of **ureteral calculi**. Ann Emerg Med. 2007 Nov;50(5):552-63. Epub 2007 Aug 3. Our results suggest that "medical expulsive therapy," using either alpha-antagonists or calcium channel blockers, augments the stone expulsion rate compared to standard therapy for moderately sized distal ureteral stones. This meta-analysis of low-quality studies shows that ureteral stone passage can be enhanced by treating patients with an alpha-blocker such as tamsulosin (Flomax) or the calcium channel blocker nifedipine (Procardia). Better studies may refute these findings, but for now either approach is an option. (LOE = 1a-).
Ferre RM et al. Tamsulosin for ureteral stones in the emergency department: A randomized, controlled trial. Ann Emerg Med 2009 Sep; 54:432. (not useful)
John TT, Razdan S. Adjunctive tamsulosin improves stone free rate after ureteroscopic lithotripsy of large renal and ureteric calculi: a prospective randomized study. Urology. 2010 May;75(5):1040-2.
Medical Letter. **Drugs for Kidney Stones**. Nov 29, 2010. (Tamsulosin or long aciting nifedipine +/- corticosteroid) Medical Letter. **Drugs for Kidney Stones**. Nov 29, 2010. (Tamsulosin or long acting nifedipine +/- corticosteroid)
Vincendeau Sebastien; Bellissant Eric; Houlgatte Alain; et al.; for the Tamsulosin Study Group. **Tamsulosin** Hydrochloride vs Placebo for Management of Distal Ureteral Stones: A Multicentric, Randomized, Double-blind Trial. Arch Intern Med. 2010;170(22):2021-2027.
96. Shamliyan TA, Kane RL, Wyman J, Wilt TJ. Systematic Review: Randomized, Controlled Trials of Nonsurgical Treatments for Urinary Incontinence in Women. Ann Intern Med. 2008 Feb 11; [Epub ahead of print]
Society of Obstetricians and Gynaecologists of Canada, Robert M, Ross S, Farrel SA, et all. Conservative management of urinary incontinence. J Obstet Gynaecol Can 2006 Dec;28(12):1113-8. http://www.sogc.org/guidelines/documents/186E-CPG-Decembre2006.pdf
97. Landefeld CS, Bowers BJ, Feld AD, Hartmann KE, Hoffman E, Ingber MJ, et al. National Institutes of Health State-of-the-Science Statement: Prevention of Fecal and Urinary Incontinence in Adults. Ann Intern Med. 2008 Feb 11; [Epub ahead of print].
98. Wilt TJ, Mac Donald R, Rutks I. Tamsulosin for benign prostatic hyperplasia. **Cochrane** Database Syst Rev. 2003;(1):CD002081.
99. Desmopressin monitoring to prevent harm: ISMP bulletin Mar2008: http://infonet.sktnhr.ca/pharmaceutical_services/documents/ISMPCndSafetyBulletin2008-01DDAVP.pdf
100. Thomas LH, et al. Treatment of urinary incontinence **after stroke** in adults. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004462. Data from the available trials are insufficient to guide continence care of adults after stroke. However, there was suggestive evidence that professional input through structured assessment and management of care and specialist continence nursing may reduce urinary incontinence and related symptoms after stroke.
101. Cantrell MA, Bream-Rouwenhorst HR, Steffensmeier A, et al.Intraoperative Floppy Iris Syndrome Associated with {alpha}1-Adrenergic Receptor Antagonists (April). Ann Pharmacother. 2008 Mar 25; [Epub ahead of print] Other alpha1AR antagonists, including terazosin, doxazosin, and alfuzosin, have also been linked to IFIS; however, their relationship to the syndrome is not as definitive. **IFIS** is a clinical syndrome observed during cataract surgery reported in patients taking systemic alpha1AR antagonists. It has been most strongly linked to use of tamsulosin. Medication washout periods of up to 2 weeks and specific surgical procedures have been attempted to reduce risk of complications from alpha1AR antagonists in the setting of cataract surgery.
102. Wilt T, et al. **Five-alpha-reductase Inhibitors for prostate cancer prevention**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD007091. 5ARI reduce prostate cancer risk but may increase risk of high-grade disease in men who are undergoing regular screening for prostate cancer using prostate specific antigen & digital rectal examination. Effects are consistent across race, family history and age and possibly 5ARI but were limited to men with baseline PSA values <4.0 ng/mL.
103. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The Effects of **Antimuscarinic** Treatments in Overactive Bladder: An Update of a **Systematic Review** and Meta-Analysis. Eur Urol. 2008 Jun 20. [Epub ahead of print] Antimuscarinics are efficacious, safe, and well-tolerated treatments that improve HRQL. Profiles of each drug and dosage differ and should be considered in making treatment choices.
104. Burgio KL, Kraus SR, Menefee S, et al. Urinary Incontinence Treatment Network. Behavioral therapy to enable women with urge incontinence to discontinue drug treatment: a randomized trial. Ann Intern Med. 2008 Aug 5;149(3):161-9.
105. Brubaker L, Nygaard I, Richter HE, et al. Two-year outcomes after sacrocolpopexy with and without **burch** to prevent stress urinary incontinence. Obstet Gynecol. 2008 Jul;112(1):49-55. The early advantage of prophylactic Burch colposuspension for stress incontinence that was seen at 3 months remains at 2 years. Apical anatomic success rates are high and not affected by concomitant Burch.
106. Dimitrakov J, Kroenke K, Steers WD, Berde C, Zurakowski D, Freeman MR, Jackson JL. Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. Arch Intern Med. 2007 Oct 8;167(18):1922-9. Review. Erratum in: Arch Intern Med. 2007 Dec 10-22;167(22):2452.
107. Jacobsen SJ, Cheetham TC, Haque R, Shi JM, Loo RK. Association between **5-alpha reductase inhibition and risk of hip fracture**. JAMA. 2008 Oct 8;300(14):1660-4. Exposure to 5-alpha reductase inhibitors was not associated with increased risk of hip fracture. The reduction in risk observed with exposure to 5-alpha reductase inhibitors and the modest increase in risk associated with exposure to alpha-blockers require replication and warrant further investigation.
108. Bauer R, Kaufman R, Mian BM. Use of **anticholinergic therapy in men**. Can J Urol. 2008 Dec;15(6):4359-62.
109. De E. Management of **refractory overactive bladder** in adults. Can J Urol. 2008 Dec;15(6):4388-98.
110. Nickel JC, Krieger JN, McNaughton-Collins M, Anderson RU, Pontari M, Shoskes et al.; Chronic Prostatitis Collaborative Research Network. **Alfuzosin** and symptoms of **chronic prostatitis**-chronic pelvic pain syndrome. N Engl J Med. 2008 Dec 18;359(25):2663-73. Our findings do not support the use of alfuzosin to reduce the symptoms of chronic prostatitis-chronic pelvic pain syndrome in men who have not received prior treatment with an alpha-blocker.
111. Gopal M, Haynes K, Bellamy SL, Arya LA. **Discontinuation rates** of anticholinergic medications used for the treatment of lower urinary tract symptoms. Obstet Gynecol. 2008 Dec;112(6):1311-8. The median time for overall anticholinergic drug discontinuation was 4.76 months. The 6-month unadjusted cumulative incidence of discontinuation was 58.8% (95% confidence interval [CI] 58.4-59.3). The percentage of episodes in which women switched to another medication was 15.8% (95% CI 15.4-16.1). At 6 months, the adjusted cumulative incidence of discontinuation was as follows: oxybutynin 71% (95% CI 68.4-73.5), tolterodine tartrate 61% (59.4,64.3), extended-release oxybutynin 57% (95% CI 55.1-59.4), and extended-release tolterodine tartrate 54% (95% CI 52.3-57.7).Discontinuation rates for anticholinergic medications are high regardless of the class of medication used.
112. Subak LL, Wing R, West DS, et al. **PRIDE** Investigators. Weight loss to treat urinary incontinence in overweight and obese women. N Engl J Med. 2009 Jan 29;360(5):481-90. A 6-month behavioral intervention targeting **weight loss reduced the frequency of self-reported urinary-incontinence** episodes among overweight and obese women as compared with a control group. A decrease in urinary incontinence may be another benefit among the extensive health improvements associated with moderate weight reduction.
113. Herbison GP, Arnold EP. Sacral **neuromodulation** with implanted devices for urinary storage and voiding dysfunction in adults. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004202.
114. Bell Chaim M.; Hatch; Wendy V. et al. Association Between **Tamsulosin and Serious Ophthalmic Adverse** Events in Older Men Following Cataract Surgery. JAMA. 2009;301(19):1991-1996. Exposure to tamsulosin within 14 days of cataract surgery was significantly associated with serious postoperative ophthalmic adverse events. There were no significant associations with exposure to other alpha-blocker medications used to treat BPH.
115. Iliadou A, Milsom I, Pedersen NL, Altman D. Risk of urinary incontinence symptoms in **oral contraceptive** users: a national cohort study from the Swedish Twin Register. Fertil Steril. 2009 Aug;92(2):428-33. Epub 2008 Aug 15.
116. Hartmann KE, McPheeters ML, Biller DH, et al. Treatment of Overactive Bladder in Women. Evid Rep Technol Assess (2008): 187, 1-11.
117. Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375.

TOP

118. Zeif HJ, Subramonian K. **Alpha blockers** prior to removal of a catheter for acute urinary **retention** in adult men. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006744.
119. Robson WL. Clinical practice. Evaluation and management of **enuresis**. N Engl J Med. 2009 Apr 2;360(14):1429-36.
120. Glazener CM, Evans JH, Peto RE. Tricyclic and related drugs for nocturnal **enuresis** in children. Cochrane Database Syst Rev. 2003;(3):CD002117.
121. Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev. 2002;(3):CD002112.
122. Brown JS, Bradley CS, Subak LL, et al. Diagnostic Aspects of Incontinence Study (DAISy) Research Group. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. Ann Intern Med. 2006 May 16;144(10):715-23.
123. Management of **neurogenic bladder in children**. In: Tekgül S, Riedmiller H, Gerharz E, Hoebeke P, Kocvara R, Nijman R, Radmayr Chr, Stein R. Guidelines on paediatric urology. Arnhem, The Netherlands: **European** Association of Urology, European Society for Paediatric Urology; 2009 Mar. p. 31-41.
124. **Monosymptomatic enuresis**. In: Tekgül S, Riedmiller H, Gerharz E, Hoebeke P, Kocvara R, Nijman R, Radmayr Chr, Stein R. Guidelines on paediatric urology. Arnhem, The Netherlands: **European** Association of Urology, European Society for Paediatric Urology; 2009 Mar. p. 29-31.
125. Daniel R, Mallen CD, Cooper J. **Female stress urinary incontinence**-10minute Consultation. BMJ. 2010 Feb 1;340:b5533. doi: 10.1136/bmj.b5533.
126. Feb/10 Health Canada is informing health care professionals of complications associated with the transvaginal implantation of **surgical mesh** for the treatment of stress urinary incontinence and pelvic organ prolapse.
127. Dumoulin C, Hay-Smith J. **Pelvic floor muscle training** versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD005654.
128. Frithsen IL, Simpson WM Jr. Recognition and management of acute medication poisoning. Am Fam Physician. 2010 Feb 1;81(3):316-23.
129. Ostaszkiewicz J, Johnston L, Roe B. **Habit retraining** for the management of urinary incontinence in adults. Cochrane Database Syst Rev. 2004;(2):CD002801.
130. Solans-Domenech M, Sanchez E, Espuna-Pons M. Urinary and anal **incontinence during pregnancy** and postpartum: incidence, severity, and risk factors. Obstet Gynecol. 2010 Mar;115(3):618-28.
131. Kuncharape I, Maeroni B, Johnson D, **Pelvic Organ Prolapse**. Am Fam Physician. 2001 May 1;81(9):1111-1117. (Good **Pessary** overview)
132. Heliovaara-Peippo S, Halmesmaki K, Hurskainen R, et al. The effect of **hysterectomy or levonorgestrel-releasing intrauterine system** on lower urinary tract symptoms: a 10-year follow-up study of a randomised trial. BJOG. 2010 Apr;117(5):602-9. Epub 2010 Feb 15.
133. Anger JT, Weinberg A, Suttorp MJ, Litwin MS, Shekelle PG. Outcomes of **Intravesical Botulinum Toxin** for Idiopathic Overactive Bladder Symptoms: A Systematic Review of the Literature. J Urol. 2010 Apr 16.
134. Goode Patricia S.; Burgio Kathryn L.; Holly E. Richter; Alayne D. Markland. **Incontinence in Older Women**, JAMA. 2010;303(21):2172-2181.
135. Nix D, Haugen V. Prevention and management of **incontinence-associated dermatitis**. Drugs Aging. 2010 Jun 1;27(6):491-6.
136. Ahmad M, McCallum IJ, Mercer-Jones M. Management of **faecal incontinence** in adults. BMJ. 2010 Jun 15;340:c2964.
137. Thirugnanasothy S. Managing **urinary incontinence in older people**. BMJ 2010;341:c3835, doi: 10.1136/bmj.c3835 (Published 9 August 2010)
138. Sand PK, Johnson Ii TM, Rovner ES, Ellsworth PI, Oefelein MG, Staskin DR. **Trospium** chloride once-daily extended release is efficacious and tolerated in elderly subjects (aged >/=75 years) with overactive bladder syndrome. BJU Int. 2010 Aug 6.
139. Lordêlo P, Teles A, Veiga ML, Correia LC, Barroso U Jr. Transcutaneous electrical nerve stimulation (**TENS**) in children with overactive bladder: a randomized clinical trial. J Urol. 2010 Aug;184(2):683-9.
140. American Urological Association Education and Research. Guideline for the **surgical management of female stress urinary incontinence**: 2009 update. Linthicum (MD): American Urological Association Education and Research, Inc.; 2009.
141. Pharmacist's Letter. **Alpha-Blockers for Urinary Problems in Women**. Oct 2010.
142. Nieminen K, Hiltunen R, Takala T, et al. Outcomes after **anterior vaginal wall repair with mesh**: a randomized, controlled trial with a 3 year follow-up. Am J Obstet Gynecol. 2010 Sep;203(3):235.e1-8. Epub 2010 May 21.
143. Afonso AS, Verhamme KM, Stricker BH, et al. **Inhaled anticholinergic drugs** and risk of acute urinary retention. BJU Int. 2010 Sep 29. doi: 10.1111/j.1464-410X.2010.09600.x. Current use of inhaled anticholinergic drugs increases the risk of AUR, especially in patients with BPH or if administered via a nebulizer.
144. **NICE** guideline Oct/10: **Nocturnal enuresis** - the management of bedwetting in **children and young people**. http://www.nice.org.uk/nicemedia/live/13246/51367/51367.pdf
145. Kwak KW, Lee YS, Park KH, Baek M. Efficacy of **Desmopressin and Enuresis Alarm** as First and Second Line Treatment for Primary Monosymptomatic Nocturnal Enuresis: Prospective Randomized Crossover Study. J Urol. 2010 Oct 18.
146. Homma Y, Kakizaki H, Yamaguchi O, et al. Assessment of Overactive Bladder Symptoms: Comparison of **3-Day Bladder Diary and the Overactive Bladder Symptoms Score**. Urology. 2010 Oct 14.
147. Frank, Christopher, Szlanta, Agata. Office management of urinary incontinence among **older patients**. Can Fam Physician 2010 56: 1115-1120.
148. Anothaisintawee T, Attia J, Nickel JC, et al.. Management of **chronic prostatitis/chronic pelvic pain syndrome**: a systematic review and network meta-analysis. JAMA. 2011 Jan 5;305(1):78-86.
149. Wang CJ, Lin YN, Huang SW, Chang CH. Low dose oral **desmopressin for nocturnal polyuria** in patients with **benign prostatic hyperplasia**: a double-blind, placebo controlled, randomized study. J Urol. 2011 Jan;185(1):219-23.
150. Allan GM, Ivers N, Kolber M. **Medical management of renal stones**: More than analgesia? Can Fam Physician. 2011 Feb;57(2):198.
151. Lovatsis D, Easton W, Wilkie D, Urogynaecology Committee. **SOGC** Guidelines for the evaluation and **treatment of recurrent urinary incontinence following pelvic floor surgery**. J Obstet Gynaecol Can 2010 Sep;32(9):894-99. http://www.sogc.org/guidelines/documents/gui248CPG1009E_000.pdf
152. French LM, Bhambore N. **Interstitial cystitis**/painful bladder syndrome. Am Fam Physician. 2011 May 15;83(10):1175-81.
153. Friedman Bat-Chen, Friedman Boris, Goldman Ran D.. **Oxybutynin for treatment of nocturnal enuresis in children**. Canadian Family Physician. May 2011.
154. Stephenson Anne; Seitz Dallas; Bell Chaim M.; et al. Inhaled **Anticholinergic Drug Therapy and the Risk of Acute Urinary Retention** in Chronic Obstructive Pulmonary Disease: A Population-Based Study. Arch Intern Med. 2011;171(10):914-920.
155. Glazener C, Boachie C, Buckley B, et al. Urinary incontinence in men after formal one-to-one **pelvic-fl oor muscle training following radical prostatectomy or transurethral resection of the prostate** (**MAPS**): two parallel randomised controlled trials. Lancet 2011; online July 12. (unlikely to be effective))
156. FDA July/11 **Surgical placement of mesh to repair pelvic organ prolapse poses risks.** In treating pelvic organ prolapse, use of mesh, especially if placed transvaginally, "may expose patients to greater risk than other surgical options," the FDA warned this week. The agency estimates there were at least 100,000 prolapse repairs done with mesh last year, most done transvaginally. The FDA reports that the most frequent complications resulting from mesh include protrusion of the mesh out of vaginal tissue, pain, infection, bleeding, and pain during intercourse. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm262752.htm
157. Health Canada Aug/11 is informing healthcare practitioners and patients of a labelling update for **finasteride drugs to add safety information on rare reports of breast cancer in men**.
158. FDA Aug/11 Botox (onabotulinumtoxinA) has been approved to treat urinary incontinence in patients with overactive bladder due to neurologic conditions (e.g., multiple sclerosis).
159. Paquette A, Gou P, Tannenbaum C. Systematic review and meta-analysis: do clinical trials testing **antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events**?. J Am Geriatr Soc. 2011 Jul;59(7):1332-9. (More-detailed standardized measurement required)
160. Varilla V, Samala RV, Galindo D, Ciocon J. **Nocturia** in the elderly: A wake-up call. Cleve Clin J Med. 2011 Nov;78(11):757-64.
161. Nelken RS, Ozel BZ, Leegant AR, Felix JC, Mishell DR Jr. Randomized trial of **estradiol vaginal ring versus oral oxybutynin** for the treatment of overactive bladder. Menopause. 2011 Sep;18(9):962-6.
162. Duthie JB, Vincent M, Herbison GP, et al. **Botulinum toxin injections** for adults with overactive bladder syndrome. Cochrane Database Syst Rev. 2011 Dec 7;12:CD005493. Intravesical botulinum toxin appears to be an effective therapy for refractory OAB symptoms, but as yet little controlled trial data exist on benefits and safety compared with other interventions, or with placebo.
163. Pannek J, Stöhrer M, Blok B, Castro-Diaz D, Del Popolo G, Kramer G, Radziszewski P, Reitz A, Wyndaele J-J. Guidelines on **neurogenic lower urinary tract dysfunction**. Arnhem, The Netherlands: European Association of Urology (**EAU**); 2011 Mar.
164. Chung SD, Chen YK, Chen YH et al. **Hyperthyroidism** and female urinary incontinence: a population-based cohort study. Clin Endocrinol (Oxf). 2011 Nov;75(5):704-8.
165. Brazzelli M, Griffiths PV, Cody JD, et al. Behavioural and cognitive interventions with or without other treatments for the management of **faecal incontinence** in children. Cochrane Database Syst Rev. 2011 Dec 7;12:CD002240
166. Sengupta G et al. Comparison of **Murraya koenigii- and Tribulus terrestris**-Based Oral Formulation **Versus Tamsulosin** in the Treatment of Benign Prostatic Hyperplasia in Men Aged >50 Years: A Double-Blind, Double-Dummy, Randomized Controlled Trial. Clin Ther. 2011 Dec; 33(12):1943-52.
167. Madhuvrata P, Cody JD, Ellis G, et al. Which **anticholinergic drug for overactive bladder symptoms in adults**. Cochrane Database Syst Rev. 2012 Jan 18;1:CD005429. Where the prescribing choice is between oral immediate release oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth. With tolterodine, 2 mg twice daily is the usual starting dose, but a 1 mg twice daily dose might be equally effective, with less risk of dry mouth. If extended release preparations of oxybutynin or tolterodine are available, these might be preferred to immediate release preparations because there is less risk of dry mouth. Between solifenacin and immediate release tolterodine, solifenacin might be preferred for better efficacy and less risk of dry mouth. Solifenacin 5 mg once daily is the usual starting dose, this could be increased to 10 mg once daily for better efficacy but with increased risk of dry mouth. Between fesoterodine and extended release tolterodine, fesoterodine might be preferred for superior efficacy but has higher risk of withdrawal due to adverse events and higher risk of dry mouth.There is little or no evidence available about quality of life, costs, or long-term outcome in these studies. There were insufficient data from trials of other anticholinergic drugs to draw any conclusions.
168. Burgio KL, Goode PS, Johnson TM, et al. **Behavioral versus drug treatment** for overactive bladder in **men**: the Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial. J Am Geriatr Soc. 2011 Dec;59(12):2209-16.
169. Campbell SE, Glazener CM, Hunter KF, et al. Conservative management for **postprostatectomy urinary incontinence**. Cochrane Database Syst Rev. 2012 Jan 18;1:CD001843. The value of the various approaches to conservative management of postprostatectomy incontinence after radical prostatectomy remains uncertain. It seems unlikely that men benefit from one-to-one pelvic floor muscle training therapy after transurethral resection of the prostate (TURP). Long-term incontinence may be managed by external penile clamp, but there are safety problems.
170. Health Canada Mar/12 is informing health professionals and the public that the prescription drugs **finasteride and dutasteride** may be associated with an increased risk of developing a serious form of prostate cancer known as **high-grade prostate cancer**.
171. FDA: Apr/12 The labels of the alopecia drug Propecia (**finasteride** 1 mg) and the benign prostatic hyperplasia drug Proscar (finasteride 5 mg) are being updated with an expanded list of adverse **sexual effects**, the FDA has announced. Propecia label will include libido, ejaculation, and orgasm disorders that persist after treatment ends; Proscar label will include decreased libido that persists posttreatment & both labels will note reports of male infertility or poor semen quality that improved after drug discontinuation.
172. Gacci M, Corona G, Salvi M, et al. A Systematic Review and Meta-analysis on the Use of **Phosphodiesterase 5 Inhibitors** Alone or in Combination with α-Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. Eur Urol. 2012 May;61(5):994-1003.
173. Marinkovic SP, Rovner ES, Moldwin RM, et al. The **management of overactive bladder syndrome**. BMJ. 2012 Apr 17;344:e2365.
174. Robinson D, Cardozo L. **Antimuscarinic drugs** to treat overactive bladder. BMJ. 2012 Mar 27;344:e2130.
175. Nager CW, Brubaker L, Litman HJ, et al; the Urinary Incontinence Treatment Network. A Randomized Trial of **Urodynamic Testing before Stress-Incontinence Surgery**. N Engl J Med. 2012 May 2.
176. Kiddoo DA. **Nocturnal enuresis**. CMAJ. 2012 Apr 23.
177. Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Systematic Review: **Benefits and Harms of Pharmacologic Treatment for Urinary Incontinence** in Women. Ann Intern Med. 2012 Apr 9.
178. Huang AJ, Hess R, Arya LA, et al. Pharmacologic treatment for urgency-predominant urinary incontinence in women diagnosed using a **simplified algorithm**: a randomized trial. Am J Obstet Gynecol. 2012 May;206(5):444.e1-444.e11.
179. Brubaker L, Cundiff GW, Fine P, et al. **Abdominal sacrocolpopexy with Burch colposuspension** to reduce urinary stress incontinence. N Engl J Med 2006;354:1557-66.
180. Wei JT, Nygaard I, Richter HE, et al. A **midurethral sling** to reduce incontinence **after vaginal prolapse repair**. (**OPUS**) N Engl J Med 2012;366:2358-67.

TOP

Other Urinary Incontinence Patient Resources:

- Bladder Retraining: http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-4.pdf ; or http://www.fmpe.org/en/documents/handouts/handout_ui_retraining.pdf
- Pelvic Muscle Exercises (Kegel Exercises): http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-3.pdf
- Voiding Diary: http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-2.pdf
- Patient Information - Urinary Incontinence: http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-1.pdf
- CFPC: www.cfpc.ca/English/cfpc/programs/patient%20education/urinary%20incontinence
- American (ACOG): www.acog.com/publications/patient_education/bp081.cfm

TOP

1) Breaking the "cold chain"

Canadian Guidelines: Refrigerated vaccines should be stored between +2°C and +8°C. Frozen vaccines should be stored at -15°C or colder. Store light sensitive vaccines away from light. Follow manufacturer recommendations for storage & transport. Administration requires someone trained to give im/sc injections.

Fridges:

-Fridge used should be dedicated to the storage of vaccines only.

-**Use of bar fridges for vaccine storage is the leading cause of cold chain breaks in Canada. Bar fridges are not recommended for the purpose of storing vaccines.**

- Keeping temperature of fridge stable **(2-8° C)**: Avoid opening refrigerator door unnecessarily, store containers of water in refrigerators, or ice packs in the freezer

NEVER store vaccines in the vegetable bin section of the refrigerator. Ideal storage location for vaccine: In the middle compartment, away from floor, coils, walls, and venting for the freezer or cold air.

-Temperature of the compartments of the refrigerator where the vaccine is stored should be checked and logged at least twice a day. Fridge temperatures outside of the 2 to 8 degree C range must be reported immediately to obtain recommendation on the stability of the affected product.

- Fridge temperature recording logs should be retained for 2 years.

- Min-Max thermometer batteries should be routinely changed twice a year: December 1 and June 1 and the date of changing noted on the device.

Transporting Refrigerated Vaccines: Avoid breaking the cold chain

1) Transport vaccines in insulated containers at all times. Hard sided plastic insulated containers, or Styrofoam containers with walls at least 2 inch thick walls should be used. Icepacks should be placed inside the transport container to maintain the cold chain. To prevent freezing the vaccine should never be placed directly onto an ice pack. Instead an insulating barrier (i.e. bubble wrap, Styrofoam peanuts) should be placed between vaccine and ice pack.
2) Make sure vaccine is never placed in trunk of vehicle, or in direct contact with sunlight. Also the vaccine should not be placed in line with the air from the vehicles heater or air conditioner. Vaccine should never be left in a vehicle unattended.
3) If a break in the cold chain identified prior to administration of the vaccine, contact your local public health authority about the appropriate course of action. While waiting for a decision, ensure that the vaccine is stored in appropriate cold chain conditions. The vaccine should not be administered until a decision has been reached.
4) If a break in the cold chain is identified after administration of the vaccine, contact your local public health authority. The type of vaccine, duration and temperature of the exposure will be taken into account in order to determine the course of action. Serological testing or revaccination may be suggested.

Further information: available from the Public Health Agency of Canada's Website. References:

1) Vaccine Storage and Handling Guidelines. Pharmacists letter/Prescriber's letter. May 2008-Volume 24-Number 240517.
2) Canadian Immunization Guide 2006.
3) National Vaccine Storage and Handling Guidelines for immunization providers (2007). Public Health Agency of Canada. http://www.phac-aspc.gc.ca/publicat/2007/nvshglp-ldemv/index-eng.php (Good link for additional information); Other: http://www.vaccineinformation.org/;

2) Anaphylaxis Management with vaccine administration:

1) Patients should be kept under supervision for 15 minutes (JE-VAX: 30 minutes) following administration.
2) In order to treat anaphylaxis perform the following steps (note steps a-d should be performed rapidly or simultaneously, however the priority is to complete step a):
   a) **Promptly administer 0.01 mL/kg (maximum 0.5 mL) of aqueous epinephrine 1:1000 by intramuscular (or subcutaneous) injection in the opposite limb to that in which the vaccination was given (or the vastus lateralis). Prompt administration is essential.**
   b) Call for an ambulance
   c) Place the patient in a recumbent position, and elevate their feet.
   d) If necessary, establish an oral airway.
   e) Patients with severe reactions such as cyanosis, dyspnea, should be given oxygen if it is available. Pulse oximetry can be used to monitor if available.
   f) If the vaccine was administered subcutaneously, an additional dose of 0.005 mL/kg (maximum 0.3 mL) of aqueous epinephrine 1:1000, can be injected into the vaccination site to slow down absorption. This should be done shortly after administration of the first dose of epinephrine in moderate to severe cases, and generally should not be repeated. Local injection of epinephrine into an intramuscular vaccination site is contraindicated, as it speeds up absorption of the vaccine.
   g) A dose of diphenhydramine hydrochloride (Benadryl®) can be given as an adjunct to epinephrine. The oral route of diphenhydramine is preferred for conscious patients who are not seriously ill (as the intramuscular injection is painful). Oral dose: 1-2 mg/kg to a maximum single dose of 50 mg.
   h) An inhaled β-agonist should be considered if there is a bronchospasm resistant to an adequate dose of epinephrine (e.g., nebulized salbutamol 2.5-5.0 mg in 3 mL of saline or 1 puff per 3 kg to a maximum of 10 puffs by metered dose inhalers).
   i) Vital signs should be monitored continuously.
   j) Patient should be transported to emergency department for long term monitoring.

◆Epinephrine dosing can be repeated twice at 5-minute intervals if necessary, for a total of three doses. The limb in which the vaccination was given should be avoided. A different limb is preferred for each dose to maximize drug absorption.

3) **Breastfeeding and Vaccinations:** Immunizations for actively breastfeeding women are considered safe, with the exception of smallpox vaccine and yellow fever, by both the CDC and the American academy of pediatrics. Breastfeeding does not appear to influence the maternal immune response. Vaccines do not appear to affect the safety of breast milk for infants.[10,11]

RX FILES

References

We would like to acknowledge the following contributors and reviewers: Dr. B. Tan (member NACI; SHR-Ped), Dr. T. Diener (RQHR-Pub Health), Dr. J. Opondo (SHR-Medical Health Office), Jeanette Humphreys (SHR-Public Health), Kathleen Chipperfield (SHR-OHS); Pam Komonoski (RN-NP; U of S Student Health); N. Popick, (SHR Travel Clinic), Dr. T. Laubscher (SHR-FM), Dr. J. Kriegler (Saskatoon-FP), Rosalie Tuchscherer, (Public Health Nursing Consultant, Ministry of Health, SK), Shirley Blyth, (Inventory, SK Health), & the RxFiles Advisory Committee. *Prepared by*Kavita Parihar *(SPEP, U of S Pharmacy)*, Loren Regier *BSP, BA*, Brent Jensen *BSP*

[1] Therapeutic Choices 5rd Edition

[2] Micromedex 2011

[3] Advisory Committee on Immunization Practices (**ACIP**). Recommended adult immunization schedule: USA, 2009*. Ann Intern Med. 2009 Jan 6;150(1):40-4. Also accessible via : http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5753a6.htm
Committee on Infectious Diseases, Recommended **Childhood and Adolescent** Immunization Schedules--United States, **2010**. Pediatrics 2010 125: 195-196.
Advisory Committee on Immunization Practices. Recommended **Adult Immunization** Schedule: United States, **2010**. Ann Intern Med January 5, 2010 152:36-39.
http://www.annals.org/content/152/1/36.full.pdf+html ; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5901a5.htm?s_cid=mm5901a5_x
ACIP: Advisory Committee on Immunization Practices. Recommended **Adult Immunization** Schedule: **United States, 2011**. Ann Intern Med February 1, 2011 154:168-173.
CDC. **General recommendations on immunization practices**: by ACIP. MMWR Recomm Rep. 2011;60(RR-02):1–60 http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf
ACIP: Recommended **Adult Immunization Schedule**: United States, **2012**. Advisory Committee on Immunization Practices. Ann Intern Med E-388 ahead of print January 31, 2012.
AAP/ACIP: Recommended **Childhood and Adolescent** Immunization Schedules—United States, 2012. Committee on Infectious Diseases. Pediatrics **2012**; 129:2 385-386.

[4] *Public Health Agency of Canada, http://www.phac-aspc.gc.ca/im/q_a_thimerosal-eng.php*

[5] Canadian Coalition for Immunization Awareness and Promotion, http://www.immunize.cpha.ca/en/publications-resources/questions/autism.aspx)

[6] Lancet retracts Wakefield paper linking MMR vaccine to autism (01Feb, 2010). http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60175-7/fulltext
Price, CS., Thompson, WW., Goodson, B, et al. Prenatal and Infant Exposure to Thimerosal From Vaccines and Immunoglobulins and Risk of Autism. Pediatrics 2010 0: peds.2010-0309.

[7] a) Ascherio A, Zhang SM, Hernán MA, Olek MJ, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med*. 2001 Feb 1;344(5):327-32). b) Demicheli V, Rivetti A, Di Pietrantonj C, Clements CJ, Jefferson T. *J Viral Hepat*. 2003 Sep;10(5):343-4. *Hepatitis B vaccination and multiple sclerosis: evidence from a systematic review.*

[8] Canadian Immunization Guide 2006

[9] Public Health Agency of Canada PHAC. Statement on recommended use of herpes zoster vaccine. Jan 2010. (NACI) Accessed online 03Feb10 at http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-1/index-eng.php

[10] Kroger AT, Atkinson WL, Marcuse EK, Pickering LK, Advisory Committee on Immunization Practices (ACIP) Centers for Disease Contr on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-15): 1-48.

[11] Pickering LK, Baker CJ, Long SS, McMillan JA, eds. Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics.

Additional references:

Gerber JS, Offit PA. Vaccines and Autism: A Tale of Shifting Hypotheses. Clin Infect Dis. 2009 Jan 7. [Epub ahead of print]

Gruslin A, Steben M, Halperin S, et al. Immunization in pregnancy. J Obstet Gynaecol Can. 2008 Dec;30(12):1149-54.

Health Canada: HPV It's your health. Sept 2010: http://hc-sc.gc.ca/hl-vs/iyh-vsv/diseases-maladies/hpv-vph-eng.php

Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med. 2009 Jan 15;360(3):244-56.

Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009 Jan 6;180(1):48-58. {InfoPOEMs Mar 2009. The evidence to support the efficacy of pneumococcal polysaccharide vaccine (PPV) in adults is limited at best. The best studies have not shown a consistent benefit, particularly in the most vulnerable populations that we currently target. The impact of increasing herd immunity due to infant vaccination using conjugate vaccines is another factor, although that is not addressed by this analysis. An accompanying editorial argues that some studies excluded for methodologic limitations should have been included, and vice versa, and called for additional well-designed studies in relevant populations rather than a cessation of the vaccination. (LOE = 1a-).}

Juurlink DN, et al. Guillain-Barre syndrome after influenza vaccination in adults: a population-based study. Arch Intern Med. 2006 Nov 13;166(20):2217-21.

Kim JJ, et al. Cost-Effectiveness of Human Papillomavirus Vaccination & Cervical Cancer Screening in Women Older Than 30 Years in the USA. Ann Intern Med 2009; 538-545.

Medical Letter, Treatment Guidelines. Adult Immunization. Apr, 2009;7:27-36. Dec, 2011; 9(112):75-82.

Omer SB et al. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. N Engl J Med 2009 May 7; 360:1981.

Thompson WW, Vaccine Safety Datalink Team. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years.N Engl J Med. 2007 Sep 27;357(13):1281-92.

Tozzi AE, Bisiacchi P, Tarantino V, et al. Neuropsychological performance 10 years after immunization in infancy with thimerosal-containing vaccines. Pediatrics. 2009 Feb;123(2):475-82.

Canadian Pediatric Info: NACI:CIG Online Canadian Guidelines: www.naci.gc.ca

USA Pediatric Info: Pediatric USA Immunization Guideline for Ages 0-6 for **2010** http://aapredbook.aappublications.org/resources/IZSchedule0-6yrs.pdf
Adolescent USA Recommended Immunization Schedule for Persons Aged 7 Through 18 Years **2010** http://aapredbook.aappublications.org/resources/IZSchedule7-18yrs.pdf
AAP/ACIP: Recommended **Childhood and Adolescent** Immunization Schedules—United States, **2012**. Committee on Infectious Diseases. Pediatrics 2012; 129:2 385-386.
USA Catch-up Schedule for Aged 4Months Through 18Yrs who start late or who are more than 1month behind-**2010**
http://aapredbook.aappublications.org/resources/IZScheduleCatchup.pdf http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5851a6.htm

Additional references:

TOP

AAP Policy Statement--**Prevention of Varicella**: Update of Recommendations for Use of Quadrivalent and Monovalent Varicella Vaccines in Children. Pediatrics. 2011 Aug 28.

American Academy of Pediatrics (AAP). Committee on Infectious Diseases. Recommendations for **prevention and control of influenza in children, 2011-2012**. Pediatrics. 2011 Oct;128(4):813-25.

Aaby P, Whittle H, Stabell Benn C. Vaccine programmes must consider their effect on general **resistance**. BMJ. 2012 Jun 14;344:e3769.

Aylward Bruce, Yamada Tadataka. The **Polio Endgame**. N Engl J Med 2011; 364:2273-2275.

Allan, G. Michael, Ivers, Noah. The **autism-vaccine story**: fiction and deception? Can Fam Physician 2010 56: 1013.

Anderson, Evan J., Rupp, Angela, Shulman, Stanford T., et al. Impact of **Rotavirus Vaccination** on Hospital-Acquired Rotavirus Gastroenteritis in Children. Pediatrics 2011 127: e264-e270.

Baxter R, Lewis N, Bakshi N, et al. CISA Network. **Recurrent Guillain-Barre syndrome following vaccination**. Clin Infect Dis. 2012 Mar;54(6):800-4.

Bazemore A, Huntington M. The **Pretravel Consultation**. Am Fam Physician. 2009;80 (6):583-590.

Beaulieu Andrée-Anne, Boggild Andrea K.. Cases: **Enteric fever** in two vaccinated travellers to Latin AmericaCMAJ October 18, 2011 183:1740-1745; published June 20, 2011.

Bégué RE, Perrin K. Reduction in gastroenteritis with the use of **pentavalent rotavirus** vaccine in a primary practice. Pediatrics. 2010 Jul;126(1):e40-5.

Bingham CO 3rd, et al. Immunization responses in rheumatoid arthritis patients treated with **rituximab**: Results from a controlled clinical trial. Arthritis Rheum. 2009 Dec 28;62(1):64-74.

Bortolussi R, Salvadori M; Canadian Paediatric Society, Immunization and infectious diseases committee. a **new meningococcal conjugate vaccine**: What should physiciansknow and do? Paediatr child health 2009;14(8):515-517. http://www.cps.ca/english/statements/ID/ID09-02.pdf

Bozzo P, Narducci A, Einarson A. **Vaccination during pregnancy**. Can Fam Physician. 2011 May;57(5):555-7.

Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011

Brotherton JML, Fridman M, May CL, et al. **Early eff ect of the HPV vaccination** programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet 2011; 377: 2085–92.

Bryant, KA., Block, SL., Baker, SA. for the PCV13 Infant Study Group, et al. Safety and Immunogenicity of a **13-Valent Pneumococcal Conjugate Vaccine**. Pediatrics 2010 125: 866-875

Bugenske E, Stokley S, Kennedy A, Dorell C. **Middle School Vaccination Requirements** and Adolescent Vaccination Coverage. Pediatrics. 2012 May 7.

Bundy DG, Solomon BS, Kim JM et al. Accuracy and Usefulness of the **HEDIS Childhood Immunization Measures**. Pediatrics. 2012 Apr;129(4):648-56.

Campitelli MA, Inoue M, Calzavara AJ, et al. Low Rates of **Influenza** Immunization in Young Children Under Ontario's Universal Influenza Immunization Program. Pediatrics. 2012 May 14.

Castle PE, Rodríguez AC, Burk RD, et al.; Proyecto Epidemiológico Guanacaste (PEG) Group. Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study. BMJ. 2009 Jul 28;339:b2569. doi: 10.1136/bmj.b2569.

CATMAT: Canadian Committee to Advise on Tropical medicine and Travel. **Statement on older travellers**. CCDR 2011;37(ASC2):1-24. www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-2/index-eng.php

Centers for Disease Control and Prevention (CDC). Updated interim recommendations — HIV-infected adults and adolescents: Considerations for clinicians regarding 2009 **H1N1** influenza. Oct 21 , 2009. (http://www.cdc.gov/h1n1flu/guidance_HIV.htm)

Centers for Disease Control and Prevention (CDC). Pneumonia hospitalizations among young children before and after introduction of **pneumococcal conjugate vaccine**--United States, 1997-2006. MMWR Morb Mortal Wkly Rep. 2009 Jan 16;58(1):1-4.

Centers for Disease Control June 24, 2010 — The US Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) has voted to eliminate precautionary language regarding the risk for **Guillain-Barré syndrome** (GBS) after meningococcal vaccination. In addition, countering current recommendations, ACIP also recommended children aged 6 months to 9 years who have not been immunized with the 2009 H1N1 monovalent vaccine receive 2 rather than 1 dose of seasonal influenza vaccine.

CDC: **Yellow Fever Vaccine** Recommendations of the Advisory Committee on Immunization Practices (ACIP) 2010 http://www.cdc.gov/mmwr/pdf/rr/rr5907.pdf

CDC: Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the **23-Valent Pneumococcal Polysaccharide Vaccine** (PPSV23) MMWR September 3, 2010 / 59(34);1102-1106 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5934a3.htm?s_cid=mm5934a3_x

CDC: **Vaccination Coverage** among Adolescents Aged 13--17 Years --- United States, 2009 http://www.cdc.gov/mmwr/pdf/wk/mm5932.pdf

CDC : Centers for Disease Control and Prevention (CDC). National and state vaccination coverage among children aged 19--35 months --- United States, 2010. MMWR Morb Mortal Wkly Rep. 2011 Sep 2:60:1157-63. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6034a2.htm?s_cid=mm6034a2_x

CDC: Nov/11 **Immunization of Health-Care Personnel**. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Recommendations and Reports. http://www.cdc.gov/mmwr/pdf/rr/rr6007.pdf

CDC **Adult Vaccination Coverage -** United States, 2010. *Weekly*. February 3, **2012** / 61(04);66-72 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6104a2.htm?s_cid=mm6104a2_w

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. **Human Papillomavirus** and Rising Oropharyngeal Cancer Incidence in the United States. J Clin Oncol. 2011 Oct 3.

Chaves SS, Lopez AS, Watson TI, et al. **Varicella in infants after implementation of the US varicella vaccination program**. Pediatrics. 2011;128(6):1071–1077.

Chen N, Li Q, Zhang Y, et al. Vaccination for preventing **postherpetic neuralgia**. Cochrane Database Syst Rev. 2011 Mar 16;3:CD007795. There is insufficient direct evidence from specialised trials to prove the efficacy of vaccine for preventing postherpetic neuralgia beyond its effect on reducing herpes zoster, although vaccination may be efficacious and safe for preventing herpes zoster and thus reduce the incidence of postherpetic neuralgia in adults aged 60 years or older.

Chen HL, Lin LH, Hu FC et al. Effects of Maternal Screening and Universal Immunization to Prevent Mother-To-Infant Transmission of **HBV**. Gastroenterology. 2011 Dec 23.

Cherry JD. Why do **pertussis vaccines fail**? Pediatrics. 2012 May;129(5):968-70.

Chouliaras, Giorgos, Spoulou, Vana, Quinlivan, Mark, et al. Vaccine-Associated Herpes **Zoster** Opthalmicus and Encephalitis in an Immunocompetent Child. Pediatrics 2010 125: e969-e972.

Chung EY, Huang L, Schneider L. Safety of **influenza vaccine** administration in **egg-allergic** patients. Pediatrics. 2010 May;125(5):e1024-30. Epub 2010 Apr 5.

Clark SJ, Butchart A, Kennedy A, et al. Parents' experiences with and preferences for **immunization reminder/recall technologies**. Pediatrics. 2011 Nov;128(5):e1100-5.

Cobb JE, Cohen LL. A randomized controlled trial of the **ShotBlocker** for children`s immunization distress. Clin J Pain. 2009 Nov-Dec;25(9):790-6. (Data not support effectiveness)

Cohen Steven A., Chui Kenneth K.H., Naumova Elena N.. **Influenza** Vaccination in **Young Children Reduces Influenza-Associated Hospitalizations in Older Adults**, 2002–2006. Journal of the American Geriatrics Society. Article first published online: 28 JAN 2011. DOI: 10.1111/j.1532-5415.2010.03271.x.

Cohen, Arlan, Maschopoulos, Panagis, et al. **Congenital varicella syndrome**: the evidence for secondary prevention with **varicella-zoster immune globulin**. CMAJ 2011 0: cmaj.100615.

Committee on Infectious Diseases, Prevention of **Rotavirus Disease**: Updated Guidelines for Use of Rotavirus Vaccine. Pediatrics 2009 123: 1412-1420.

Committee on Infectious Diseases, **Rabies**-Prevention Policy Update: New Reduced-Dose Schedule. Pediatrics 2011 127: 785-787.

Committee on Practice and Ambulatory Medicine and Council on Community Pediatrics, **Increasing Immunization Coverage**, Pediatrics 2010 125: 1295-1304

Committee on Infectious Diseases. Additional recommendations for use of **tetanus toxoid, reduced-content diphtheria toxoid, and acellular pertussis** vaccine (tdap). Pediatrics. 2011 Oct;128(4):809-12.

Committee on Infectious Diseases. Recommendations for administering **hepatitis a** vaccine to contacts of international adoptees. Pediatrics. 2011 Oct;128(4):803-4.

Committee on Infectious Diseases. **Meningococcal conjugate vaccines** policy update: booster dose recommendations. Pediatrics. 2011 Dec;128(6):1213-8.

Coulson E, Saravanan V, Hamilton J, et al. **Pneumococcal antibody** levels after **pneumovax** in patients with rheumatoid arthritis on **methotrexate**. Ann Rheum Dis. 2011 Jul;70(7):1289-91.

Cortes JE, Curns AT, Tate JE, et al. **Rotavirus** Vaccine and Health Care Utilization for Diarrhea in U.S. Children. N Engl J Med 2011;365:1108-17.

Cortese MM, LeBlanc J, White KE, et al. Leveraging state immunization **information systems** to measure the effectiveness of **rotavirus** vaccine. Pediatrics. 2011;128(6).

Corti D, Voss J, Gamblin SJ, et al. A **neutralizing antibody** selected from plasma cells that binds to group 1 and group 2 **influenza** A hemagglutinins. Science 2011;333:850-6.

CPS: Canadian Paediatric Society Sep/11. Two shots are better than one to ward off **chickenpox**.

Crowe SR, Merrill JT, Vista ES, Dedeke AB, et al. Influenza vaccination responses in human systemic **lupus erythematosus**: impact of clinical and demographic features. Arthritis Rheum. 2011 May 19. doi: 10.1002/art.30388.

de Sanjose S, Quint WG, Alemany L, et al. on behalf of the Retrospective International Survey and **HPV** Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010 Oct 15. (HPV types 16, 18, 31, 33, 35, 45, 52, and 58 should be given priority)

Deeks SL, Lim GH, Simpson MA, et al. An assessment of **mumps** vaccine effectiveness by dose during an outbreak in Canada. CMAJ. 2011 May 16.

Demicheli V, Rivetti A, Debalini MG, et al. Vaccines for **measles, mumps and rubella** in children. Cochrane Database Syst Rev. 2012 Feb 15;2:CD004407. The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate.

Dempsey AF, Schaffer S, Singer D, et al. **Alternative Vaccination Schedule** Preferences Among Parents of Young Children. Pediatrics. 2011 Oct 3.

Desai R, Curns AT, Patel MM, Parashar UD. Trends in **Intussusception-Associated Deaths** among US Infants from 1979-2007. J Pediatr. 2011 Sep 16.

Desai S, Shane A, Lewis R. **Measles**. CMAJ. 2012 May 28.

DeVries Aaron S., Harper Jane, Murray Andrew, et al. **Vaccine-Derived Poliomyelitis** 12 Years after Infection in Minnesota. N Engl J Med 2011; 364:2316-2323.

Donovan B et al. Quadrivalent **human papillomavirus vaccination** and trends in genital warts in Australia: Analysis of national sentinel surveillance data. Lancet Infect Dis 2010 Nov 9

Dorell CG, Yankey D, Santibanez TA, Markowitz LE. **Human Papillomavirus Vaccination Series Initiation and Completion**, 2008 -2009. Pediatrics. 2011 Oct 17.

Dorell CG, Yankey D, Byrd KK, Murphy TV. **Hepatitis A Vaccination Coverage** Among Adolescents in the United States. Pediatrics. 2012 Jan 23.

Dransfield MT, Nahm MH, Han MK, et al.; COPD Clinical Research Network. Superior immune response to protein-**conjugate** versus free **pneumococcal** polysaccharide vaccine in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Sep 15;180(6):499-505. Epub 2009 Jun 25.

Drolet, M, Brisson, M, Schmader, KE., et al. The impact of **herpes zoster** and postherpetic neuralgia on health-related quality of life: a prospective study. CMAJ 2010 0: cmaj.091711

Einstein MH, Baron M, Levin MJ, et al. Comparison of the immunogenicity and safety of **Cervarix and Gardasil** (human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccin. 2009 Oct;5(10):705-19. Epub 2009 Oct 14.

Erlewyn-Lajeunesse M et al. **Anaphylaxis** as an adverse event following immunisation in the UK and Ireland. Arch Dis Child [Epub ahead of print] 23 January 2012

Farez MF, Correale J. **Yellow Fever** Vaccination and Increased Relapse Rate in Travelers With **Multiple Sclerosis**. Arch Neurol. 2011 Jun 13.

FDA Oct/10 **Rotarix**: The risk of intussusception with Rotarix has been evaluated in a hospital-based Postmarketing Active Surveillance Study (PASS) in a birth cohort of infants in Mexico. An interim analysis of this study suggests an increased risk of intussusception in the 31-day period following administration of the first dose of Rotarix[Relative Risk: 1.8 (99% CI: 1.0, 3.1)]. In this study, within the 31-day period after the first dose, most cases of intussusception occurred in the first 7 days.

Fischer M, Lindsey N, Staples JE, Hills S, Centers for Disease Control and Prevention (CDC). **Japanese encephalitis** vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2010 Mar 12;59(RR-1):1-27.

Forinash Alicia B, Yancey Abigail M, Pitlick Jamie M, et al. Safety of the **HPV** Bivalent and Quadrivalent Vaccines **During Pregnancy**. Articles Ahead of Print published on 1 February 2011, DOI 10.1345/aph.1P396. Ann Pharmacother ;45:258-262.

Franck L, Gay CL, Lynch M, Lee KA. Infant **sleep following immunization**: a randomized controlled trial of prophylactic acetaminophen. Pediatrics. 2011;128(6):1100 –1108.

Freed, Gary L., Clark, Sarah J., Butchart, Amy T., et al. **Parental Vaccine Safety Concerns** in 2009. Pediatrics 2010 0: peds.2009-1962.

Friedman, Bat-Chen, Goldman, Ran D. **Influenza** vaccination for children with **asthma**. Can Fam Physician 2010 56: 1137-1139.

French, Neil, Gordon, Stephen B., Mwalukomo, Thandie, et al. A Trial of a **7-Valent Pneumococcal Conjugate Vaccine (Prevnar) in HIV**-Infected Adults. N Engl J Med 2010 362: 812-822.

FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus (**HPV**) to prevent high-grade cervical lesions. N Engl J Med. 2007 May 10;356(19):1915-27.

FUTURE I/II Study Group. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine (**HPV**) against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ 2010;341:c3493, doi: 10.1136/bmj.c3493.

Gagnon R, Primeau MN, Roches AD, et al. on behalf of the PHAC-CIHR influenza Research Network (PCIRN). Safe vaccination of patients with **egg allergy** with an adjuvanted pandemic H1N1 vaccine. J Allergy Clin Immunol. 2010 Jun 23.

Gargano LM, Pazol K, Sales JM, et al. **Multicomponent interventions** to enhance **influenza** vaccine delivery to adolescents. Pediatrics. 2011 Nov;128(5):e1092-9.

Gatrad AR, Sheikh A. **The hajj**. BMJ. 2011 Sep 15;343:d5593. doi:10.1136/bmj.d5593.

Georgousakis M, Jayasinghe S, Brotherton J, et al. Population-wide vaccination against **human papillomavirus** in adolescent boys: Australia as a case study. Lancet Infect Dis. 2012 Mar 22.

Gould PL, Leung J, Scott C, et al. Outbreak of varicella in elementary school children with two-dose **varicella** vaccine recipients-Arkansas, 2006. Pediatr Infect Dis J. 2009 Aug;28(8):678-81.

Glanz, Jason M., McClure, et al. **Parental Refusal of Pertussis** Vaccination Is Associated With an Increased Risk of Pertussis Infection in Children Pediatrics 2009 123: 1446-1451 "Children whose parents refuse their pertussis vaccinations are at 23-fold higher risk for pertussis relative to vaccinated controls"

Glanz JM, McClure DL, Magid DJ, et al. **Parental refusal of varicella** vaccination and the associated risk of varicella infection in children. Arch Pediatr Adolesc Med. 2010 Jan;164(1):66-70. Children of parents who refuse varicella immunizations are at high risk of varicella infection relative to vaccinated children. (odds ratio, 8.6; 95% confidence interval, 2.2-33.3)

Glass Roger I., Patel Manish, Parashar Umesh. Lessons From the US **Rotavirus Vaccination** Program. JAMA. 2011;306(15):1701-1702.doi:10.1001/jama.2011.1475

GlaxoSmithKline Vaccine HPV-007 Study Group, Romanowski B, de Borba PC, Naud PS, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine (**Cervarix**): analysis of a randomized placebo-controlled trial up to 6.4 years. Lancet. 2009 Dec 12;374(9706):1975-85.

Gossger N, Snape MD, Yu L-M, et al; for the European MenB Vaccine Study Group. Immunogenicity and tolerability of **recombinant serogroup B meningococcal vaccine** administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA. 2012; 307(6):573-582.

Gostin Lawrence O.. **Mandatory HPV Vaccination** and Political Debate. JAMA. 2011;306(15):1699-1700.Published online October 6, 2011.doi:10.1001/jama.2011.1525

Grandjean P, Andersen EW, Budtz-Jørgensen E, et al. Serum vaccine antibody concentrations in children **exposed to perfluorinated compounds (PFCs)**. JAMA. 2012 Jan 25;307(4):391-7.

Greenberg Harry B., **Rotavirus** Vaccination and Intussusception — Act Two. N Engl J Med 2011; 364:2354-2355.

Gruslin A, Steben M, Halperin S, et al.. **Immunization in pregnancy**. J Obstet Gynaecol **Can**. 2008 Dec;30(12):1149-54. Erratum in: J Obstet Gynaecol Can. 2009 Mar;31(3):209. 1. All women of childbearing age should be evaluated for the possibility of pregnancy before immunization. (III-A) 2. Health care providers should obtain an immunization history from all women accessing prenatal care. (III-A) 3. In general, live and/or live-attenuated virus vaccines are contraindicated during pregnancy, as there is a, largely theoretical, risk to the fetus. (II-3) 4. Women who have inadvertently received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of a teratogenic risk. (II-2) 5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks. (III) 6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy. (II-1) 7. Women who are breastfeeding can still be immunized (passive-active immunization, live or killed vaccines). (II-1) 8. Pregnant women should be offered the influenza vaccine when pregnant during the influenza season. (II-1). http://www.sogc.org/guidelines/documents/gui220CPG0812.pdf

Gruslin A, Steben M, Halperin S, Money DM, Yudin MH. **Immunization in pregnancy**. J Obstet Gynaecol **Can 2009 Nov**;31(11):1085-92. 1. All women of childbearing age should be evaluated for the possibility of pregnancy before immunization. (III-A) 2. Health care providers should obtain an immunization history from all women accessing prenatal care. (III-A) 3. In general, live and/or live-attenuated virus vaccines should not be administered during pregnancy, as there is a, largely theoretical, risk to the fetus. (II-3B) 4. Women who have inadvertently received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of a teratogenic risk. (II-2A) 5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks. (III-B) 6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy. (II-1A) 7. Women who are breastfeeding can still be immunized (passive-active immunization, live or killed vaccines). (II-1A) 8. Pregnant women should be offered the influenza vaccine when pregnant during the influenza season. (II-1A) 9. Pregnant women with suspected or documented H1N1 infection should be treated with oseltamivir (Tamiflu, 75 milligrams twice daily for 5 days) within 48 hours of onset of symptoms. (III-B) http://www.sogc.org/guidelines/documents/gui236CPG0911.pdf

Giuliano Anna R., Palefsky Joel M., Goldstone Stephen, et al. Efficacy of Quadrivalent HPV Vaccine against **HPV Infection and Disease in Males**. N Engl J Med 2011; 364:401-411.

Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and **Guillain-Barré syndrome**. Drug Saf. 2009;32(4):309-23. doi: 10.2165/00002018-200932040-00005.

Han F, Lin L, Warby SC, Faraco J, Li J, et al. **Narcolepsy onset** is seasonal and increased following the 2009 **H1N1** pandemic in china. Ann Neurol. 2011 Sep;70(3):410-7.

Harrington JW, Logan S, Harwell C, et al. Effective **Analgesia Using Physical Interventions for Infant Immunizations**. Pediatrics. 2012 Apr 16.

Haug Charlotte. The Risks and Benefits of **HPV** Vaccination. JAMA. 2009;302(7):795-796.

Health Canada **Childhood Vaccination Information** http://hc-sc.gc.ca/hl-vs/iyh-vsv/med/immuniz-eng.php

Health Canada May/10 is advising Canadians and Canadian healthcare practitioners that we are currently reviewing new information regarding the presence of porcine circovirus (PCV-1 and PCV-2) DNA in **rotavirus vaccines**. Porcine circovirus is a single stranded DNA virus, and is considered a contaminant in these vaccines.

Heijstek MW, Ott de Bruin LM, Bijl M, et al. EULAR recommendations for **vaccination in paediatric patients with rheumatic diseases**. Ann Rheum Dis. 2011 Oct;70(10):1704-12.

Heijstek MW, van Gageldonk PG, et al. Differences in persistence of **measles, mumps, rubella, diphtheria and tetanus antibodies** between children with **rheumatic disease** and healthy controls: a retrospective cross-sectional study. Ann Rheum Dis. 2012 Jun;71(6):948-54. (lower antibody rates in: mumps, rubella, diphtheria and tetanus)

Heinonen Santtu, Silvennoinen Heli, Lehtinen Pasi, et al. Effectiveness of inactivated **influenza vaccine in children aged 9 months to 3 years**: an observational cohort study, The Lancet Infectious Diseases, Volume 11, Issue 1, January 2011

Hirth JM, Tan A, Wilkinson GS, Berenson AB. Completion of the **human papillomavirus vaccine** series among insured females between 2006 and 2009. Cancer. 2012 Apr 27.

Huang, Susan, Hinrichsen, Virginia L., et al. Continued Impact of **Pneumococcal Conjugate Vaccine** on Carriage in Young Children.Pediatrics 2009 124: e1-e11. The virtual disappearance of vaccine serotypes in S pneumoniae carriage has occurred in young children, with rapid replacement with penicillin-nonsusceptible nonvaccine serotypes, particularly **19A and 35B**. Except for the age group at highest risk, previous predictors of carriage, such as child care attendance and the presence of young siblings, have not been changed by the vaccine.

Huang WT, Gargiullo PM, et al.; for the Vaccine Safety Datalink Team. Lack of Association Between Acellular **Pertussis Vaccine and Seizures** in Early Childhood. Pediatrics. 2010 Jul 19.

Hurst FP, Lee JJ, Jindal RM, et al. Outcomes Associated with Influenza Vaccination in the First Year **after Kidney Transplantation**. Clin J Am Soc Nephrol. 2011 Apr 28. April 28

Immunization Work Group of the National and Global Public Health Committee of the Infectious Diseases Society of America. Actions to **strengthen adult and adolescent immunization** coverage in the United States: policy principles of the Infectious Diseases Society of America. Clin Infect Dis. 2007;44: e104-8.

IOM Aug 2011: Adverse Effects of Vaccines: Evidence and Causality www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.Aspx

Iorio A, Basileo M, Marcucci M, et al. **Influenza vaccination and vitamin K antagonist** treatment: a placebo-controlled, randomized, double-blind crossover study. Arch Intern Med. 2010 Apr 12;170(7):609-16.

Institute of Medicine's **Immunization Safety Committee Reports** www.iom.edu/imsafety

In the Clinic. Management of Newly Diagnosed **HIV Infection**. (& **Vaccinations**) Annals of Internal Medicine 4 October 2011.

pp M, Parkin PC, Lear N, et al. **Order of vaccine** injection and infant pain response. Arch Pediatr Adolesc Med. 2009 May;163(5):469-72. Pain was reduced when the DPTaP-Hib vaccine was administered before the PCV in infants undergoing routine vaccination. We recommend that the order of vaccine injections be the DPTaP-Hib vaccine followed by the PCV.

Ixiaro- A new Japanese Encephalitis Vaccine. Medical Letter. Aug,2009.

Jackson LA, Janoff EN. **Pneumococcal vaccination of elderly** adults: new paradigms for protection. Clin Infect Dis. 2008 Nov 15;47(10):1328-38.

JacksonLA., Yu O, et al. Vaccine Safety Datalink Team, **Fifth Dose of Diphtheria and Tetanus Toxoids and Acellular Pertussis** Vaccine. **(DTaP)** Pediatrics 2011 0: peds.2010-1886.

Jackson LA, Yu O, Nelson JC, et al; for the Vaccine Safety Datalink Team. Injection Site (Thish less SE than arm)and Risk of Medically Attended Local Reactions to Acellular Pertussis Vaccine. Pediatrics. 2011 Mar;127(3):e581-e587.

Jansen AG, Hak E, Veenhoven RH, et al. **Pneumococcal conjugate vaccines** for preventing otitis media. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD001480. Based on current evidence of the effectiveness of PCVs for the prevention of AOM, the currently licensed 7-valent PCV administered during infancy has marginal beneficial effects. Discrete reductions of 6% to 7% may mean substantial reductions from a public health perspective. Administering PCV7 in older children with a history of AOM appears to have no benefit in preventing further episodes.

Jefferson T, Di Pietrantonj C, Rivetti A, et al. **Vaccines for preventing influenza** in healthy adults. Cochrane Database Syst Rev. 2010 Jul 7;7:CD001269. Influenza vaccines have a modest effect in reducing influenza symptoms and working days lost. There is no evidence that they affect complications, such as pneumonia, or transmission.

Jenkins, Helen E., Aylward, R. Bruce, Gasasira, Alex, et al. Implications of a Circulating **Vaccine-Derived Poliovirus in Nigeria**. N Engl J Med 2010 362: 2360-2369.

Jentes ES, Poumerol G, Gershman MD, et al. Informal WHO Working Group on Geographic Risk for **Yellow Fever**. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. Lancet Infect Dis. 2011 Aug;11(8):622-32.

Jiménez S, Schiller JT, Lowy DR, et al. for the CVT Vaccine Group. Efficacy of a bivalent **HPV** 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol. 2011 Sep;12(9):862-870.

Jit M, Chapman R, Hughes O, Choi YH. Comparing **bivalent and quadrivalent human papillomavirus vaccines**: economic evaluation based on transmission model. BMJ 2011;343:d5775.

Joura EA, Garland SM, Paavonen J, et al. Effect of the human papillomavirus (**HPV**) quadrivalent vaccine in a subgroup of women with **cervical and vulval disease**: retrospective pooled analysis of trial data. BMJ 2012;344:e1401.

Juckett G, Hartman-Adams H. **Human papillomavirus**: clinical manifestations and prevention. Am Fam Physician. 2010 Nov 15;82(10):1209-13.

Kahn, Jessica A.HPV Vaccination (**HPV**) for the Prevention of Cervical Intraepithelial Neoplasia. N Engl J Med 2009 361: 271-278.

Kang LW, Crawford N, Tang ML, et al. Hypersensitivity reactions to **human papillomavirus vaccine** in Australian schoolgirls: retrospective cohort study. BMJ. 2008 Dec 2;337:a2642. doi: 10.1136/bmj.a2642.

Kang JH, Ho JD, Chen YH, Lin HC. Increased Risk of **Stroke** After a **Herpes Zoster** Attack. A Population-Based Follow-Up Study. Stroke. 2009 Oct 8. [Epub ahead of print]

Kapetanovic MC, Roseman C, Jönsson G, et al. **Methotrexate** but not TNF-blockers reduces antibody response following **pneumococcal vaccination** using 7-valent conjugate pneumococcal vaccine in adult patients with established arthritis. Arthritis Rheum. 2011 Aug 10.

Kaplan, SL., Barson, WJ., Lin, Philana L., et al. **Serotype 19A** Is the Most Common Serotype Causing Invasive **Pneumococcal** Infections in Children. Pediatrics 2010 125: 429-436.

Kelly RS, Walker P, Kitchener H, et al. Incidence of cervical intraepithelial neoplasia grade 2 or worse in colposcopy-negative/**human papillomavirus**-positive wom

TOP

cytological abnormalities. BJOG. 2012 Jan;119(1):20-5.

Kelso JM, Li JT, Nicklas RA, et al. Joint Task Force on Practice Parameters. **Adverse reactions to vaccines**. Ann Allergy Asthma Immunol. 2009 Oct;103(4 Suppl 2):S1-14.

Kempe A, Barrow J, Stokley S, et al. Effectiveness and Cost of Immunization **Recall at School-Based Health Centers**. Pediatrics. 2012 May 7.

Kim JJ, Targeted **human papillomavirus vaccination** of men who have sex with men in the USA: cost-effectiveness modelling analysis, Lancet Infectious Diseases, Vol10, Issue 12, Dec'10

Klein NP, Fireman B, Yih WK et al; Vaccine Safety Datalink. **Measles-mumps-rubella-varicella** combination vaccine and the risk of **febrile seizures**. Pediatrics. 2010 Jul;126(1):e1-8.

Klein NP, Lewis E, Baxter R et al. **Measles-Containing Vaccines and Febrile Seizures** in Children Age 4 to 6 Years. Pediatrics. 2012 Apr 2.

Koskimaa HM, Waterboer T, Pawlita M, et al. **Human Papillomavirus** Genotypes Present in the Oral Mucosa of Newborns and their Concordance with Maternal Cervical Human Papillomavirus Genotypes. J Pediatr. 2012 May;160(5):837-43.

Kreimer AR, Rodriguez AC, et al; CVT Vaccine Group. Proof-of-Principle Evaluation of the Efficacy of Fewer Than Three Doses of a Bivalent **HPV**16/18 Vaccine.J Natl Cancer Inst. 2011Sep9.

Kreimer AR, González P, Katki HA, et al. for the CVT Vaccine Group. Efficacy of a bivalent HPV 16/18 vaccine against **anal HPV 16/18** infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol. 2011 Sep;12(9):862-870.

Kuhn S , Twele-Montecinos L, MacDonald J, et al. Case report: probable transmission of vaccine strain of **yellow fever virus to an infant via breast milk**. **CMAJ 2011 0: cmaj.100619.**

Lamontagne, Francois, Garant, Marie-Pierre, Carvalho, Jean-Christophe, et al. **Pneumococcal** vaccination and risk of **myocardial infarction** CMAJ 2008 179: 773-777

Lan J , Chen Y , Hsieh TC , et al. Kinetics of viral loads and risk of **HBV** reactivation in HBcAbpositive RA patients undergoing **anti-TNF-α therapy** . Ann Rheum Dis 2011 ; 70:1719–25 .

Launay Odile, van der Vliet Diane, Rosenberg Arielle R., et al. Safety and Immunogenicity of 4 Intramuscular Double Doses and 4 Intradermal Low Doses vs Standard **Hepatitis B Vaccine** Regimen in Adults With **HIV-1**: A Randomized Controlled Trial. for the ANRS HB03 VIHVAC-B Trial. *JAMA*. 2011;305(14):1432-1440.doi:10.1001/jama.2011.351

Lazarus R et al. A randomized study comparing combined **pneumococcal conjugate and polysaccharide vaccination in adults**. Clin Infect Dis. 2011;52:736-42.

Lehtinen M, Paavonen J, Wheeler CM, et al. Overall effi cacy of **HPV-16/18** AS04-adjuvanted vaccine against grade 3 or greater **cervical intraepithelial neoplasia**: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2011; published online Nov 9. DOI:10.1016/ S1470-2045(11)70286-8.

Leonardi S, et al. Hepatitis B vaccination failure in **celiac** disease: is there a need to reassess current immunization strategies? Vaccine. 2009 Oct 9;27(43):6030-3. Epub 2009 Aug 12.

Leonardi M, Bromberg K, Baxter R, et al. **Immunogenicity and safety of MMRV and PCV-7 vaccines** administered **concomitantly** in healthy children. Pediatrics. 2011;128(6).

Liao MT, Chang MH, Lin FG, et al. Universal **Hepatitis B Vaccination Reduces Childhood Hepatitis B Virus-Associated Membranous Nephropathy**. Pediatrics. 2011 Aug 22.

Lindley MC., Lorick SA., Spinner JR., et al. **Student Vaccination Requirements** of U.S. Health Professional Schools: A Survey. *Ann Intern Med* March 15, 2011 154:391-400

Löbermann M, et al. Vaccination and multiple sclerosis. Nervenarzt. 2009 Oct 17. Some vaccines, for example against yellow fever, are not indicated in MS due to the risk of MS exacerbation.

Loeb M; Russell ML.; Moss L; et al. Effect of **Influenza Vaccination** of Children on Infection Rates in Hutterite Communities: A Randomized Trial. JAMA. 2010;303(10):943-950.

Lopez, Adriana S., Zhang, John, Brown, Cedric, et al. Varicella-Related Hospitalizations in the United States, 2000-2006: The **1-Dose Varicella Vaccination Era**. Pediatrics 2011.

Lopman BA, Curns AT, Yen C, et al. Infant **rotavirus** vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis. 2011 Oct 1;204(7):980-6.

Macneil JR, Cohn AC, Farley M, et al. Current Epidemiology and Trends in **Invasive Haemophilus influenzae** Disease--United States, 1989-2008. Clin Infect Dis. 2011 Dec;53(12):1230-6.

Lessin HR, Edwards KM; the Committee on Practice and Ambulatory Medicine and the Committee on Infectious Diseases. **Immunizing Parents and Other Close Family Contacts** in the Pediatric Office Setting. Pediatrics. 2012 Jan;129(1):e247-e253.

Lodolce AE. Shortened interval between **tetanus vaccines**. Ann Pharmacother. 2012 Jun;46(6):884-8.

Madhi, Shabir A., Cunliffe, Nigel A., Steele, Duncan, et al. Effect of Human **Rotavirus** Vaccine on Severe Diarrhea in African Infants. N Engl J Med 2010 362: 289-298.

Manoff SB, Liss C, Caulfield MJ, et al. Revaccination with a 23-valent **pneumococcal polysaccharide** vaccine induces elevated and persistent functional antibody responses in adults aged 65 > or = years. J Infect Dis. 2010 Feb 15;201(4):525-33.

Marin M, Zhang JX, Seward JF. Near **elimination of varicella deaths** in the US after implementation of the vaccination program. Pediatrics. 2011;128:214-220.

Marks JS, Halpin TJ. **Guillain-Barré syndrome** in recipients of A/New Jersey influenza vaccine. JAMA. 1980 Jun 27;243(24):2490-4.

Marin M, Zhang JX, Seward JF. Near elimination of **varicella deaths** in the US after implementation of the vaccination program. Pediatrics. 2011 Aug;128(2):214-20.

Maruyama T, Taguchi O, Niederman MS, et al. Efficacy of **23-valent pneumococcal** vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. BMJ. 2010 Mar 8

McCormack PL, Joura EA. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (**Gardasil®**): a review of its use in the prevention of premalignant genital lesions, genital cancer and genital warts in women. Drugs. 2010 Dec 24;70(18):2449-74. doi: 10.2165/11204920-000000000-00000.

McElligott, James T., Darden, Paul M. Are **Patient-Held Vaccination Records** Associated With Improved Vaccination Coverage Rates? Pediatrics 2010 125: e467-e472.

McIntosh AM, McMahon J, Dibbens LM et al. Effects of vaccination on onset and outcome of **Dravet syndrome**: a retrospective study. Lancet Neurol. 2010 May 4.

Medical Letter. Treatment Guidelines: **Advice for Travelers**. Nov 2009. Updated **May 2012**.

Mehanna H, Jones TM, Gregoire V, Ang KK. **Oropharyngeal carcinoma** related to **human papillomavirus**. BMJ. 2010 Mar 25;340:c1439. doi: 10.1136/bmj.c1439.

Metlay Joshua P.; Lautenbach Ebbing; Li Yimei; et al. Exposure to Children as a Risk Factor for Bacteremic **Pneumococcal** Disease: Changes in the **Post-Conjugate Vaccine Era**. Arch Intern Med. 2010;170(8):725-731.

Middleman, Amy B., Anding, Roberta, Tung, Celestine. Effect of **Needle Length** When Immunizing Obese Adolescents With Hepatitis B Vaccine. Pediatrics 2010 0: peds.2009-1592

Miller E, Andrews NJ, Waight PA, Slack MPE, George RC.Herd immunity and serotype replacement 4 years after seven-valent **pneumococcal** conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis 2011; published online May 27. DOI:10.1016/S1473-3099(11)70090-1.

Mirdamadi K, Einarson A. **H1N1** and influenza viruses: Why **pregnant** women might be hesitant to be vaccinated. Can Fam Physician. 2011 Sep;57(9):1003-4.

Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for **preventing pneumococcal** infection in adults. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD000422.

Moss WJ, Griffin DE. **Measles**. Lancet. 2011 Aug 17.

Muñoz N, Manalastas R Jr, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent **human papillomavirus** (types 6, 11, 16, 18) recombinant vaccine in women **aged 24-45 years**: a randomised, double-blind trial. Lancet. 2009 Jun 1. [Epub ahead of print]

Musher DM, Manof SB, Liss C, et al. Safety and antibody response, including antibody persistence for 5 years, after primary vaccination or revaccination with **pneumococcal polysaccharide** vaccine in middle-aged and older adults. J InfectDis. 2010 Feb 15;201(4):516-24.

NACI Jan/12: National Advisory Committee on Immunization. Update human papillomavirus HPV vaccines.www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-8/index-eng.php

Neuzil Kathleen M., Canh Do Gia, Thiem Vu Dinh, et al. Immunogenicity and Reactogenicity of **Alternative Schedules of HPV** Vaccine in Vietnam: A Cluster Randomized Noninferiority Trial. *JAMA*. 2011;305(14):1424-1431.doi:10.1001/jama.2011.407

O'Brien, Megan A., Prosser, Lisa A., et al. New Vaccines Against Otitis Media: Projected Benefits and Cost-effectiveness Pediatrics 2009 123: 1452-1463

O'Brien KL, Hochman M, et al. Combined schedule of **pneumococcal conjugate and polysaccharide vaccines**: is hyporesponsiveness an issue? Lancet Infect Dis. 2007 Sep;7(9):597-606.

O'Leary ST, Glanz JM, et al. The Risk of **Immune Thrombocytopenic Purpura** (ITP) After Vaccination in Children and Adolescents. Pediatrics. 2012 Jan 9 (**MMR** risk in early childhood)

Offit PA. Should childhood **vaccination be mandatory**? **Yes**. BMJ. 2012 May 15;344:e2434.

Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of **influenza vaccines**: a systematic review and meta-analysis. Lancet Infect Dis 2011; online Oct 26.

Omeñaca Félix, Merino Jose Manuel, et al. Immunization of Preterm Infants With **10-Valent Pneumococcal** Conjugate Vaccine. Pediatrics 2011; peds.2010-1184; July 4, 2011.

Paavonen J, Naud P, Salmerón J, Wheeler C, et al. for the HPV PATRICIA Study Group. Efficacy of human papillomavirus (**HPV**)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009 Jul 6

Palefsky JM et al. **HPV vaccine** against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011 Oct 27; 365:1576.

Pasternak B, Svanström H, et al. Vaccination against **pandemic A/H1N1 2009 influenza in pregnancy** and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.

Patel M, et al. Association between pentavalent rotavirus vaccine and severe **rotavirus** diarrhea among children in Nicaragua. JAMA. 2009 Jun 3;301(21):2243-51.

Patel MM., López-Collada VR, Bulhões MM, et al. **Intussusception Risk** and Health Benefits of **Rotavirus** Vaccination (Rotarix) in Mexico and Brazil. N Engl J Med 2011; 364:2283-2292.

Pavia, Maria, Bianco, Aida, et al. Efficacy of **Pneumococcal Vaccination** in Children Younger Than 24 Months: A Meta-Analysis Pediatrics 2009 123: e1103-e1110.

Phrommintikul A, Kuanprasert S, et al. **Influenza vaccination reduces cardiovascular events** in patients with acute coronary syndrome. Eur Heart J. 2011 Jul;32(14):1730-5.

Pichichero ME, Casey JR. Emergence of a multiresistant serotype **19A pneumococcal** strain not included in the 7-valent conjugate vaccine as an otopathogen in children. JAMA. 2007 Oct 17;298(15):1772-8. In the years following introduction of PCV7, a strain of S pneumoniae has emerged in the United States as an otopathogen that is resistant to all FDA-approved antibiotics for treatment of AOM in children.

Pickering LK, Baker CJ, Freed GL, et al. Infectious Diseases Society of America-**IDSA**. Immunization programs for **infants, children, adolescents, and adults**: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2009 Sep 15;49(6):817-40.

Pilishvili T, Zell ER, Farley MM, et al. Risk factors for **invasive pneumococcal disease** in children in the era of conjugate vaccine use. Pediatrics. 2010 Jul;126(1):e9-17.

Poehling KA et al. New Vaccine Surveillance Network. Impact of **maternal immunization on influenza** hospitalizations in infants. Am J Obstet Gynecol. 2011 Jun;204(6 Suppl 1):S141-8.

Pottie K, Greenaway C, Feightner J, et al. coauthors of the Canadian Collaboration for Immigrant and Refugee Health. Evidence-based clinical guidelines for **immigrants and refugees**. CMAJ. 2011 Sep 6;183(12):E824-925.

Powell B, Ford C. **Risks of travel,** benefits of a specialist consult. Cleve Clin J Med. 2010 Apr;77(4):246-54.

Prevnar 13: December 22, 2009 -- Health Canada has approved a pneumococcal 13-valent conjugate vaccine (Diphtheria CRM197 Protein [Prevnar 13] for children aged 6 weeks through 5 years for active immunisation against invasive pneumococcal disease. The 13-valent vaccine is designed to provide the broadest coverage of any pneumococcal conjugate vaccine. The new vaccine includes strains 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F -- responsible for the greatest remaining burden of invasive disease in young children worldwide.

Price, CS., Thompson, WW., Goodson, B. et al. Prenatal and Infant Exposure to **Thimerosal** From Vaccines and Immunoglobulins and Risk of **Autism**. Pediatrics 2010 0: peds.2010-0309.

Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic **paracetamol/acetaminophen** administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet. 2009 Oct 17;374(9698):1339-50.

Public Health Agency of Canada. Canada Communicable Disease Report. Committee to Advise on Tropical Medicine and Travel (CATMAT) statement. Statement on **pregnancy and travel**. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-2/index-eng.php Mar 2010.

Public Health Agency of Canada. **Yellow fever vaccination** in Canada. E-learning module for health care professionals advising travellers. www.phac-aspc.gc.ca/tmp-pmv/el-mf-eng.php

Pupco Anna, Bozzo Pina, Koren Gideon. **Herpes zoster** during pregnancy. Can Fam Physician October 2011 57: 1133.

Rabies CDC recommendations Mar/2010 : Mar/10 Routine **rabies post-exposure prophylaxis** will now entail a total of five shots — four of vaccine and one of rabies immune globulin — according to an article in MMWR Recommendations and Reports. The change to fewer doses was made based on studies showing that the fifth vaccine shot did not improve outcomes. The Advisory Committee on Immunization Practices recommends: Two shots — one of vaccine and one of rabies immune globulin — given as soon as possible after exposure. Taking the day of the first shots as Day 0, the other vaccine shots should be administered on Days 3, 7, and 14. If immune globulin is not given on Day 0, it should be given by Day 7. Immunocompromised patients should continue to receive all five vaccine shots, with the fifth on Day 28. Vaccine shots may be delivered to the outer aspect of the thigh in younger children and to the deltoid in older children and adults. The gluteal region should never be used.The authors note that their recommendations will differ from vaccine label instructions into the foreseeable future.MMWR Recommendations and Reports: http://cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm

Reisinger KS, Block SL, Collins-Ogle M, et al. Safety, Tolerability, & Immunogenicity of **Gardasil Given Concomitantly With Menactra and Adacel**. Pediatrics. 2010 Jun;125(6):1142-1151.

Reyes IS, Hsieh DT, Laux LC, Wilfong AA. **Alleged Cases of Vaccine Encephalopathy Rediagnosed Years Later as Dravet Syndrome**. Pediatrics. 2011 Aug 15.

Ribeiro AC, Guedes LK, Moraes JC, et al. **Reduced seroprotection after pandemic H1N1** influenza adjuvant-free vaccination in patients with **rheumatoid arthritis**: implications for clinical practice. Ann Rheum Dis. 2011 Dec;70(12):2144-7.

Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, et al. Effect of **Rotavirus** Vaccination on Death from Childhood Diarrhea in Mexico. N Engl J Med 2010 362: 299-305

Richmond PC, Marshall HS, Nissen MD, et al. Safety, immunogenicity, and tolerability of **meningococcal serogroup B** bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, singleblind, placebo-controlled, phase 2 trial. Lancet Infect Dis 2012; online May 7.

Rodenburg GD, van Gils EJ, Veenhoven RH, et al. Lower Immunoglobulin G Antibody Responses to **Pneumococcal Conjugate** Vaccination at the Age of 2 Years after Previous Nasopharyngeal Carriage of Streptococcus pneumoniae. J Pediatr. 2011 Dec;159(6):965-970.e1.

Rolfe A, Sheikh A. **Measles, mumps, and rubella vaccination in a child with suspected egg allergy**. BMJ. 2011 Aug 3:343:d4536.

Rothman Sheila M.; Rothman David J. Marketing HPV Vaccine: Implications for Adolescent Health and Medical Professionalism. JAMA. 2009;302(7):781-786.

Rozenbaum Mark H, Sanders Elisabeth A M, van Hoek Albert Jan et al. Cost effectiveness of **pneumococcal** vaccination among Dutch infants: economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines. BMJ 2010;340:c2509, doi: 10.1136/bmj.c2509

Rupprecht CE, Briggs D, Brown CM, et al., Centers for Disease Control and Prevention (CDC). Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human **rabies**: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2010 Mar 19;59(RR-2):1-9.

Salisbury DM. Should childhood **vaccination be mandatory**? **No**. BMJ. 2012 May 15;344:e2435.

Santolaya ME, O´Ryan ML, Valenzuela MT, et al. Immunogenicity and tolerability of a multicomponent **meningococcal serogroup B** (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet. 2012 Jan 17.

Sauerbrei, Andreas. **Preventing congenital varicella syndrome with immunization**. CMAJ 2011 0: cmaj.110055.

Schauner S, Lyon C. Bivalent HPV Recombinant Vaccine (**Cervarix**) for the Prevention of Cervical Cancer. Am Fam Physician. 2010 Dec 15;82(12):1541-2.

Schechter NL, Bernstein BA, Zempsky WT, Bright NS, Willard AK. **Educational Outreach to Reduce Immunization Pain** in Office Settings. Pediatrics. 2010 Nov 15.

Schenkein JG, Nahm MH, Dransfield MT. Pneumococcal vaccination for patients with COPD: current practice and future directions. Chest. 2008 Mar;133(3):767-74. Epub 2007 Sep 21.

Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, safety, and tolerability of **herpes zoster vaccine** in persons aged 50-59 years. Clin Infect Dis. 2012 Apr;54(7):922-8.

Schwartz BS, Larocque RC, Ryan ET. **Travel medicine**. Ann Intern Med. 2012 Jun 5;156(11):ITC61.

Shapiro ED, Vazquez M, Esposito D, et al. Effectiveness of **2 doses of varicella vaccine** in children. J Infect Dis. 2011 Feb;203(3):312-5.

Shapiro Marla, Kvern Brent, Watson Peter, et al. Update on **herpes zoster vaccination**: A family practitioner's guideCan Fam Physician October 2011 57: 1127-1131.

Shen AK, Sobczyk E, Simonsen L, Kahn F, Esber A, Andreae MC. **Financial impact to providers** using pediatric combination vaccines. Pediatrics. 2011;128(6):1087–1093.

Shi Z, Yang Y, et al. **Breastfeeding** of Newborns by Mothers Carrying **Hepatitis B** Virus: A Meta-analysis and Systematic Review. Arch Pediatr Adolesc Med. 2011 Sep;165(9):837-46.

Shui IM, Baggs J, Patel M, et al. Risk of **intussusception** following administration of a pentavalent **rotavirus** vaccine (RV5) in US infants. JAMA. 2012 Feb 8;307(6):598-604. (not increased)

Simberkoff MS, Arbeit RD, Johnson GR, et al. Shingles Prevention Study Group. **Safety of herpes zoster vaccine** in the shingles prevention study: a randomized trial. Ann Intern Med. 2010 May 4;152(9):545-54.

Sinclair D, Abba K, Zaman K, Qadri F, Graves PM. **Oral vaccines for preventing cholera**. Cochrane Database Syst Rev. 2011 Mar 16;3:CD008603.

Siriwardena AN, Gwini SM, Coupland C. Influenza vaccination, pneumococcal vaccination and **risk of AMI**: Matched case-control study. CMAJ 2010; DOI:10.1503/cmaj.091891.

Skowronski Danuta M, Janjua Naveed Z, De Serres Gaston, et al. Effectiveness of **AS03 adjuvanted pandemic H1N1 vaccine**: case-control evaluation based on sentinel surveillance system **in Canada**, autumn 2009. BMJ 2011;342:doi:10.1136/bmj.c7297 (Published 3 February 2011)

Slade Barbara A.; Leidel Laura; Vellozzi Claudia; et al. Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine (**HPV**). JAMA. 2009;302(7):750-757. {The overall adverse event rate was 53.9 per 100,000 doses; some 94% were considered "nonserious." The most common events were syncope, injection site reactions, dizziness, nausea, and headache. Rates of syncope and venous thromboembolic events were higher than expected (8.2 and 0.2, respectively, per 100,000 doses).}

Smith KJ, Wateska AR, Nowalk MP, et al. Cost-effectiveness of adult vaccination strategies using **pneumococcal** conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA. 2012 Feb 22;307(8):804-12.

Smith EA, Jacques-Carroll L, Walker TY, et al. The national perinatal **hepatitis B** prevention program, 1994-2008. Pediatrics. 2012 Apr;129(4):609-16.

Soares-Weiser K, Maclehose H, Ben-Aharon I, et al. Vaccines for preventing **rotavirus** diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2010 May 12;5:CD008521.

Sohn M-W, Yoo J, Oh EH, Amsden LB, Holl JL. **Welfare, maternal work,** and on-time childhood vaccination rates. Pediatrics. 2011; 128(6):1109 –1116.

Sow Samba O., Okoko Brown J., Diallo Aldiouma, et al. Immunogenicity and Safety of a **Meningococcal** A Conjugate Vaccine in Africans. N Engl J Med 2011; 364:2293-2304.

Staat MA, Payne DC, et al. New Vaccine Surveillance Network (NVSN). Effectiveness of **pentavalent rotavirus vaccine** against severe disease. Pediatrics. 2011 Aug;128(2):e267-75.

Steinhoff MC, Omer SB, Roy E, Arifeen et al. Neonatal outcomes after **influenza immunization during pregnancy**: a randomized controlled trial. CMAJ. 2012 Apr 3;184(6):645-53.

Stockwell MS, Kharbanda EO, Martinez RA, et al. Effect of a **text messaging** intervention on influenza vaccination in an urban, low income pediatric and adolescent population: a randomized controlled trial. JAMA. 2012;307(16):1702-1708.

Stokley S, Cohn A, Dorell C, et al. **Adolescent vaccination coverage levels in the United States**: 2006 –2009. Pediatrics. 2011;128(6): 1078 –1086.

Sugerman, David E., Barskey, Albert E., Delea, Maryann G., et al. **Measles Outbreak** in a Highly Vaccinated Population, San Diego, 2008: Role of the Intentionally Undervaccinated. Pediatrics 2010 125: 747-755.

Suh CA, Saville A, Daley MF, et al. Effectiveness and Net **Cost of Reminder/Recall** for Adolescent Immunizations. Pediatrics. 2012 May 7.

Sun Y, Christensen J, Hviid A, et al. Risk of **febrile seizures** and epilepsy after vaccination with **diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus** influenzae type B. JAMA. 2012 Feb 22;307(8):823-31.

Sutcliffe CG, Moss WJ. Do children infected with **HIV receiving HAART need to be revaccinated**? Lancet Infect Dis. 2010 Sep;10(9):630-42.

Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade anal neoplasia with quadrivalent **human papillomavirus vaccination** of men who have sex with men: a nonconcurrent cohort study. Clin Infect Dis. 2012 Apr;54(7):891-8.

Tan, Lionel K.K., Carlone, George M., Borrow, Ray. Advances in the Development of Vaccines against **Neisseria meningitides**. N Engl J Med 2010 362: 1511-1520.

Task Force on Sudden Infant Death Syndrome. **SIDS** & Other Sleep-Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment. Pediatrics. 2011 Oct 17.

Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in the United States following the introduction of **rotavirus vaccine** in 2006. Pediatr Infect Dis J. 2011 Jan;30(1 Suppl):S30-4.

Tate JE, Burton AH, Boschi-Pinto C, et al. 2008 estimate of worldwide **rotavirus-associated mortality** in children younger than 5year before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2011; published online Oct 25.

Tessmer A, Welte T, Schmidt-Ott R et al. for CAPNETZ study group. **Influenza vaccination** is associated with reduced severity of community acquired pneumonia. Eur Respir J. 2010 Dec 9.

Tetanus and Pertussis Vaccination Coverage Among Adults Aged ≥18 Years --- United States, 1999 and 2008 Weekly MMWR. October 15, 2010 / 59(40);1302-1306. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5940a3.htm

Tseng Hung Fu; Slezak Jeffrey M.; Quinn Virginia P.; et al. **Pneumococcal** Vaccination and Risk of Acute **Myocardial Infarction** and Stroke in Men. JAMA. 2010;303(17):1699-1706.

Tseng Hung Fu, Smith Ning, Harpaz Rafael, et al. **Herpes Zoster Vaccine** in Older Adults and the Risk of Subsequent Herpes Zoster Disease. *JAMA*. 2011;305(2):160-166.

Tseng HF, Liu A, Sy L, et al; for the Vaccine Safety Datalink (VSD) Team. **Safety of zoster vaccine** in adults from a large managed-care cohort: a Vaccine Safety Datalink study. J Intern Med. 2012 May;271(5):510-520.

Tung J, Carlisle E, Smieja M, Kim PT, Lee CH. A randomized clinical trial of immunization with combined **hepatitis A and B** versus hepatitis B alone for hepatitis B seroprotection in **hemodialysis patients**. Am J Kidney Dis. 2010 Oct;56(4):713-9. Epub 2010 Jul 13.

van Assen S, et al. Humoral responses after influenza vaccination are severely reduced in patients with **rheumatoid arthritis** treated with rituximab. Arthritis Rheum. 2009 Dec28;62(1):75-81.

van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with **autoimmune inflammatory rheumatic diseases**. Ann Rheum Dis 2011;70:414-422. Online: 3 Dec 2010 doi:10.1136/ard.2010.137216

van Gils Elske J. M.; Veenhoven Reinier H.; Hak Eelko; et al. **Pneumococcal Conjugate Vaccination** and Nasopharyngeal Acquisition of **Pneumococcal Serotype 19A Strains**. JAMA. 2010;304(10):1099-1106.

Vaughn JA, Miller RA. **Update on immunizations in adults**. Am Fam Physician. 2011 Nov 1;84(9):1015-20.

Vesikari T et al. Oil-in-water emulsion **adjuvant with influenza vaccine** in young children. N Engl J Med 2011 Oct 13; 365:1406. (has MF59 contains squalene)

Wacholder Sholom, Chen Bingshu Eric, Wilcox Allen, et al. for the CVT group. Risk of **miscarriage** with bivalent vaccine against human papillomavirus (**HPV**) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ 2010;340:c712, doi: 10.1136/bmj.c712 (Published 2 March 2010)

Wasan SK, Baker SE, Skolnik PR, Farraye FA. A Practical Guide to Vaccinating the **Inflammatory Bowel Disease Patient**. Am J Gastroenterol. 2010 Jan 26. [Epub ahead of print]

Wheeler CM, Castellsagué X, Garland SM, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against **cervical** infection and precancer caused by non-vaccine oncogenic **HPV** types: 4-year end-ofstudy analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2011; published online Nov 9. DOI:10.1016/S1470-2045(11)70287-X.

Weinberger Daniel M, Malley Richard, Lipsitch Marc. **Serotype replacement in disease after pneumococcal vaccination**. www.thelancet.com Published online April 13, 2011.

Wightman A, Opel DJ, Marcuse EK, Taylor JA.Washington State pediatricians' attitudes toward **alternative childhood immunization schedules**. Pediatrics. 2011;128(6):1094 –1099

Wilson Jennifer F.. In the Clinic: **Herpes Zoster**. *Ann Intern Med* March 1, 2011 154:ITC3-1.

Wilson SE, Deeks SL, Hatchette TF, Crowcroft NS. The role of **seroepidemiology** in the comprehensive surveillance of vaccine-preventable diseases. CMAJ. 2012 Jan 10;184(1):E70-6.

Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. **Herpes zoster recurrences** more frequent than previously reported. Mayo Clin Proc. 2011 Feb;86(2):88-93.

Yen C, Tate JE, Wenk JD, et al. Diarrhea-associated hospitalizations among US children over 2 **rotavirus** seasons after vaccine introduction. Pediatrics. 2011 Jan;127(1):e9-e15.

Zhang L, Prietsch SO, Axelsson I, et al. **Acellular vaccines** for preventing **whooping cough** in children. Cochrane Database Syst Rev. 2012 Mar 14;3:CD001478.

TOP

Anti-inflammatory properties of topical antifungal preparations:

It is difficult to determine the anti-inflammatory effects of topical antifungals in humans as the majority of studies are completed as *in vitro* studies or in animal models. Some studies compared antifungal drugs alone to a combination of antifungal plus steroid combination and had similar efficacies in treatment. A small study (n=20) assessed and compared *in vivo* anti-inflammatory effects of terbinafine, ciclopirox, ketoconazole and other antifungals (econazole, oxiconazole- not commonly used in Canada) with hydrocortisone 2.5%. This study looked at the ability to decrease erythema due to UVB exposure which is thought to mimic the response in dermatophyte infections. It did not study the effects in an actual dermatophyte–induced inflammatory reaction. Terbinafine, ciclopirox, and ketoconazole all demonstrated anti-inflammatory effects. Terbinafine and ciclopirox exhibited statistically significant difference in erythema when compared to control than ketoconazole, econazole, oxiconazole, and hydrocortisone. Ketoconazole exhibited intermediate anti-inflammatory effects. May consider use of these antifungals if there is an inflammatory component to the fungal infection.

Lassus A, Nolting KS, Saropoulos C. Comparison of ciclopirox olamine 1% cream with ciclopirox i%-hydrocortisone acetate 1% cream in the treatment of inflamed superficial mycoses. Clin Therapeutics 1988;10: 594-599.
Smith EB, Breneman DL, Griffith RF, et al. Double-blind comparison of naftifine cream and clotrimazole/betamethasone dipropionate cream in the treatment of tinea pedis. / Am Acad Dermatol 1992; 26: 125-127.
Evans EGV, James IGV, et al. Does naftifine have anti-inflammatory properties? A doubleblind comparative study with 1% clotrimazole-i% hydrocortisone in clinically diagnosed fungal infections of the skin. Br J Dermatol 1993; 129: 437-442
Rosen T, Schell BJ, Orengo I. Anti-inflammatory activity of antifungal preparations. Int J Dermat 1997;36:788-792

References: **Antifungal Treatment Chart**

[1] CPS 2010
[2] Micromedex 2010
[3] Hansten and Horn. Drug interactions
[4] Medical letter. Treatment guidelines : Antifungal drugs. The Medical Letter 2008(Jan);6(65):1-8. (Medical Letter-Treatment Guidelines-Antifungal drugs. Dec,2009.)
[5] Mohr J, Johnson M, Cooper T, et al. Current options in antifungal pharmacotherapy. Pharmacotherapy 2008;28(5):614–645
[6] Pappas PG, Kauffman CA, Andes D, et al: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48(5):503-535
[7] Sanford's Guide to Antimicrobial Therapy 2010.
Limper Andrew H., Knox Kenneth S., Sarosi George A., et al. and on behalf of the American Thoracic Society (ATS) Fungal Working Group. An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients. Am. J. Respir. Crit. Care Med. 183: 96-128. January 3, 2011
[8] Crawford F, Hollis S. Topical treatments for fungal infections of the skin skin and nails of the foot. Cochrane Database Syst Rev 2007; (3) CD001434.
[9] Goldstein AO, Goldstein BG. Onychomycosis. Up-to-date. Accessed 18 August 2009
[10] Olde Hartman TC, van Rijswick E. Fungal Nail Infection. BMJ 2008 Jul 10; 337: a429.
[11] Chang CH, Young-Xu Y, Kurth T et al. The Safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis : a meta-analysis. Am J Med 2007 Sep; 120(9):791-8
[12] Crawford F, Young P, Godfrey C, Bell-Syer SE et al. Oral Treatments for toenail onychomycosis: a systematic review. Arch Dermatol 2002 Jun; 138(6):811-6
[13] Hart R, Bell-Syer SE, Crawford F, Torgerson DJ, Young P, Russell I. Systematic review of topical treatments for fungal infections of the skin and nails of the feet. BMJ. 1999 Jul 10;319(7202):79-82
[14] Gupta AK; Jain HC; Lynde CW; Macdonald P; Cooper EA, et al. Prevalence and epidemiology of onychomycosis in patients visiting physicians' offices: a multicenter canadian survey of 15,000 patients. J Am Acad Dermatol 2000 Aug;43(2 Pt 1):244-8
[15] Sigurgeirsson B; Steingrimsson O. Risk factors associated with onychomycosis. J Eur Acad Dermatol Venereol 2004 Jan;18(1):48-51
[16] Pierard GE; Pierard-Franchimont C. The nail under fungal siege in patients with type II diabetes mellitus. Mycoses 2005 Sep;48(5):339-42
[17] Sigurgeirsson B, Olaffsson JH, Steinson JB, et al. Long-term effectiveness of treatment of treatment of terbinafine vs itraconazole in onychomycosis : a 5-year blinded prospective follow-up study. Arch Dermat 2002;138:353-7
Piraccini BM, Sisti A, Tosti A. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. J Am Acad Dermatol. 2010 Mar;62(3):411-4.
[18] Evans EG, Sigurgeirsson B. Double blind, randomized study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. BMJ 1999;318:1031-35
[19] Warshaw EM; Fett DD; Bloomfield HE, et al. Pulse versus continuous terbinafine for onychomycosis: a randomized, double-blind, controlled trial. J Am Acad Dermatol 2005 Oct;53(4):578-84
[20] Natural Medicine Comprehensive Database. Tea tree oil monograph. Accessed 2 October, 2009. (http://www.naturaldatabase.com/)
[21] Pappas PG, Kauffman CA, Andes D, et al: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48(5):503-535
[22] Kauffman CA. Treatment of oropharyngeal and esophageal candidiasis. Up-to-date Accessed 7August 2009
[23] Gonsalves WC, Stevens Wrightson A, Henry RG. Common oral conditions in older persons. Am Fam Physician. 2008;78(7):845-852
[24] Kulak Y, Arikan A, Delibalta N. Comparison of three different treatment methods for generalized denture stomatitis. J Prosthet Dent. 1994 Sep;72(3):283-8
[25] Su CW, Jamieson B. Clinical Inquiries. What is the best treatment for oral thrush in healthy infants? J Fam Pract. 2008 Jul;57(7):484-5.
[26] Goins RA, Ascher D, Waecker N, et al. Comparison of fluconazole and nystatin oral suspensions for treatment of oral thrush in infants. Pediatric Infect Dis J. 2002;21:1165-67.
[27] Leung AK. Gentian violet in the treatment of oral candidiasis. Pediatr Infect Dis J. 1988 Apr;7(4):304-5
[28] Walker M Conquering Common Breast-feeding Problems. J Perinat Neonat Nurs 2007;22:267-274
[29] Hoddinott P, Tappin D, Wright C. Breast feeding. BMJ 2008;336:881-7
[30] Naldi L, Rebora A. Seborrheic dermatitis. N Engl J Med 2009;360:387-96.
[31] Korting HC, Kiencke P, Nelles S, Rychlik R. Comparable efficacy and safety of various topical formulations of terbinafine in Tinea pedis irrespective of the treatment regimen. Results of a mata-analysis. Am J Clin Dermat 2007;8(6):357-364
[32] Schwartx A. Superficial fungal infections. Lancet 2004;364:1173-82
[33] Goldstein AO, Goldstein BG. Tinea versicolor. Up-to-date. Accessed 21August 2009
[34] Leeming JP; Sansom JE; Burton JL. Susceptibility of Malassezia furfur subgroups to terbinafine. Br J Dermatol 1997 Nov;137(5):764-7
[35] Janniger CK, Schwartz RA, Szepietowski JC, et al. Intertrigo and common secondary skin infections. Am Fam Physician 2005; 72:833-8,840
[36] Gupta AK, Chow M, Daniel CR, Aly R. Treatments of tinea pedis. Dermatol Clin. 2003 Jul;21(3):431-62.
[37] Gupta AK, Chaudhry M, Elewski B. Tinea corporis, tinea cruris, tinea nigra, and piedra. Dermatol Clin. 2003 Jul;21(3):395-400
[38] Andrews MD, Burns, M. Common Tinea infections in children. Am Fam Physician. 2008;77(10):1415-1420
[39] Sobel JD. Vulvovaginal candidosis. Lancet 2007; 369:1961-1971
40 Treatment of complicated vaginal yeast infections. Pharmacist's Letter/Prescriber's Letter 2010;26(8):260806
[41] Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral Therapy for Recurrent Vulvovaginal Candidiasis. N Engl J Med. 2004 Aug 26;351(9):876-83.
[41] Carter TC, Druschel CM, Romitti PA, et al. Antifungal drugs and the risk of selected birth defects. Am J Obstet Gynecol 2008; 198:191.e1-191.e7
[42] Sobel JD., Wiesenfeld HC., et al. Maintenance Fluconazole Therapy for Recurrent Vulvovaginal Candidiasis. N Engl J Med. 2004 Aug 26;351(9):876-83
Fischer G, Bradford J. Persistent vaginitis. BMJ 2011;343:d7314 doi: 10.1136/bmj.d7314 (Published 28 November 2011)
[43] Canadian STI guidelines 2008 http://www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php
[44] Stary A, Soeltz-Szoets J, Ziegler C et al. Comparison of the efficacy and safety of oral fluconazole and topical clotrimazole in patients with candida balanitis. Genitourin Med. 1996 Apr;72(2):98-102.
[45] Edwards, SK. European guideline for the management of balanoposthitis. Int J STD AIDS 2001; 12 Suppl 3:68.
[46] Carter TC, Druschel CM, Romitti PA, et al. Antifungal drugs and the risk of selected birth defects. Am J Obstet Gynecol 2008; 198:191.e1-191.e7
[47] Sobel Jd, Chaim W, Nagappan V, Leaman D. Treatment of vaginitis caused by Candida Glabrata: use of topical boric acid and flucytosine. Am J Obstet Gynecol 2003; 189:1297-1300
[48] Pirotta M. et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. BMJ. 2004 Sep 4; 329 (7465): 548.
[49] Das Neves J, Pinto E, Teixera B, et al. Local treatment of vulvovaginal candidosis. Drugs 2008;68(13):1787-1802.
[50] Scheinfeld N. Diaper dermatitis. A Review and Brief Survey of Eruptions of the Diaper Area. Am J Clin Dermat 2005; 6(5):273-81
[51] Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.
[52] Brüggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis. 2009 May 15;48(10):1441-58.
[53]Chambers WM, Millar A, Jain S, Burroughs AK. Terbinafine-induced hepatic dysfunction. Eur J Gastroenterol Hepatol. 2001 Sep;13(9):1115-8
[54] Joseph Mo, Pope E. Dermatology, Dipchand A, Friedman J, Bismilla Z, Gupta S, Lam C. The hospital for sick children: Handbook of pediatrics. Elsevier Canada 2009 p.194-207
[55] Lau, E. Pediatric drug dosing guidelines. In: Dipchand A, Friedman J, Bismilla Z, Gupta S, Lam C. The hospital for sick children: Handbook of pediatrics. Elsevier Canada 2009. p883-996
[56] Brown,SJ. Efficacy of fluconazole for the treatment of onychomycosis. Ann Pharmcother 2009;43:1684-91
[57] Garey KW, Pai MP, Suda KJ, et al. Inadequacy of fluconazole dosing in patients with candidemia based on Infectious Diseases Society of America (IDSA) guidelines. Pharmacoepidemiol Drug Saf 2007;16:919–27.
[58] Janssen Pharmaceutical Products LP. Sporanox (itraconazole) oral solution prescribing information. Titusville, NJ; 2004.
[59] Hickman JG. A double-blind, randomized, placebo-controlled evaluation of short-term treatment with oral itraconazole in patients with tinea versicolor. J Am Acad Dermatol 1996 May;34(5 Pt 1):785-7
[60] Kose O; Bulent Tastan H; Riza Gur A, et al. Comparison of a single 400 mg dose versus a 7-day 200 mg daily dose of itraconazole in the treatment of tinea versicolor. J Dermatolog Treat 2002 Jun;13(2):77-9
[61] Feranandez-Nava HD, Laya-Cuadra B, Tianco EAV. Comparison of single dose 400mg versus 10-day 200mg daily dose ketoconazole in the treatment of tinea versicolor. Int J Dermatol 1997;36:64-66

TOP

Extras:

- AOM: Prophylactic tx no longer recommended
- Conjunctivitis: 85% viral in adults. Suggest antibiotics if there's no improvement within 5 days or sooner (if the school or daycare requires treatment to come back). Handwashing important to help prevent spread. Bacterial infections are infectious for 24-48 hours after ABX initiation, viral are infectious until the eye clears. Consider washing contact case and replacing contacts if disposable, replace bottle of eye drops if any are used (eg glaucoma). Bacterial=Purulent discharge, swelling of the eye, and a burning sensation, usually persisting throughout the day, red or pink colour of the eye and pts often complain of waking up with eyes "glued shut". Red flag sx: a great deal of discomfort and pain, changes in vision, nausea, vomiting, or severe headache, eyelid edema, severe, continuous, copious, purulent discharge or whose symptoms have persisted for longer than 72 hours should be examined by a medical practitioner. A mild, watery discharge, with itching associated with a concurrent upper respiratory infection signals viral-if only one eye affected, other eye becomes involved in half of the cases. Corticosteroid eyedrops may quickly relieve symptoms, but should be avoided as they can worsen or mask accompanying conditions such as herpetic keratitis.
- Impetigo: [Retapamulin Altargo topical USA: for impetigo if resistance]
- Pharyngitis: *Fusobacterium necrophorum* just as common as GAS (~10%) in ages 15-24 and can cause Lemierre syndrome, a life-threatening condition. ABX tx can shorten symptom duration by ~16 hours.

STI

- EPT or Expedited Partner Treatment : a practice where a second prescription is given for chlamydia or gonorrhea, often to the index patient, for the partner
- External Genital Warts (EGW) - adult: caused by human papilloma virus (HPV) especially types 6 & 11; Tx options : 1) Imiquimod 5% cream Apply HS 3x/week; 2) Podofilox 0.5% soln Apply BID x3 days, then no tx x4 days; repeat cycle up to 3x.; 3) Cryotherapy Physician to apply liquid nitrogen q1-2 weeks for maximum 8 weeks; 4)Podophyline 10-25% resin in tincture of benzoin Apply small amount, allow to dry, repeat weekly if necessary (may wash resin off after 1-4hrs application; 5) Trichloroacetic acid 80-90% in 70% alcohol Apply small amount to warts, allow to dry, repeat weekly if necessary (5% EMLA cream pre-application may be used to ↓ burning; 6) Laser tx; 7) Surgical removal.
- Follow-up testing for Chlamydia & gonorrhea: retesting recommended at 3 months after tx.

Acknowledgements: Dr. Yvonne Shevchuk (College of Pharmacy, U of S); Dr. S. Takaya (SHR-Infectious Disease); Dr. T. Laubscher CCFP (FM, U of S), M. Jin (Pharm D, Hamilton) & the RxFiles Advisory Committee.
Shannon Stone BSP, Loren Regier BSP, BA , Brent Jensen BSP

Produced by RxFiles – a provincial academic detailing service funded by Saskatchewan Health.
For more information check our website at *www.RxFiles.ca* or contact us
c/o Saskatoon City Hospital, 701 Queen Street,
Saskatoon, SK. S7K 0M7

Extra Refs: Anti-infectives for Common Infections – Overview

Achiam CC, Fernandes CM, McLeod SL, et al. **Methicillin-resistant Staphylococcus aureus in skin** and soft tissue infections presenting to the Emergency Department of a Canadian Academic Health Care Center. Eur J Emerg Med. 2010 Feb 17.

Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. **Ciprofloxacin safety in paediatrics**: a systematic review. Arch Dis Child. 2011 Sep;96(9):874-80.

Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al. Antibiotics for acute maxillary **sinusitis**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD000243. Antibiotics have a small treatment effect in patients with uncomplicated acute sinusitis in a primary care setting with symptoms for more than seven days. However, 80% of participants treated without antibiotics improve within two weeks. Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level.

Albert RH. Diagnosis and treatment of **acute bronchitis**. Am Fam Physician. 2010 Dec 1;82(11):1345-50.

Allen SJ, Martinez EG, Gregorio GV, Dans LF. **Probiotics for treating acute infectious diarrhoea**. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub3. Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.

Altamimi S, Khalil A, Khalaiwi KA, et al. Short versus standard duration antibiotic therapy for **acute streptococcal pharyngitis in children**. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD004872. Three to six days of oral antibiotics had comparable efficacy compared to the standard duration 10 day oral penicillin in treating children with acute GABHS pharyngitis. In countries with low rates of rheumatic fever, it appears safe and efficacious to treat children with acute GABHS pharyngitis with short duration antibiotics. In areas where the prevalence of rheumatic heart disease is still high, our results must be interpreted with caution.

Albert RK, Connett J, Bailey WC, et al. **Azithromycin** (up to 1yr) for prevention of exacerbations of COPD. N Engl J Med 2011;365: 689-98.

American Academy of Pediatric Dentistry Clinical Affairs Committee, American Academy of Pediatric Dentistry Council on Clinical Affairs. Guideline on antibiotic **prophylaxis for dental patients** at risk for infection. Pediatr Dent 2008-2009;30(7 Suppl):215-8. http://www.aapd.org/media/Policies_Guidelines/G_AntibioticProphylaxis.pdf

American Academy of Pediatrics (AAP) Committee on Infectious Diseases. The Use of **Systemic and Topical Fluoroquinolones**. Pediatrics. 2011 Oct;128(4):e1034-e1045.

Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/

Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in **exacerbation** of chronic obstructive pulmonary disease. Ann Intern Med 1987;106(2):196-204.

Antoniou T, Gomes T, Mamdani MM, et al. **Trimethoprim-sulfamethoxazole induced hyperkalaemia** in elderly patients receiving **spironolactone**: nested case-control study. BMJ. 2011 Sep 12;343:d5228.

Arias CA, Panesso D, McGrath DM, et al. Genetic basis for in vivo **daptomycin resistance** in enterococci. N Engl J Med. 2011 Sep 8;365(10):892-900.

Aring AM, Chan MM. **Acute rhinosinusitis in adults**. Am Fam Physician. 2011 May 1;83(9):1057-63.

Balter M, La Forge J, Low D, Mandell L, Grossman R. Canadian guidelines for the management of acute **exacerbations of chronic bronchitis**. Can Respir J 2003;10(Suppl B):3B-32B.

Belshe RB et al. Efficacy results of a trial of a **herpes simplex vaccine**. N Engl J Med 2012 Jan 5; 366:34

Bernaola Aponte G, Bada Mancilla CA, Carreazo Pariasca NY, Rojas Galarza RA. **Probiotics for treating persistent diarrhoea** in children. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD007401. DOI: 10.1002/14651858.CD007401.pub2. There is limited evidence suggesting probiotics may be effective in treating persistent diarrhoea in children.

Bezáková N et al. Recurrence up to 3.5 years after antibiotic treatment of acute **otitis media** in very young Dutch children: Survey of trial participants. BMJ 2009 Jun 30; 338:b2525. BMJ. 2007 Nov 10;335(7627):991.

Breda L, Marzetti V, Gaspari S, et al. Population-based study of incidence and clinical characteristics of **rheumatic Fever** in abruzzo, central Italy, 2000-2009. J Pediatr. 2012 May;160(5):832-836.e1.

Breen JO. **Skin and soft tissue infections** in immunocompetent patients. Am Fam Physician. 2010 Apr 1;81(7):893-9.

Brill JR. Diagnosis and treatment of **urethritis in men**. Am Fam Physician. 2010 Apr 1;81(7):873-8.

Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.

Butler CC, Simpson SA, Dunstan F, Rollnick S, Cohen D, Gillespie D, et al. Effectiveness of multifaceted **educational programme** to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. BMJ 2012.344:d8173.

Cadena J et al. Dose of **trimethoprim-sulfamethoxazole** to treat skin and skin structure infections caused by **methicillin-resistant Staphylococcus aureus**. Antimicrob Agents Chemother 2011: 55: 5430-2.

Cals JW, Butler CC, Hopstaken RM, et al. Effect of point of care testing for C reactive protein (**CRP**) and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ. 2009

Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of **cephalosporins in penicillin-allergic** patients. J Emerg Med. 2012;42(5):612-620.

Carter MJ, Tingley-Kelley K, Warriner RA 3rd. Silver treatments and **silver-impregnated** dressings for the healing of leg wounds and ulcers: a systematic review and meta-analysis. J Am Acad Dermatol. 2010 Oct;63(4):668-79. Epub 2010 May 14.

CDC July/11 **Cephalosporin Susceptibility Among Neisseria gonorrhoeae** Isolates --- United States, 2000--2010 http://www.cdc.gov/mmwr/pdf/wk/mm6026.pdf

CDC Sep/11 Office-Related **Antibiotic Prescribing for Persons Aged ≤14 Years** --- United States, 1993--1994 to 2007—2008. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6034a1.htm?s_cid=mm6034a1_x

Centor Robert M. Expand the **Pharyngitis** Paradigm for Adolescents and Young Adults.Ann Intern Med December 1, 2009 151:812-815; doi:10.1059/0003-4819-151-11-200912010-00011.

Chen AE, Carroll KC, Diener-West M, et al. Randomized controlled trial of **cephalexin versus clindamycin for uncomplicated pediatric skin infections**. Pediatrics. 2011 Mar;127(3):e573-80.

Choby BA. Diagnosis and treatment of **streptococcal pharyngitis**. Am Fam Physician. 2009 Mar 1;79(5):383-90.

Chiappini E, Regoli M, Bonsignori F, et al. Analysis of different recommendations from international guidelines for the management of **acute pharyngitis in adults and children**. Clin Ther. 2011 Jan;33(1):48-58.

Chow AW, Benninger MS, Brook I et al. **IDSA** Clinical Practice Guideline for Acute Bacterial **Rhinosinusitis in Children and Adults**. Clin Infect Dis. 2012Apr;54(8):e72-e112.

Coco, Andrew, Vernacchio, Louis, Horst, Michael, Anderson, Angela. Management of **Acute Otitis Media** After Publication of the 2004 AAP and AAFP Clinical Practice Guideline. Pediatrics 2010 0: peds.2009-1115.

TOP

Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. Clinical practice guidelines for **Clostridium difficile** infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (**IDSA**). Infect Control Hosp Epidemiol. 2010 May;31(5):431-55.
Cohen, Arlan, Maschopoulos, Panagis, Stiehm, Richard E., Koren, Gideon. **Congenital varicella syndrome**: the evidence for secondary prevention with **varicella-zoster immune globulin**. CMAJ 2011 0: cmaj.100615.
Copp HL, Shapiro DJ, et al. National Ambulatory Antibiotic Prescribing Patterns for Pediatric **Urinary Tract Infection**,1998-2007.*Pediatrics*, 2011; DOI: 10.1542/peds.2010-3465
Cornia PB, Hersh AL, Lipsky BA, et al. Does this coughing adolescent or adult patient have **pertussis**?. JAMA. 2010 Aug 25;304(8):890-6.
Costelloe Céire, Metcalfe Chris, Lovering Andrew, et al. Effect of **antibiotic prescribing** in primary care on **antimicrobial resistance** in individual patients: systematic review and meta-analysis. BMJ 2010;340:c2096
Daniels JM, Snijders D, de Graaff CS, et al. Antibiotics in Addition to Systemic **Corticosteroids for Acute Exacerbations** of COPD. Am J Respir Crit Care Med. 2009 Oct 29. While equivalent to placebo on clinical success at day 30, doxycycline showed superiority on clinical success and clinical cure at day 10, microbiological success, the use of open label antibiotics and symptoms.
Datta Rupak; Platt Richard; Yokoe Deborah S.; et al. **Environmental Cleaning Intervention** and Risk of Acquiring Multidrug-Resistant Organisms From Prior Room Occupants. Arch Intern Med. 2011;171(6):491-494.
Davies L, Angus RM, Calverley PM. Oral **corticosteroids** in patients admitted to hospital with **exacerbations** of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999;354(9177):456-60.
Davenport RJ. ACP Journal Club. Review: Adding **antiviral drugs to steroids did not improve facial muscle recovery in Bell palsy**. Ann Intern Med. 2010 Feb 16;152(4):JC-210.
de Smet AM, Kluytmans JA, Blok HE, et al. **Selective digestive tract decontamination and selective oropharyngeal decontamination** and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infect Dis. 2011 Mar 18.
Deleo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated **methicillin-resistant Staphylococcus aureus**. Lancet. 2010 May 1;375(9725):1557-68.
Desrosiers M, Evans GE, Keith PK, et al. **Canadian clinical practice guidelines for acute and chronic rhinosinusitis**. Allergy Asthma Clin Immunol 2011;7:2. www.aacijournal.com/content/pdf/1710-1492-7-2.pdf
Dhiwakar M, Clement WA, Supriya M, McKerrow W. Antibiotics to reduce **post-tonsillectomy** morbidity. Cochrane Database Syst Rev. 2010 Jul 7;7:CD005607. The present systematic review, including meta-analyses for select outcomes, suggests that although individual studies vary in their findings, there is no evidence to support a consistent, clinically important impact of antibiotics in reducing the main morbid outcomes following tonsillectomy (i.e. pain, need for analgesia and secondary haemorrhage rates). Limited benefit apparent with antibiotics may be a result of positive bias introduced by several important methodological shortcomings in the included trials. Based on existing evidence therefore, we would advocate against the routine prescription of antibiotics to patients undergoing tonsillectomy. Whether a subgroup of patients who might benefit from selective administration of antibiotics exists is unknown and needs to be explored in future trials.
Di Pentima MC, Chan S, Hossain J. Benefits of a **Pediatric Antimicrobial Stewardship Program** at a Children's Hospital. Pediatrics. 2011 Dec;128(6):1062-70.
Dixon JM, Khan LR. Treatment of **breast infection**. BMJ. 2011 Feb 11;342:d396. doi: 10.1136/bmj.d396.
Drekonja DM, Butler M, MacDonald R, Bliss D, Filice GA, Rector TS, Wilt TJ. Comparative effectiveness of Clostridium difficile treatments: a systematic review. Ann Intern Med. 2011 Dec 20;155(12):839-47.
Elias, Jackie, Bozzo, Pina, Einarson, Adrienne. Are **probiotics safe for use during pregnancy and lactation**? Can Fam Physician 2011 57: 299-301.
Edwards J, Stapley S. **Debridement of diabetic foot ulcers**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003556. There is evidence to suggest that hydrogel increases the healing rate of diabetic foot ulcers compared with gauze dressings or standard care and larval therapy resulted in significantly greater reduction in wound area than hydrogel.
European Respiratory Society. **COPD guidelines**. Lausanne, Switz: European Respiratory Society; 2004. Available from: www.ersnet.org/ers/default. aspx?id=1418. Accessed 2008 Oct 31.
Evans AT, Husain S, Durairaj L, et al. Azithromycin for **acute bronchitis**: a randomized, double-blind, controlled trial. Lancet 2002;359(9318):1648-54.
Evensen AE. **Management of COPD Exacerbations**. Am Fam Physician. 2010 Mar 1;81(5):607-13.
Faden, Howard, Lesse, Alan J., Trask, Jennifer, et al. Importance of **Colonization** Site in the Current Epidemic of **Staphylococcal Skin Abscesses**. Pediatrics 2010 125: e618-e624.
Fang L, Oliver A, Jayaraman GC, Wong T. Trends in age disparities between younger and middle-age adults among reported rates of **chlamydia, gonorrhea, and infectious syphilis** infections in Canada: findings from 1997 to 2007. Sex Transm Dis. 2010 Jan;37(1):18-25.
FitzGerald M; on behalf of the British Association of Sexual Health and HIV Clinical Effectiveness Group. **Gonorrhoea treatment**—suggested changes. 2011. www.bashh.org/documents/3256 .
Forster AJ, Taljaard M, Oake N, et al. The effect of **hospital acquired** infection with **Clostridium dificile** on length of stay in hospital. CMAJ 2012;184:37-42.
Fraser CL, Biousse V, Newman NJ. **Minocycline-Induced Fulminant Intracranial Hypertension**. Arch Neurol. 2012 Apr 9.
Fritz SA, Hogan PG, Hayek G, et al. **Household versus individual approaches to eradication of community-associated Staphylococcus aureus in children**: a randomized trial. Clin Infect Dis. 2012 Mar;54(6):743-51.
Ganske CM, Horning KK. **Levofloxacin-induced tendinopathy** of the hip. Ann Pharmacother. 2012 May;46(5):e13.
Garbutt Jane M, Banister Christina, Spitznagel E, et al. **Amoxicillin for Acute Rhinosinusitis**: A Randomized Controlled Trial. *JAMA*. 2012;307(7):685-692. (not effective)
Garcia Miguel Sanchez; Maria Torre Angeles De la; Morales Gracia et al; Clinical Outbreak of **Linezolid-Resistant Staphylococcus aureus** in an Intensive Care Unit, JAMA. 2010;303(22):2260-2264.
Gebre T, Ayele B, Zerihun M, et al. Comparison of **annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma** in Ethiopia: a cluster-randomised trial. Lancet 2011; published online Dec 21.
Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute **Streptococcal Pharyngitis**. A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation. 2009 Feb 26.
Gillison ML, Broutian T, Pickard R, et al. Prevalence of **oral HPV infection** in the United States, 2009-2010. JAMA. doi:10.1001/jama.2012.101.
GOLD Initiative. Guidelines. **GOLD COPD** Initiative; 2008. Available from: www.goldcopd. com/GuidelineList.asp. Accessed 2008 Oct 31.
Gottesman BS, Carmeli Y, Shitrit P, Chowers M. Impact of **quinolone restriction on resistance** patterns of Escherichia coli isolated from urine by culture in a community setting. Clin Infect Dis. 2009 Sep 15;49(6):869-75.
Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Epididymitis and orchitis**: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar. http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Urological_Infections.pdf
Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Sexually transmitted infections**: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.
Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Urethritis**: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.
Gradison M. **Pelvic inflammatory disease**. Am Fam Physician. 2012 Apri15;85(8):791-6.
Grijalva Carlos G.; Nuorti J. Pekka; Griffin Marie R.. **Antibiotic Prescription Rates** for Acute Respiratory Tract Infections in US Ambulatory Settings. JAMA. 2009;302(7):758-766.
Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of **infective endocarditis** (new version **2009**). Eur Heart J 2009; DOI:10.1093/eurheartj/ehp285. http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-IE-FT.pdf
Hainer BL, Gibson MV. **Vaginitis**: Diagnosis and Treatment.Am Fam Physician. 2011 Apr 1;83(7):807-815.
Harnden Anthony .**Whooping cough**. BMJ 2009;338:b1772, doi: 10.1136/bmj.b1772 (Published 21 May 2009)
Health Canada Nov/11 **Fluoroquinolone** antibiotics: patients with **myasthenia gravis** may risk increased muscle weakness.
Hersh AL et al. **Antibiotic prescribing in ambulatory pediatrics** in the United States. Pediatrics. 2011 Dec;128(6):1053-61.
Ho JM, Juurlink DN. Considerations when prescribing **trimethoprim-sulfamethoxazole**. CMAJ. 2011 Oct 11.
Hurst JR, Wedzicha JA. Management and prevention of chronic obstructive pulmonary disease **exacerbations**: a state of the art review. BMC Med. 2009 Aug 7;7:40.
Huskins WC et al. **Intervention to reduce transmission of resistant bacteria** in intensive care. N Engl J Med 2011 Apr 14; 364:1407.
Imamura H, KurokawaY, Tsujinaka T, et al. **Intraoperative versus extended antimicrobial prophylaxis** after gastric cancer surgery: a phase 3, open-label, randomised controlled, non-inferiority trial. Lancet Infect Dis 2012; published online Jan 31.
Ivers Noah, Arroll Bruce, Allan G. Michael. **Delayed antibiotic prescriptions** for URTIs. Can Fam Physician November 2011 57: 1287.
Iyer PG, Murphy TF. **Chronic obstructive pulmonary disease**: role of **bacteria** and updated guide to antibacterial selection in the older patient. Drugs Aging. 2009;26(12):985-95. doi: 10.2165/11315700-000000000-00000. Penicillin, amoxicillin, cotrimoxazole (trimethoprim/sulfamethoxazole) and doxycycline should not be used as an initial antibacterial because of resistance patterns. We recommend second-/third-generation cephalosporins, amoxicillin/clavulanic acid, azithromycin and respiratory fluoroquinolones as initial choices.
Jahanfar S, Ng CJ, Teng CL. Antibiotics for **mastitis** in breastfeeding women. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD005458.
Jain R et al. Veterans Affairs initiative to **prevent methicillin-resistant Staphylococcus aureus infections**. N Engl J Med 2011 Apr 14; 364:1419.
Jarlier Vincent; Trystram David; Brun-Buisson Christian; et al.; for the Collegiale de Bacteriologie-Virologie-Hygiene des Hopitaux Universitaires de l'Ile de France **Curbing Methicillin-Resistant Staphylococcus** aureus in 38 French Hospitals Through a 15-Year Institutional Control Program. Arch Intern Med. 2010;170(6):552-559.
Jenkins Timothy C.; Knepper Bryan C.; Sabel Allison L.; et al. **Decreased Antibiotic Utilization After Implementation of a Guideline for Inpatient Cellulitis and Cutaneous Abscess**. Arch Intern Med. 2011;171(12):1072-1079.
Joachim L, Campos D Jr, Smeesters PR. Pragmatic **Scoring System for Pharyngitis in Low-Resource Settings**. Pediatrics. 2010 Aug 9. [Epub ahead of print]
Johnston C, Saracino M, Kuntz S, et al. **Standard-dose and high-dose daily antiviral** (aciclovir, valaciclovir) therapy for short episodes of **genital HSV-2 reactivation**: three randomised, open-label, cross-over trials. Lancet 2012; published online Jan.
Kalwij Sebastian, Macintosh Mary, Baraitser Paula. **Screening** and treatment of **Chlamydia** trachomatis infections. BMJ 2010;340:c1915, doi: 10.1136/bmj.c1915 (Published 21 April 2010)
Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, et al. Fluoroquinolones compared with beta-lactam antibiotics for the treatment of **acute bacterial sinusitis**: a meta-analysis of randomized controlled trials. CMAJ. 2008 Mar 25;178(7):845-54. In the treatment of acute bacterial sinusitis, newer fluoroquinolones conferred no benefit over beta-lactam antibiotics. The use of fluoroquinolones as first-line therapy cannot be endorsed. The authors found no benefit to fluoroquinolones over beta-lactams for acute bacterial rhinosinusitis (ABRS). The more important and relevant questions are whether we can distinguish ABRS from viral sinusitis (not very well) and whether antibiotics are needed at all (probably not for most patients). If you decide to prescribe an antibiotic because of severity of illness or duration of symptoms, a beta-lactam will work as well as a fluoroquinolone. (LOE = 1a)

TOP

Katz AR et al. **Neisseria gonorrhoeae** with high-level **resistance to azithromycin**: Case report of the first isolate identified in the United States. Clin Infect Dis 2012 Mar 15; 54:841.

Kaushik V, Malik T, Saeed SR. Interventions for acute **otitis externa**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD004740.

Kim Nak-Hyun, Kim Moonsuk, Lee Shinwon, et al. Effect of Routine **Sterile Gloving on Contamination Rates** in Blood Culture: A Cluster Randomized Trial. *Ann Intern Med* February 1, 2011 154:145-151.

Kim SJ, Toma HS. **Antimicrobial resistance and ophthalmic antibiotics**: 1-year results of a longitudinal controlled study of patients undergoing intravitreal injections. Arch Ophthalmol. 2011 Sep;129(9):1180-8.

Kimberlin DW et al. Oral **acyclovir suppression** and neurodevelopment after **neonatal herpes**. N Engl J Med 2011 Oct 6; 365:1284.

Klotz SA, Ianas V, Elliott SP. **Cat-scratch Disease**. Am Fam Physician. 2011 Jan 15;83(2):152-155.

Kluytmans J, Struelens M. **Meticillin resistant Staphylococcus** aureus in the hospital. BMJ. 2009 Feb 12;338:b364. doi: 10.1136/bmj.b364.

Koning S, van der Sande R, Verhagen AP, et al. **Interventions for impetigo**. Cochrane Database Syst Rev. 2012 Jan 18;1:CD003261. There is good evidence that topical mupirocin and topical fusidic acid are equally, or more, effective than oral treatment. Due to the lack of studies in people with extensive impetigo, it is unclear if oral antibiotics are superior to topical antibiotics in this group. Fusidic acid and mupirocin are of similar efficacy. Penicillin was not as effective as most other antibiotics. There is a lack of evidence to support disinfection measures to manage impetigo.

Korb K, Scherer M, Chenot JF. **Steroids** as adjuvant therapy for acute pharyngitis in ambulatory patients: a systematic review. Ann Fam Med. 2010 Jan-Feb;8(1):58-63.

Korbila IP, Manta KG, Siempos II, et al. Penicillins vs trimethoprim-based regimens for acute bacterial **exacerbations of chronic** bronchitis: meta-analysis of randomized controlled trials. Can Fam Physician. 2009 Jan;55(1):60-7.

Kozyrskyj A, Klassen TP, Moffatt M, et al. **Short-course antibiotics for acute otitis media**. Cochrane Database Syst Rev. 2010 Sep 8;9:CD001095. Clinicians need to evaluate whether the minimal short-term benefit from longer treatment of antibiotics is worth exposing children to a longer course of antibiotics.

Kuehn Bridget M. FDA Targets Antibiotic Use in **Livestock**. JAMA. 2010;304(4):396.

Lamont RF, Nhan-Chang CL, Sobel JD, et al. Treatment of **abnormal vaginal flora** in early pregnancy with **clindamycin** for the prevention of spontaneous **preterm birth**: a systematic review and metaanalysis. Am J Obstet Gynecol. 2011 Sep;205(3):177-90.

Lee Dong Heun; Vielemeyer Ole. Analysis of Overall **Level of Evidence Behind Infectious Diseases Society of America (IDSA) Practice Guidelines**. Arch Intern Med. 2011;171(1):18-22.

Lee AS, Macedo-Vinas M, François P, et al. Impact of combined low-level **mupirocin** and genotypic **chlorhexidine resistance** on persistent methicillin-resistant Staphylococcus aureus carriage after decolonization therapy: case-control study. Clin Infect Dis. 2011 Jun 15;52(12):1422-30.

Leffler DA, Lamont JT. Treatment of **Clostridium difficile**-associated disease. Gastroenterology. 2009 May;136(6):1899-912. Epub 2009 May 7.

Lennon DR Fracp, Farrell E Mhsc, et al. Once-daily Amoxicillin versus Twice-daily Penicillin V in Group A {beta}-Hemolytic **Streprococcus Pharyngitis**. Arch Dis Child. 2008 Mar 12; [Epub ahead of print] In this adequately-powered study, once-daily oral amoxicillin is not inferior to twice-daily penicillin V for the treatment and eradication of GABHS in children with pharyngitis.

Li M, Al-Sarraf A, Sinclair G, Frohlich J. **Fish odour syndrome**. CMAJ. 2011 Mar 21.

Lin JS, Whitlock E, O'Connor E, Bauer V. **Behavioral counseling to prevent sexually transmitted infections**: a systematic review for the U. S. Preventive Services Task Force. Ann Intern Med. 2008;149(7):497–508.

Linden JA. Clinical practice. Care of the adult patient **after sexual assault**. N Engl J Med. 2011 Sep 1;365(9):834-41.

Liu Catherine, Bayer Arnold, Cosgrove Sara E., et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) for the Treatment of **Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children.** Clin Infect Dis. ciq146 Jan 4, 2011.

Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America-**IDSA** clinical practice guideline for the diagnosis and treatment of **diabetic foot infections**. Clin Infect Dis. 2012 Jun;54(12):e132-73.

Logan LK, McAuley JB, Shulman ST. **Macrolide treatment** failure in streptococcal pharyngitis resulting in acute **rheumatic fever**. Pediatrics. 2012 Mar;129(3):e798-802.

Lowy, IM, DC., Leav, BA., et al. Treatment with Monoclonal Antibodies against **Clostridium difficile** Toxins.N Engl J Med 2010 362: 197-205.

Luce H, Schrager S, Gilchrist V. **Sexual assault of women**. Am Fam Physician. 2010 Feb 15;81(4):489-95.

Lucet J-C et al. Carriage of **methicillin-resistant Staphylococcus aureus** in home care settings: Prevalence, duration, and transmission to household members. Arch Intern Med 2009 Aug 10/24; 169:1372.

Macfarlane J, Holmes W, Gard P, et al. Reducing antibiotic use for **acute bronchitis** in primary care: blinded, randomized controlled trial of patient information leaflet. BMJ. 2002 Jan 12;324(7329):91-4.

McIvor A, Little P. **Chronic obstructive pulmonary disease**. BMJ 2007;334(7597):798.

Medical Letter. Treatment Guidelines. **Drugs for Bacterial Infections**. June 2010.

Medical Letter-Treatment Guidelines. **Drugs for Sexually Transmitted Diseases**. July 2010.

Melese M, Alemayehu W, Lakew T, et al. Comparison of **annual and biannual mass antibiotic administration for elimination of infectious trachoma**. JAMA 2008; 299: 778–84.

Meltzer JA, Kunkov S, Crain EF. Identifying children at low risk for bacterial **conjunctivitis**. Arch Pediatr Adolesc Med. 2010 Mar;164(3):263-7. Age 6 years or older, presentation in April through November, no or watery discharge, and no glued eye in the morning were the clinical factors found to be independently associated with a negative conjunctival culture.

Mitjà O, Hays R, Ipai A, et al. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. Lancet 2012; published online Jan 11

Moellering Robert C. NDM-1 — A Cause for Worldwide Concern. . N Engl J Med 2010; 363:2377-2379.

Money D, Steben M, Wong T, et al. Infectious Disease Committee, Executive and Council of the Society of Obstetricians and Gynaecologists of Canada. Genital herpes: gynaecological aspects. J Obstet Gynaecol Can 2008 Apr;30(4):347-53. http://www.sogc.org/guidelines/documents/gui207CPG0804_000.pdf

Morgan DJ, Okeke IN, Laxminarayan R, et al. **Non-prescription (OTC) antimicrobial use worldwide**: a systematic review. Lancet Infect Dis. 2011 Jun 7.

Morales G, Picazo JJ, Baos E, Candel FJ, Arribi A, Pelaez B, Andrade R, de la Torre MA, Fereres J, Sanchez-Garcia M. **Resistance to linezolid** is mediated by the cfr gene in the first report of an outbreak of linezolid-resistant Staphylococcus aureus. Clin Infect Dis 50 (6): 821-5, 2010.

Murdoch DR, Corey GR, Hoen B, et al. International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of **infective endocarditis** in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009 Mar 9;169(5):463-73.

NICE- Mar 2011 Clinical Guideline 119. **Diabetic foot** - inpatient management of people with diabetic foot ulcers and infection. http://www.nice.org.uk/nicemedia/live/13416/53556/53556.pdf

NICE- National Institute for Health and Clinical Excellence. Surgical management of children with **otitis media with effusion (OME**). (Clinical guideline 60.) 2008. www.nice.org.uk/CG060

Niland ML, Bonsu BK, Nuss KE, Goodman DG. A pilot study of 1 versus 3 days of **dexamethasone** as add-on therapy in children with **streptococcal pharyngitis**. Pediatr Infect Dis J 2006;25(6):477-81.

Nishimura RA, Carabello BA, Faxon DP, et al. **ACC/AHA 2008** Guideline update on valvular heart disease: focused update on **infective endocarditis**: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, & Society of Thoracic Surgeons.J Am Coll Cardiol. 2008 Aug 19;52(8):676-85.

Nitschke M, Sayk F, Härtel C et al. Association between **azithromycin** therapy and duration of bacterial shedding among patients with Shiga toxin-producing enteroaggregative **Escherichia coli O104:H4**. JAMA. 2012 Mar 14;307(10):1046-52. (lower carriage)

Noble J, Lloyd JC. The **red eye**. CMAJ. 2010 Oct 4.

Nouira S, Marghli S, Besbes L, et al. **Standard versus newer antibacterial agents** (Bactrim vs Cipro) in the treatment of severe acute exacerbation of chronic obstructive pulmonary disease: a randomized trial of trimethoprim-sulfamethoxazole versus ciprofloxacin. Clin Infect Dis. 2010 Jul 15;51(2):143-9.

Oake Natalie; Taljaard Monica; van Walraven Carl; et al. The Effect of **Hospital-Acquired Clostridium** difficile Infection on In-Hospital Mortality. Arch Intern Med. 2010;170(20):1804-1810.

O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, et al. **Canadian** Thoracic Society recommendations for management of **chronic obstructive pulmonary disease**—2007 update. Can Respir J 2007;14(Suppl B):5B-32B.

Oehler RL, Velez AP, Mizrachi M, Lamarche J, Gompf S. **Bite-related** and septic syndromes caused by **cats and dogs**. Lancet Infect Dis. 2009 Jul;9(7):439-47.

Olympia RP, Khine H, Avner JR. Effectiveness of oral **dexamethasone** in the treatment of moderate to **severe pharyngitis** in children. Arch Pediatr Adolesc Med 2005;159(3):278-82.

Ota KV, Jamieson F, Fisman DN, et al. Prevalence of and risk factors for **quinolone-resistant Neisseria gonorrhoeae** infection in Ontario. CMAJ. 2009 Feb 3;180(3):287-90.

Pankhania Miran, Judd Owen, Ward Andy. Practice: 10-Minute Consultation: **Otorrhoea**. (otitis externa) BMJ 2011;342:doi:10.1136/bmj.d2299 (Published 20 May 2011)

Pasternak B, Hviid A. Use of **acyclovir**, valacyclovir, and famciclovir in the **first trimester of pregnancy** and the risk of birth defects. JAMA. 2010 Aug 25;304(8):859-66.

Patel RA, Gallagher JC. **Drug Fever**. Pharmacotherapy. 2010 Jan;30(1):57-69.

Paul I. M., Maselli J. H., Hersh A. L., et al. Antibiotic Prescribing During Pediatric Ambulatory Care **Visits for Asthma**. *Pediatrics*, 2011; DOI: 10.1542/peds.2011-0218

Pegler S, Healy B. In patients **allergic to penicillin**, consider second and third generation cephalosporins for life threatening infections. BMJ. 2007 Nov 10;335(7627):991.

Pillai, Dylan R., McGeer, Allison, Low, Donald E. New Delhi metallo-{beta}-lactamase-1 (**NDM-1**) in Enterobacteriaceae: emerging resistance. CMAJ 2011 183: 59-64.

Pinninti SG, Angara R, Feja KN, et al. **Neonatal Herpes Disease following Maternal Antenatal Antiviral Suppressive Therapy**: A Multicenter Case Series. J Pediatr. 2012 Feb 14.

Plitt S, Boyington C, Sutherland K, et al. Antimicrobial **Resistance in Gonorrhea**: Influence of Epidemiologic and Laboratory Surveillance Data on Treatment Guidelines: Alberta, Canada 2001-2007. Sex Transm Dis. 2009 Aug 21.

Power M, Wigglesworth N, Donaldson E, et al. **Reducing Clostridium difficile** infection in acute care by using an improvement collaborative. BMJ. 2010 Jul 21

Public Health Agency of Canada. Important notice – public health information update on the treatment for **gonococcal infection**. Public Health Agency of Canada issued important notice on gonococcal infection. December 21, 2011. www.phac-aspc.gc.ca/std-mts/sti-its/alert/2011/alert-gono-eng.php (accessed December 21, 2011).

Rajan S**. Skin and soft-tissue infections**: Classifying and treating a spectrum. Cleve Clin J Med. 2012 Jan;79(1):57-66.

Ray WA, Murray KT, Hall K, et al. **Azithromycin and the risk of cardiovascular death**. N Engl J Med 2012; 366:1881-90.

Romøren M, Lindbaek M, Nordeng H. Pregnancy outcome after **gestational exposure to erythromycin**-a population-based register study from Norway. Br J Clin Pharmacol. 2012 Mar 30.

Rosenfeld RM, Brown L, Cannon CR, et al. American Academy of Otolaryngology--Head and Neck Surgery Foundation. Clinical practice guideline: **acute otitis externa**. Otolaryngol Head Neck Surg. 2006 Apr;134(4 Suppl):S4-23. http://www.entnet.org/Practice/upload/AOE-cpg.pdf

Rothberg Michael B.; Pekow Penelope S.; Lahti Maureen; et al. Antibiotic Therapy and Treatment Failure in Patients Hospitalized for Acute Exacerbations of **Chronic Obstructive Pulmonary Disease**. JAMA. 2010;303(20):2035-2042.

Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease **exacerbations**. A meta-analysis. JAMA 1995;273(12):957-60.

TOP

Sauerbrei, Andreas. **Preventing congenital varicella syndrome with immunization**. CMAJ 2011 0: cmaj.110055.
Schmitz GR, Bruner D, Pitotti R, et al. Randomized controlled trial of **trimethoprim-sulfamethoxazole for uncomplicated skin abscesses** in patients at risk for community-associated methicillin-resistant Staphylococcus aureus infection. Ann Emerg Med. 2010 Sep;56(3):283-7.
Schuetz P; Christ-Crain M; Thomann R; et al. Effect of **Procalcitonin-Based** Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: ProHOSP RCT. JAMA. 2009;302(10):1059-1066.
Schuetz P, Chiappa V, Briel M, et al. **Procalcitonin algorithms** for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011 Aug 8;171(15):1322-31.
Seemungal TA, Wilkinson TM, Hurst JR, et al. **Long-term erythromycin** therapy is associated with decreased chronic obstructive pulmonary disease **exacerbations**. Am J Respir Crit Care Med. 2008 Dec 1;178(11):1139-47.
Seltz LB, Smith J, Durairaj VD, Enzenauer R, Todd J. Microbiology and antibiotic management of **orbital cellulitis**. Pediatrics. 2011 Mar;127(3):e566-72.
Shannon-Lowe J, Matheson N J, Cooke F J, Aliyu S H. Prevention and medical management of **Clostridium difficile** infection. BMJ 2010;340:c1296, doi: 10.1136/bmj.c1296
Shapiro DJ, Gonzales R, Cabana MD, Hersh AL. National Trends in Visit Rates and Antibiotic Prescribing for Children With **Acute Sinusitis**. Pediatrics. 2010 Dec 27.
Shepherd JP, Frampton GK, Harris P. Interventions for encouraging **sexual behaviours intended to prevent cervical cancer**. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD001035. DOI: 10.1002/14651858.CD001035.pub2.
Shorr AF, Sun X, Johannes RS, et al. Validation of a Novel **Risk Score** for Severity of Illness in **Acute Exacerbations of COPD**. (**BAP-65**) Chest. 2011 Nov;140(5):1177-83.
SIGN-Scottish Intercollegiate Guidelines Network. Diagnosis and management of **childhood otitis media** in primary care. (Guideline 66.) 2003. www.sign.ac.uk/guidelines/fulltext/66/index.html .
Skalet AH, Cevallos V, Ayele B, Gebre T, Zhou Z, et al. 2010 Antibiotic Selection Pressure and **Macrolide Resistance (azithromycin)** in Nasopharyngeal Streptococcus pneumoniae: A Cluster-Randomized Clinical Trial. PLoS Med 7(12): e1000377. doi:10.1371/journal.pmed.1000377
Smith SR, Montgomery LG, Williams JW Jr. Treatment of **mild to moderate sinusitis**. Arch Intern Med. 2012 Mar 26;172(6):510-3. Antibiotics should not be prescribed for mild to moderate sinusitis within the first week of the illness. So-Hee Kang, Angela Chua-Gocheco, Pina Bozzo, et al. Safety of antiviral **medication for the treatment of herpes during pregnancy** Can Fam Physician April 2011 57: 427-428.
Soper DE. **Pelvic inflammatory disease**. Obstet Gynecol. 2010 Aug;116(2 Pt1):419-28.
Stevens R, Moll H, Lakhanpaul M, et al. **Diagnostic value of laboratory tests** in identifying serious infections in febrile children: systematic review. BMJ 2011;342:d3082.
Su JR, Beltrami JF, Zaidi AA, Weinstock HS. **Primary and secondary syphilis among black and Hispanic men who have sex with men**: case report data from 27 States. Ann Intern Med. 2011 Aug 2;155(3):145-51.
Tan T, Little P, Stokes T; Guideline Development Group. **Antibiotic prescribing** for **self limiting respiratory tract infections** in primary care: summary of NICE guidance. BMJ. 2008 Jul 23;337:a437. doi: 10.1136/bmj.a437.
Teltsch Dana Y.; Hanley James; Loo Vivian; et al. Infection Acquisition Following Intensive Care Unit **Room Privatization**. Arch Intern Med. 2011;171(1):32-38.
Thompson PL, Gilbert RE, Long PF, et al. Effect of antibiotics for **otitis media on mastoiditis** in children: a retrospective cohort study using the United kingdom general practice research database. Pediatrics. 2009 Feb;123(2):424-30.
Thornhill Martin H, Dayer Mark J, Forde Jamie M, et al. Impact of the NICE guideline recommending **cessation of antibiotic prophylaxis for prevention of infective endocarditis**: before and after study. BMJ 2011;342:doi:10.1136/bmj.d2392 (Published 3 May 2011)
Tobian AA, Serwadda D, Quinn TC, et al. Male **circumcision** for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med. 2009;360(13):1298- 1309.
Todd DC, McIvor RA, Pugsley SO, Cox G. Approach to **chronic obstructive pulmonary disease** in primary care. Can Fam Physician 2008;54:7-11.
Tronstein Elizabeth, Johnston Christine, Huang Meei-Li, et al. **Genital Shedding of Herpes Simplex Virus (HSV)** Among Symptomatic and Asymptomatic Persons With HSV-2 Infection. *JAMA*. 2011;305(14):1441-1449.doi:10.1001/jama.2011.420.
van den Aardweg MT, Boonacker CW, Rovers MM, Hoes AW, Schilder AG. Effectiveness of **adenoidectomy** in children with recurrent upper respiratory tract infections: open randomised controlled trial. BMJ. 2011 Sep 6;343:d5154. Van den Bruel A, Thompson M, Haj-Hassan T,
van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for **group A streptococcal pharyngitis**. Cochrane Database Syst Rev. 2010 Oct 6;10:CD004406. Evidence is insufficient for clinically meaningful differences between antibiotics for GABHS tonsillopharyngitis. Limited evidence in adults suggests cephalosporins are more effective than penicillin for relapse, but the NNTB is high.
Walsh Edward E.; Greene Linda; Kirshner Ronald. Sustained Reduction in **Methicillin-Resistant Staphylococcus aureus** Wound Infections After Cardiothoracic Surgery. Arch Intern Med. 2010;0(2010):archinternmed.2010.326.
This MRSA intervention program, in which all patients receive intranasal mupirocin and patients colonized with MRSA receive vancomycin prophylaxis, has resulted in a near-complete and sustained elimination of MRSA wound infections after cardiac surgery.
Walsh TR, Weeks J, Livermore DM. Dissemination of **NDM-1** positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. www.thelancet.com/infection Online April 7, 2011 DOI:10.1016/S1473-3099(11)70059-7
Weiss K, Blais R, Fortin A, Lantin S, Gaudet M. Impact of a Multipronged **Education Strategy on Antibiotic Prescribing** in Quebec, Canada. Clin Infect Dis. 2011 Jul 25.
Wessels Michael R, **Streptococcal Pharyngitis**. N Engl J Med 2011; 364:648-655.
WHO-Global action plan to control the spread and impact of antimicrobial resistance in **Neisseria gonorrhoeae**. 2012 http://whqlibdoc.who.int/publications/2012/9789241503501_eng.pdf
Williams DJ, Cooper WO, Kaltenbach LA, et al. Comparative Effectiveness of Antibiotic Treatment Strategies for Pediatric **Skin and Soft-Tissue Infections**. Pediatrics. 2011 Aug 15.
Wilson Jennifer F. In the Clinic: **Acute Sinusitis**. *Ann Intern Med* September 7, 2010 153:ITC3-1. September 7, 2010
Worrall, Graham, Kettle, Angela, Graham, Wendy, et al. **Postdated versus usual delayed antibiotic prescriptions** in primary care: Reduction in antibiotic use for acute respiratory infections? Can Fam Physician 2010 56: 1032-1036.
Worrall Graham. **Acute sinusitis**. Canadian Fam Physician. 2011 May.
Wu HM, Harcourt BH, Hatcher CP, et al. Emergence of **ciprofloxacin-resistant Neisseria meningitidis** in North America. N Engl J Med. 2009 Feb 26;360(9):886-92.
Ya W, Reifer C, Miller LE. Efficacy of **vaginal probiotic** capsules for recurrent bacterial vaginosis: a double-blind, randomized, placebo-controlled study. Am J Obstet Gynecol. 2010 Aug;203(2):120.e1-120.
Young Ryan C.; Hodge David O.; Liesegang Thomas J.; et al. Incidence, Recurrence, and Outcomes of **Herpes Simplex Virus Eye Disease** in Olmsted County, Minnesota, 1976-2007: The Effect of Oral Antiviral Prophylaxis. Arch Ophthalmol. 2010;128(9):1178-1183.
Young J, De Sutter A, Merenstein D, et al. Antibiotics for adults with clinically diagnosed **acute rhinosinusitis**: a meta-analysis of individual patient data. Lancet. 2008 Mar 15;371(9616):908-14. Common clinical signs and symptoms cannot identify patients with rhinosinusitis for whom treatment is clearly justified. Antibiotics are not justified even if a patient reports symptoms for longer than 7-10 days.
Zhang Yuting; Lee Bruce Y.; Donohue Julie M.. **Ambulatory** Antibiotic Use and Prescription Drug Coverage in Older Adults. Arch Intern Med. 2010;170(15):1308-1314.
Zoorob R, Sidani M, Murray J. **Croup**: an overview. Am Fam Physician. 2011 May 1;83(9):1067-73.

NNTs:
www.thennt.com: Antibiotics for Acute Otitis Media: http://www.thennt.com/antibiotics-for-otitis-media

References

[1] Bugs and Drugs 2006; Capital Health Region, Edmonton, AB. Accessed Jan 2010 at: http://www.bugsanddrugs.ca/ .
[2] Anti-infective Review Panel. Anti-infective Guidelines for Community-acquired Infections. Canadian - New-2012. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/
[3] Pharmacist's Letter. September 2009, volume 22, number 220915; Update: Pharmacist's Letter April 2011, Volume 27, number 270423: Recurrent Bacterial vaginosis: Consider longer treatment duration 500mg po BID x 10-14 days or topical metronidazole gel x 10 days , then suppressive therapy with gel twice weekly x 4-6 months. "Clindamycin cream found to be as effective as metronidazole regimens; but is oil-based and may cause failure of latex condoms or diaphragms." Clindamycin cream contains mineral oil.
[4] Sanford's Guide to Antimicrobial Therapy 2011.
[5] Thirion JG (Editor). Snippets for Snappy Antimicrobial Therapy. A concise Canadian Guide 2007. Publications PRISM inc. Dorval QC.
[6] Medical Letter: Handbook of Antimicrobial Therapy, 18th Ed. 2008. (Medical Letter. Treatment Guidelines. Drugs for Bacterial Infections. June 2010).
Medical Letter-Treatment Guidelines. Drugs for Sexually Transmitted Diseases. July 2010.
[7] van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD006216.
[8] Lowy, NEJM 2010. Treatment with monoclonal antibodies against Clostridium difficile toxins.
Hsu J, Abad C, Dinh M, Safdar N. Prevention of Endemic Healthcare-Associated Clostridium difficile Infection: Reviewing the Evidence. Am J Gastroenterol. 2010 Jul 6.
Hessen Margaret Trexler. In the Clinic: Clostridium difficile Infection. *Ann Intern Med* October 5, 2010 153:ITC4-1; doi:10.1059/0003-4819-153-7-201010050-01004.
Bernaola Aponte G, Bada Mancilla CA, Carreazo Pariasca NY, Rojas Galarza RA. Probiotics for treating persistent diarrhoea in children. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD007401. DOI: 10.1002/14651858.CD007401.pub2. There is limited evidence suggesting probiotics may be effective in treating persistent diarrhoea in children.
Allen SJ, Martinez EG, Gregorio GV, Dans LF. **Probiotics for treating acute infectious diarrhoea**. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub3. Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.
Bauer MP, Notermans DW, Van Benthem BHB. **Clostridium difficile infection in Europe**: a hospital-based survey. The Lancet, Early Online Publication, 16 November 2010. doi:10.1016/S0140-6736(10)61266-4.
Louie TJ et al. **Fidaxomicin** versus vancomycin for Clostridium difficile infection. N Engl J Med 2011 Feb 3; 364:422.
Perras C, Tsakonas E, Ndegwa S, et al. Vancomycin or metronidazole for treatment of Clostridium difficile infection: clinical and economic analyses. Canadian Agency for Drugs and Technologies In Health (CADTH). 2011 Jan: 1-144 http://www.cadth.ca/media/pdf/H0499_Cdifficile_tr_e.pdf
Settle Chris, Kerr Kevin G. Rational Testing: Diarrhoea after broad spectrum antimicrobials. BMJ 2011;342:doi:10.1136/bmj.d3798 (27 June 2011)
Mullane KM, Miller MA, Weiss K, et al. Efficacy of **fidaxomicin versus vancomycin** as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. Clin Infect Dis. 2011 Sep;53(5):440-7.
Loo VG et al. Host and pathogen factors for Clostridium difficile infection and colonization. N Engl J Med 2011 Nov 3; 365:1693.
Kamboj M et al. **Relapse** versus reinfection: Surveillance of **Clostridium difficile infection**. Clin Infect Dis 2011 Nov 15; 53:1003.

TOP

Forster AJ, Taljaard M, Oake N, et al. The effect of **hospital acquired** infection with **Clostridium dificile** on length of stay in hospital. CMAJ 2012;184:37-42.
Kassam Z, Hundal R, Marshall JK, Lee CH. **Fecal Transplant** via Retention Enema for Refractory or Recurrent Clostridium difficile Infection. Arch Intern Med. 2012 Jan 23;172(2):191-3.
Cornely OA, Crook DW, Esposito R, et al, the OPT-80-004 Clinical Study Group. **Fidaxomicin versus vancomycin** for infection with Clostridium di cile infection in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised, controlled trial. Lancet Infect Dis 2012.
Khanna S, Pardi DS, Aronson SL et al. The Epidemiology of **Community-Acquired Clostridium difficile** Infection: A Population-Based Study. Am J Gastroenterol. 2012 Jan;107(1):89-95.
Morrison RH, Hall NS, Said M, et al. **Risk factors** associated with complications and mortality in patients with **Clostridium difficile** infection. Clin Infect Dis. 2011 Dec;53(12):1173-8.
Mattila E, Uusitalo-Seppälä R, Wuorela M et al. **Fecal Transplantation**, Through Colonoscopy, Is Effective Therapy for Recurrent Clostridium difficile Infection. Gastroenterology. 2012 Mar;142(3):490-6.

[9] Nishimura RA, Carabello BA, Faxon DP, et al. ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Aug 19;52(8):676-85.
Baddour Larry M., Epstein Andrew E., Erickson Christopher C., et al. on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. Update on Cardiovascular Implantable Electronic Device Infections and Their Management: A Scientific Statement From the American Heart Association (AHA). Circulation 121: 458-477; published online before print as doi:10.1161/CIRCULATIONAHA.109.192665. http://circ.ahajournals.org/cgi/reprint/121/3/458
Baddour, Larry M., Epstein, Andrew E., Erickson, Christopher C., et al. on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, , Council on Cardiovascular Surgery and Anesthesia, , Council on Cardiovascular Nursing, , Council on Clinical Cardiology, , the Interdisciplinary Council on Quality of Care and Outcomes Research, A Summary of the Update on Cardiovascular Implantable Electronic Device Infections and Their Management: A Scientific Statement From the American Heart Association (AHA). J Am Dent Assoc 2011 142: 159-165. http://jada.ada.org/cgi/reprint/142/2/159
Thornhill Martin H, Dayer Mark J, Forde Jamie M, et al. Impact of the NICE guideline recommending **cessation of antibiotic prophylaxis for prevention of infective endocarditis**: before and after study. BMJ 2011;342:doi:10.1136/bmj.d2392 (Published 3 May 2011)

[10] McIsaac WJ, Kellner JD, Aufricht P, et al. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA. 2004 Apr 7;291(13):1587-95. Erratum in: JAMA. 2005 Dec 7;294(21):2700.
van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. Cochrane Database Syst Rev. 2010 Oct 6;10:CD004406. Evidence is insufficient for clinically meaningful differences between antibiotics for GABHS tonsillopharyngitis. Limited evidence in adults suggests cephalosporins are more effective than penicillin for relapse, but the NNTB is high.
Wessels Michael R, **Streptococcal Pharyngitis**. N Engl J Med 2011; 364:648-655.
Fine AM, Nizet V, Mandl KD. Improved diagnostic accuracy of group a streptococcal pharyngitis with use of real-time biosurveillance. Ann Intern Med. 2011 Sep 20;155(6):345-52.
Shaikh N, Swaminathan N, Hooper EG. Accuracy and Precision of the Signs and Symptoms of Streptococcal Pharyngitis in Children: A Systematic Review. J Pediatr. 2011 Oct 31.
Fine AM, Nizet V, Mandl KD. Large-Scale Validation of the Centor and McIsaac Scores to Predict Group A Streptococcal Pharyngitis. Arch Intern Med. 2012 May 7.

[11] Forgie S, Zhanel G, RobinsonJ; Canadian Paediatric Society (CPS). Management of acute otitis media. Paediatr Child Health 2009;14(7):457-60. http://www.cps.ca/ENGLISH/statements/ID/ID09-01.htm
Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD001095. DOI: 10.1002/14651858.CD001095.pub2. Clinicians need to evaluate whether the minimal short-term benefit from longer treatment of antibiotics is worth exposing children to a longer course of antibiotics.
Courter JD, Baker WL, Nowak KS, Smogowicz LA, Desjardins LL, Coleman CI, Girotto JE. Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. Ann Pharmacother. 2010 Mar;44(3):471-8. Epub 2010 Feb 11.
Coker Tumaini R.; Chan Linda S.; Newberry Sydne J.; et al. Diagnosis, Microbial Epidemiology, and Antibiotic Treatment of Acute Otitis Media in Children: A Systematic Review. JAMA. 2010;304(19):2161-2169.
Shekelle PG, Takata G, Newberry SJ, et al. Management of acute otitis media: update. Evid Rep Technol Assess. 2010 Nov: 1-426.
Hoberman Alejandro, Paradise Jack L., Rockette Howard E., et al. Treatment of Acute Otitis Media in Children under 2 Years of Age. N Engl J Med 2011; 364:105-115.
Tähtinen Paula A., Laine Miia K., Huovinen Pentti, et al. A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media. N Engl J Med 2011; 364:116-126.
Simpson SA, Lewis R, van der Voort J, et al. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. Cochrane Database Syst Rev. 2011 May 11;5:CD001935.
Azarpazhooh A, Limeback H, Lawrence HP, et al. Xylitol for preventing acute otitis media in children up to 12 years of age. Cochrane Database of Systematic Reviews 2011, Issue 11. Art. No.: CD007095. DOI: 10.1002/14651858.CD007095.pub2. There is fair evidence that the prophylactic administration of xylitol among healthy children attending day care centres reduces the occurrence of AOM by 25%.

[12] Korbila IP, Manta KG, Siempos II, et al. Penicillins vs trimethoprim-based regimens for acute bacterial exacerbations of chronic bronchitis: meta-analysis of randomized controlled trials. Can Fam Physician. 2009 Jan;55(1):60-7.
Nouira S et al. Standard versus newer antibacterial agents in the treatment of severe acute exacerbation of chronic obstructive pulmonary disease: A randomized trial of trimethoprim-sulfamethoxazole versus ciprofloxacin. Clin Infect Dis 2010 Jul 15; 51:143
Albert RH. Diagnosis and treatment of acute bronchitis. Am Fam Physician. 2010 Dec 1;82(11):1345-50.

[13] Canadian Sexually Transmitted Infections -STI guidelines 2008 http://www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php
Medical Letter-Treatment Guidelines. Drugs for Sexually Transmitted Diseases. July 2010.
Hook EW 3rd, Behets F, Van Damme K, Ravelomanana N, Leone P, Sena AC, Martin D, Langley C, McNeil L, Wolff M. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis. 2010 Jun 1;201(11):1729-35.
Soper DE. Pelvic inflammatory disease. Obstet Gynecol. 2010 Aug;116(2 Pt 1):419-28.
CDC: "Trends in Sexually Transmitted Diseases in the United States: 2009 National Data for Gonorrhea, Chlamydia, and Syphilis." CDC Media Fact Sheet, November 2010.
Wiehe, Sarah E., Rosenman, Marc B., Wang, Jane, et al. Chlamydia Screening Among Young Women: Individual- and Provider-Level Differences in Testing. Pediatrics 2011 127: e336-e344.
Hawkes S, Matin N, Broutet N, Low N. Eff ectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. Lancet Infect Dis 2011; published online June 16.
Ohnishi M, Golparian D, Shimuta K, Saika T, Hoshina S, Iwasaku K, et al. Is Neisseria gonorrhoeae initiating a future era of untreatable gonorrhea? Detailed characterization of the first strain with high-level resistance to ceftriaxone. Antimicrob Agents Chemother 2011;55(7):3538-45.
Linden JA. Clinical practice. Care of the adult patient after sexual assault. N Engl J Med. 2011 Sep 1;365(9):834-41.
Macdonald NE, Stanbrook MB, Flegel K, Hébert PC, Rosenfield D. Gonorrhea: what goes around comes around. CMAJ. 2011 Sep 19.
Centers for Disease Control and Prevention (CDC). Chlamydial infections. In: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010 Dec 17;59(RR-12):44-9.
Centers for Disease Control and Prevention (CDC). Diseases characterized by urethritis and cervicitis. In: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010 Dec 17;59(RR-12):40-4.
Centers for Disease Control and Prevention (CDC). Diseases characterized by vaginal discharge. In: Sexually transmitted diseases treatment guidelines, 2010 [Erratum appears in MMWR Recomm Rep. 2011 Jan 14;60(1):18]. MMWR Recomm Rep 2010 Dec 17;59(RR-12):56-63.
Centers for Disease Control and Prevention (CDC). Genital warts. In: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010 Dec 17;59(RR-12):70-4.
Centers for Disease Control and Prevention (CDC). Gonococcal infections. In: Sexually transmitted diseases treatment guidelines, 2010 [Erratum appears in MMWR Recomm Rep. 2011 Jan 14;60(1):18]. MMWR Recomm Rep 2010 Dec 17;59(RR-12):49-55.
Centers for Disease Control and Prevention (CDC). Human papillomavirus (HPV) infection. In: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010 Dec 17;59(RR-12):69-70.
Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections. Gonococcal infections. Updated January 2010. www.phac-aspc.gc.ca/std-mts/sti-its/pdf/506gonococcal-eng.pdf
Public Health Agency of Canada. Important notice – public health information update on the treatment for gonococcal infection. Public Health Agency of Canada issued important notice on gonococcal infection. December 21, 2011. www.phac-aspc.gc.ca/std-mts/sti-its/alert/2011/alert-gono-eng.php (accessed December 21, 2011).
Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. N Engl J Med. 2012 Feb 9;366(6):485-7.
García PJ, Holmes KK, Cárcamo CP, et al, Peru PREVEN Study Team. Prevention of sexually transmitted infections in urban communities (Peru PREVEN): a multicomponent community-randomised trial. Lancet 2012;
Van den Broek IVF, van Bergen JEAM, et al. Effectiveness of yearly, register based screening for chlamydia in the Netherlands: controlled trial with randomised stepped wedge implementation. BMJ 2012;345:e4316.

[14] Fang L, Oliver A, Jayaraman G, Wong T, et al. Trends in age disparities between younger and middle-age adults among reported rates of Chlamydia, gonorrhea, and infectious syphilis infections in Canada: Findings from 1997 to 2007. *Sexually Transmitted Infections*. 2010 Jan;37(1):18-25.
{Canadian data: STIs increasing in middle age group (age 40-59yrs); Chlamydia ↑ 66%; gonorrhea ↑ 210%; syphilis ↑ 11x.}

[15] Stone, S. RxFiles Antifungal Treatment Chart. Accessed 25 January, 2010 at: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-antifungal.pdf

[16] Ota KV, Jamieson F, Fisman DN, et al. Prevalence of and risk factors for quinolone-resistant Neisseria gonorrhoeae infection in Ontario. CMAJ. 2009 Feb 3;180(3):287-90.

TOP

[62] Goodless DR, Ramos-caro Fa, Flowers FP. Ketoconazole in the treatment of pityriasis versicolor: International review of clinical trial. DICP1991;25:395
[63] Mohr J, Johnson M, Cooper T, et al. Current Options in Antifungal Therapy. Pharmacotherapy 2008;28(5):614–645
[64] Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408–15
[65] Smith J,Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother. 2006 Apr;50(4):1570-2
[66] Balian JD, Sukhova N, Harris JW, et al. The hydroxylation of omeprazole correlates with S-mephenytoin metabolism: a population study. Clin Pharmacol Ther 1995; 57:662–9.
[67] Spriafil (posaconazole). Pharmacist's Letter/Prescriber's Letter 2007;23(7):230714.
[68] Zonios DI, Bennett JE. Update on azole antifungals. Semin Respir Crit Care Med. 2008 Apr;29(2):198-210
[69] Krishna G, Moton A, Ma L, Savant I, et al. of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: a phase I, randomized, open-label, crossover study in healthy volunteers. Clin Ther. 2009 Feb;31(2):286-98
[70] Pappas PG, Kauffman CA, Andes D, et al: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America (IDSA). Clin Infect Dis 2009; 48(5):503-535
[71] Goodwin SD, Cleary JD, Walawander CA, Taylor JW, Grasela TH Jr. Pretreatment regimens for adverse events related to infusion of amphotericin B. Clin Infect Dis 1995;20:755–61
[72] Burks LC, Aisner J, Fortner CL, Wiernik PH. Meperidine for the treatment of shaking chills and fever. Arch Intern Med 1980;140:483–4

Other useful reading :

Abdel-Rahman SM, Farrand N, Schuenemann E, et al. The Prevalence of Infections With Trichophyton tonsurans in Schoolchildren: the CAPITIS Study. Pediatrics. 2010 Apr 19.
Abdullah, Lina, Abbas, Ossama. Common nail changes and disorders in older people: Diagnosis and management. Can Fam Physician 2011 57: 173-181.
Andrews E, Damle BD, Fang A, Foster G, Crownover P, LaBadie R, Glue P. Pharmacokinetics and tolerability of voriconazole and a combination oral contraceptive co-administered in healthy female subjects. Br J Clin Pharmacol. 2008 Apr;65(4):531-9. Epub 2008 Feb 21
Anti-infective Review Panel. Anti-infective Guidelines for Community-acquired Infections. Canadian - New-2012. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/
Blot SI, Taccone FS, Van den Abeele AM, et al; the AspICU Study Investigators. A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients. Am J Respir Crit Care Med. 2012 Apr 19.
Bow EJ, Evans G, Fuller J, et al. Canadian clinical practice guidelines for invasive candidiasis in adults. Can J Infect Dis Med Microbiol 2010;21(4):e122-e150.
Canadian Sexually Transmitted Infections -STI guidelines 2008 http://www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php
De Berker D. Fungal nail disease. N Engl J Med. 2009;360:2108-16
Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy. 2010 Aug;30(8):842-54.
Donders G, Bellen G, Byttebier G, et al. Individualized decreasing-dose maintenance fluconazole regimen for recurrent vulvovaginal candidiasis (ReCiDiF trial). Am J Obstet Gynecol. 2008 Dec;199(6):613.e1-9. Epub 2008 Oct 30.
Elewski BE, Cáceres HW, DeLeon L, et al. Terbinafine hydrochloride oral granules versus oral griseofulvin suspension in children with tinea capitis: results of two randomized, investigator-blinded, multicenter, international, controlled trials. J Am Acad Dermatol. 2008 Jul;59(1):41-54
Ferwerda B, Ferwerda G, Plantinga TS, et al.. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2009 Oct 29;361(18):1760-7.
Garcia-Doval I, Cabo F, Monteagudo B, et al. Clinical diagnosis of toenail onychomycosis is possible in some patients: cross-sectional diagnostic study and development of a diagnostic rule. Br J Dermatol. 2010 Oct;163(4):743-51. doi: 10.1111/j.1365-2133.2010.09930.x.
Glocker EO, Hennigs A, Nabavi M, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med. 2009 Oct 29;361(18):1727-35.
FDA Mar/12 has received reports of fungal endophthalmitis (eye infections) in patients who were given Brilliant Blue G (BBG) during eye surgeries. Clinicians in several states reported the adverse events. FDA, along with CDC and local and state public health agencies, are actively investigating these adverse events.
Giglio M, Caggiano G, Dalfino L, et al. Oral nystatin prophylaxis in surgical/trauma ICU patients: a randomised clinical trial. Crit Care. 2012 Apr 10;16(2):R57.
Gupta AK, Bluhm R, Summerbell R. Pityriasis versicolor. J Eur Acad Dermatol Venereol. 2002 Jan;16(1):19-33
Hainer BL. Dermatophyte infections. Am Fam Physician. 2003;67:101-8
Hussaini T, Rüping MJ, Farowski F, Vehreschild JJ, Cornely OA. Therapeutic drug monitoring of voriconazole and posaconazole. Pharmacotherapy. 2011 Feb;31(2):214-25.
Jansman FG, Reyners AK, van Roon EN, et al; Scientific Institute for Dutch Pharmacists (WINAp), the Dutch Society for Medical Oncology (NVMO); Dutch Society of Clinical Pharmacology and Biopharmacy (NVKF&B). Consensus-Based Evaluation of Clinical Significance and Management of Anticancer Drug Interactions. Clin Ther. 2011 Apr 1.
Kaufman DA, Cuff AL, Wamstad JB, et al. Fluconazole prophylaxis in extremely low birth weight infants and neurodevelopmental outcomes and quality of life at 8 to 10 years of age. J Pediatr. 2011 May;158(5):759-765.e1.
Laties Alan M., Fraunfelder Frederick T., Tomaszewski Konrad, et al, Long-term visual safety of voriconazole in adult patients with paracoccidioidomycosis, Clinical Therapeutics, Volume 32, Issue 13, December 2010, Pages 2207-2217, ISSN 0149-2918, DOI: 10.1016/S0149-2918(10)80024-4.
Laudenbach JM, Epstein JB. Treatment strategies for oropharyngeal candidiasis. Expert Opin. Pharmacother. 2009; 10(9):1413-1421
León C, Ruiz-Santana S, Saavedra P, et al. EPCAN Study Group. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med. 2006 Mar;34(3):730-7.
Limper Andrew H., Knox KS., Sarosi GA., et al. and on behalf of the American Thoracic Society (ATS) Fungal Working Group. An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients. Am. J. Respir. Crit. Care Med. 183: 96-128. January 3, 2011
Manzoni P et al. on behalf of the Italian Task Force for the Study and Prevention of Neonatal Fungal Infections–the Italian Society of Neonatology. Bovine Lactoferrin Prevents Invasive Fungal Infections in Very Low Birth Weight Infants: A Randomized Controlled Trial. Pediatrics. 2012 Jan;129(1):116-123.
Miceli Marisa H, Diaz Jose A, Lee Samuel A. Emerging opportunistic yeast infections, The Lancet Infectious Diseases, Volume 11, Issue 2, February 2011, Pages 142-151, ISSN 1473-3099, DOI: 10.1016/S1473-3099(10)70218-8.
Nurbhai M, Grimshaw J, Watson M, Bond C, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). Cochrane Database Syst Rev. 2007 Oct 17;(4):CD002845. No statistically significant differences were observed in clinical cure rates of anti-fungals administered by the oral and intra-vaginal routes for the treatment of uncomplicated vaginal candidiasis.
Neoh CF, Leung L, Vajpayee RB, et al. Treatment of alternaria keratitis with intrastromal and topical caspofungin in combination with intrastromal, topical, and oral voriconazole. Ann Pharmacother. 2011 May;45(5):e24.
Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother 2011;55:2601-5.
Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010 Feb 1;50(3):291-322.
Pharmacist's Letter. Treatment of Uncomplicated Vaginal Yeast Infections. May 2010.
Pienaar ED, Young T, Holmes H. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. Cochrane Database Syst Rev. 2010 Nov 10;11:CD003940.
Safdar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. Medicine (Baltimore) 89 (4): 236-244, 2010.
Samaranayake LP, Keung Leung W & Jin L. Oral mucosal fungal infections. Periodontology 2000 2009; 49:39–59
Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. N Engl J Med. 2010 Feb 11;362(6):504-12. RA, Gallagher JC. Drug Fever. Pharmacotherapy. 2010 Jan;30(1):57-69.
Subissi A, Monti D, Togni G, Mailland F. Ciclopirox: recent nonclinical and clinical data relevant to its use as a topical antimycotic agent. Drugs 70 (16): 2133-52, 2010.
Topical treatment of superficial fungal infections. Pharmacist's letter/Prescriber's letter. 2009; (8):250806
Wang JL, Chang CH, Young-Xu Y, Chan KA. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. Antimicrob Agents Chemother. 2010 Jun;54(6):2409-19. Epub 2010 Mar 22.
Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal agents for the treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. BJOG. 2002 Jan;109(1):85-95.
Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. Clin Dermatol 28 (2): 151-9, 2010.
Wermers RA, Cooper K, Razonable RR, Deziel PJ, Whitford GM, Kremers WK, Moyer TP. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. Clin Infect Dis 52 (5): 604-11, 2011.
Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. Clin Infect Dis 31 (5): 1155-63, 2000.
Worthington HV, Clarkson JE, Khalid T, et al. Interventions for treating oral candidiasis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD001972. There is insufficient evidence to claim or refute a benefit for any antifungal agent in treating candidiasis.
Ziakas PD, Kourbeti IS, Voulgarelis M, et al. Effectiveness of systemic antifungal prophylaxis in patients with neutropenia after chemotherapy: a meta-analysis of randomized controlled trials. Clin Ther. 2010 Dec;32(14):2316-36.

TOP

ANTI-INFECTIVES - ORAL Additional references:

1. Guay D. Short-course antimicrobial therapy of respiratory tract infections. Drugs. 2003;63(20):2169-84.
2. Micromedix 2011
3. **Sanford** Guide to Antimicrobial Therapy 2011; Orange PAACT: **2012 Anti-infective Guidelines for Community –acquired infections**.
   Bugs and Drugs 2006; Capital Health Region, Edmonton, AB. Accessed Jan 2010 at: http://www.bugsanddrugs.ca/ .
   Medical Letter. Treatment Guidelines. **Drugs for Bacterial Infections**. June 2010.
4. CPS 2011
5. Telithromycin (Ketek) for respiratory infections. Med Lett Drugs Ther. 2004 Aug 16;46(1189):66-8.
6. QT Interval Drug Lists www.torsades.org and Drug Interaction Information http://medicine.iupui.edu/flockhart
7. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med 2004; 164:2206-16.
8. Le Saux, Nicole et al. A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age CMAJ • February 1, 2005; 172 (3). doi:10.1503/cmaj.1040771.
9. Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005 Feb 12;365(9459):579-87.
10. Stephens DS. et al; Incidence of marolide resistance in Streptococcus pneumoniae after introduction of the pneumococcal conjugate vaccine: population-based assessment. Lancet. 2005 Mar 5;365: 855-63.
11. Tozzi AE, Celentano LP, Ciofi degli Atti ML, Salmaso S. Diagnosis and management of pertussis. CMAJ. 2005 Feb 15;172(4):509-15. (Galanis E, King AS, Varughese P, Halperin SA; IMPACT investigators. Changing epidemiology and emerging risk groups for pertussis. CMAJ. 2006 Feb 14;174(4):451-2.)
12. Carratala J, Fernandez-Sabe N, Ortega L, et al. Outpatient care compared with hospitalization for community-acquired pneumonia. Ann Intern Med 2005; 142:165-72.
13. O'Connor CM, Dunne MW, Pfeffer MA, Muhlestein JB, Yao L, Gupta S, Benner RJ, Fisher MR, Cook TD; Investigators in the WIZARD Study. Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. JAMA. 2003 Sep 17;290(11):1459-66.
14. Grayston JT, et al. Azithromycin for the Secondary Prevention of Coronary Events. N Engl J Med 2005;352:1637-45.
15. Cannon Christopher P., et al. Antibiotic Treatment (gatifloxacin) of Chlamydia pneumoniae after Acute Coronary Syndrome. N Engl J Med 2005;352:1646-54.
16. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HM, Rowlands S, Stricker BH. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. Arch Intern Med. 2003 Aug 11-25;163(15):1801-7.
17. Cooper JG, Harboe K, Frost SK, Skadberg O. Ciprofloxacin interacts with thyroid replacement therapy. BMJ. 2005 Apr 30;330(7498):1002.
18. Mills GD, Oehley MR, Arrol B. Effectiveness of {beta} lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. BMJ 2005; 330:456-60. (InfoPOEMs: Strange, but true: Oral beta-lactam antibiotics -- amoxicillin, amoxicillin/clavulanate (Augmentin), or a cephalosporin -- are as effective in the treatment of community-acquired pneumonia as antibiotics active against atypical pathogens, even in patients infected with Mycoplasma pneumoniae or Chlamydia pneumoniae. These old standbys can be used instead of the more expensive drugs for most patients. Legionella infection still requires treatment with an antibiotic effective against atypical pathogens, but in these studies only 1.1% of the patients with nonsevere pneumonia had Legionella. These results are backed up by similar findings from clinical practice (Hedlund J, et al. Scand J Infect Dis 2002; 34:887-92). (LOE = 1a))
19. Golden MR, Whittington WL, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. N Engl J Med 2005; 352:676-85. (InfoPOEMs: Giving the pt a prescription for their partner(s) or having a staff member contact the pt's partners directly to offer treatment without an examination slightly reduces the risk of recurrent infection in the original pt. It is most helpful for patients with gonorrhea. (LOE = 1b-))
20. Olympia RP, et al. Effectiveness of oral dexamethasone in the treatment of moderate to severe pharyngitis in children. Arch Pediatr Adolesc Med 2005; 159:278-82. (InfoPOEMs: Children with moderate to severe throat pain, given a single oral dose of dexamethasone, experience faster resolution of pain and significant relief in the first 24 hours than those given placebo. After 24 hours, however, there was no significant difference in pain between groups. Interestingly, dexamethasone is more effective in children who test negative for strep. In fact, those who have a positive rapid strep assay are unlikely to have any benefit. This study is too small to have detected any important but uncommon complications of treatment. (LOE = 2b))
21. Shams WE, Evans ME. Guide to selection of fluoroquinolones in patients with lower respiratory tract infections. Drugs. 2005;65(7):949-91.
22. Richard Andraws, MD; Jeffrey S. Berger, MD; David L. Brown, MD. Effects of Antibiotic Therapy on Outcomes of Patients With Coronary Artery Disease: A Meta-analysis of Randomized Controlled Trials. JAMA. 2005;293:2641-2647. (Evidence available to date does not demonstrate an overall benefit of antibiotic therapy in reducing mortality or cardiovascular events in patients with CAD.)
23. Rovers MM, Black N, Browning GG, Maw R, Zielhuis GA, Haggard MP. Grommets in otitis media with effusion: an individual patient data meta-analysis. Arch Dis Child 2005; 90:480-85. (InfoPOEMs: Compared with watchful waiting, inserting pressure-equalizing tubes improves hearing in children with otitis media with effusion over the short term. Outcomes within 18 months, however, are the same. The tubes has no effect on language development. Watchful waiting is a reasonable option in most of these children. (LOE = 1a))
24. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med. 2005 Jun 21;142(12 Pt 1):979-95. CONCLUSIONS: Antibiotic prophylaxis for neutropenic patients undergoing cytotoxic therapy reduces mortality. Mortality was substantially reduced when analysis was limited to fluoroquinolones. Antibiotic prophylaxis, preferably with a fluoroquinolone, should be considered for neutropenic patients.
25. Fuller JD, Low DE. A review of Streptococcus pneumoniae infection treatment failures associated with fluoroquinolone resistance. Clin Infect Dis. 2005 Jul 1;41(1):118-21. Epub 2005 May 26. There were 20 ciprofloxacin and levofloxacin treatment failures reported. Physicians should be aware, when treating pneumococcal respiratory tract infections in older patients with a fluoroquinolone, that clinical failures might occur, especially for patients with comorbid illnesses and a history of recent fluoroquinolone use.
26. Little P, Rumsby K, et al. Information leaflet & antibiotic prescribing strategies for acute lower respiratory tract infection: an RCT. JAMA. 2005 Jun 22;293(24):3029-35. CONCLUSION: No offer or a delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection is acceptable, associated with little difference in symptom resolution, and is likely to considerably reduce antibiotic use and beliefs in the effectiveness of antibiotics.
27. Doern GV, Richter SS, Miller A, et al. Antimicrobial resistance among Streptococcus pneumoniae in the United States: have we begun to turn the corner on resistance to certain antimicrobial classes? Clin Infect Dis. 2005 Jul 15;41(2):139-48. Epub 2005 Jun 7.
28. Sharland M, Kendall H, Yeates D, et al. Antibiotic prescribing in general practice and hospital admissions for peritonsillar abscess, mastoiditis, and rheumatic fever in

TOP

time trend analysis. BMJ. 2005 Aug 6;331(7512):328-9. A fall of 50% in the prescribing of antibiotics to children in English general practice has not been accompanied by an increase in hospital admissions for peritonsillar abscess or rheumatic fever. (InfoPOEMs: More judicious prescribing of antibiotics for childhood respiratory infections has not increased the number of episodes of peritonsillar abscess or rheumatic fever. The effect on mastoidectomy is unclear, but a clinically important increase appears unlikely. (LOE = 2c))

29. Hoberman A, Dagan R, Leibovitz E, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. Pediatr Infect Dis J. 2005 Jun;24(6):525-32. CONCLUSION: Amoxicillin/clavulanate was clinically & bacteriologically more effective than azithromycin among children with bacterial AOM, incl. cases caused by penicillin-resistant S. pneumoniae & beta-lactamase-positive H. influenzae.
30. Yates J. Traveler's diarrhea. Am Fam Physician. 2005 Jun 1;71(11):2095-100. (see also Treatment Guidelines from the Medical Letter: **Advice for Travelers** May 2006, Updated May 2012) or good Information at www.cdc.gov/travel (DuPont HL. Travellers' diarrhoea: contemporary approaches to therapy and prevention. Drugs. 2006;66(3):303-14.) (Pharmacist's Letter. May 2007. Update on Traveler's Diarrhea.) (Hill D, Ryan E. Management of travellers' diarrhoe. BMJ 2008;337: p863-867.)
31. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. Ann Intern Med 2005;142:805-12. (InfoPOEMs: Treatment with rifaximin instead of placebo decreases the likelihood of travelers' diarrhea in students traveling to Mexico from the United States and living with local families. It has not been compared with less expensive prophylaxis with bismuth or with acute treatment of diarrhea, and it hasn't been compared in situations where travelers' diarrhea is less likely (for example, traveling for shorter periods or staying in resorts instead of living in local communities). (LOE = 1b))
32. Gavranich J, Chang A. Antibiotics for community acquired lower respiratory tract infections (LRTI) secondary to Mycoplasma pneumoniae in children. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004875.
33. Ziganshina L, Vizel A, Squire S. Fluoroquinolones for treating tuberculosis. Cochrane Database Syst Rev. 2005 Jul 20;3:CD004795.
34. Weigelt J, Itani K, Stevens D, et al, for the Linezolid CSSTI Study Group. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2005; 49:2260-66. (InfoPOEMs:) Linezolid provides an alternative to vancomycin in the treatment of complicated skin and soft tissue infections, many of which are caused by methicillin-resistant Staph aureus (MRSA). The unblinded nature of this study, post hoc subgroup analyses, and failure to describe criteria for initiating oral versus intravenous therapy are serious limitations. Any trends toward an advantage for linezolid should be interpreted very cautiously. (LOE = 2b)
35. Margolis DJ, Bowe WP, Hoffstad O, Berlin JA. Antibiotic treatment of acne may be associated with upper respiratory tract infections. Arch Dermatol. 2005 Sep;141(9):1132-6.
36. Sabria M, Pedro-Botet ML, Gomez J, Roig J, et al. Fluoroquinolones vs Macrolides in the Treatment of Legionnaires Disease. Chest. 2005 Sep;128(3):1401-5.
37. Saha D, et al. Single-dose ciprofloxacin versus 12-dose erythromycin for childhood cholera: a randomised controlled trial. Lancet. 2005 Sep 24;366(9491):1085-93.
38. Riedner G, Rusizoka M, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med. 2005 Sep 22;353(12):1236-44. (InfoPOEMs: A 2-g oral dose of azithromycin is equivalent in effectiveness to intramuscular penicillin in the treatment of primary or latent syphilis. Clinicians should be aware that macrolide-resistant Treponema pallidum has already begun to emerge in North America and Ireland. (LOE = 1b))
39 Medical Letter Sept 26/05 Azithromycin Extended Release (ZMAX) for Sinusitis and Pneumonia p. 78.
40. Paradise JL, Campbell TF, Dollaghan CA, et al. Developmental outcomes after early or delayed insertion of tympanostomy tubes. N Engl J Med 2005; 353:576-86. (InfoPOEMs: Early insertion of tympanostomy tubes does not improve long-term clinical outcomes of importance (speech acquisition and hearing) in children with persistent otitis media with effusion. Delaying 6 months for bilateral effusion and 9 months for unilateral effusion before revisiting the decision to insert tubes is the preferred approach to management, since it results in fewer procedures with equivalent outcomes. (LOE = 1b))
41. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing **cephalosporin antibiotics for penicillin-allergic** patients. Pediatrics. 2005 Apr;115(4):1048-57. Pichichero ME. Cephalosporins can be prescribed safely for penicillin-allergic patients. J Fam Pract. 2006 Feb;55(2):106-12. (InfoPOEMs: The risk of cross-reactivity between penicillin and cephalosporins has been overestimated for second- and third-generation drugs. It is only a significant risk in first-generation cephalosporins that have a similar side chain to penicillin (cephalothin, cephalexin, cefadroxil, and cefazolin). With appropriate monitoring physicians could consider using second- and third-generation cephalosporins in these patients. (LOE = 2a))
42. Fogarty C, de Wet R, Mandell L, et al. Five-day telithromycin once daily is as effective as 10-day clarithromycin twice daily for the treatment of acute exacerbations of chronic bronchitis and is associated with reduced health-care resource utilization. Chest. 2005 Oct;128(4):1980-8.
43. **Sulfonamide Cross-Reactivity** Pharmacist Letter Nov 2005.
44. Cullen M, Steven N, Billingham L, et al.; Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotic in a Number of Tumours (SIGNIFICANT) Trial Group. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med. 2005 Sep 8;353(10):988-98. (InfoPOEMs: When given prophylactically to cancer patients at risk for neutropenia, levofloxacin modestly reduces the likelihood of fever, infection, and hospitalization (number needed to treat [NNT] = 16 - 20). However, there was no significant reduction in the likelihood of serious infection or death, and the benefit must be balanced against the cost and probable adverse effect on bacterial resistance. (LOE = 1b))
45. Arnold S, Straus S. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev. 2005 Oct 19;4:CD003539.
46. Pepin J, Saheb N, Coulombe MA, et al. Emergence of **fluoroquinolones** as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis. 2005 Nov 1;41(9):1254-60. Epub 2005 Sep 20. CONCLUSIONS: Administration of fluoroquinolones emerged as the most important risk factor for CDAD in Quebec during an epidemic caused by a hypervirulent strain of C. difficile. (see also Medical Letter: Treatment of C. difficile-associated disease. Nov 6,2006.)
47. Baddour LM, Wilson WR, Bayer AS, et al. **Infective endocarditis**: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the committee on rheumatic Fever, endocarditis, and kawasaki disease, council on cardiovascular disease in the young, and the councils on clinical cardiology, stroke, and cardiovascular surgery & anesthesia, american heart association--executive summary: endorsed by the infectious diseases society of america. Circulation. 2005 Jun 14;111(23):3167-84. http://circ.ahajournals.org/cgi/content/full/111/23/3167 (see updated reference 127)
48. Rimoin AW, Hamza HS, Vince A, et al. Evaluation of the WHO clinical decision rule for streptococcal pharyngitis. Arch Dis Child. 2005 Oct;90(10):1066-70. Epub 2005 Jun 7.
49. Drehobl MA, et al. **Single-dose azithromycin** microspheres vs clarithromycin extended release for treatment of mild-to-moderate CAP in adults. Chest. 2005 Oct;128(4):2230-7.
50. Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral **probiotics** prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr. 2005 Aug;147(2):192-6.
51. Fogarty C, de Wet R, Mandell L, et al. **Five-day telithromycin** once daily is as effective as 10-day clarithromycin twice daily for the treatment of acute exacerbations of chronic bronchitis and is associated with reduced health-care resource utilization. Chest. 2005 Oct;128(4):1980-8.
52. Kristo A, Uhari M, Luotonen J, et al. Cefuroxime axetil versus **placebo** for children with acute respiratory infection and imaging evidence of sinusitis: a randomized, controlled trial. Acta Paediatr. 2005 Sep;94(9):1208-13. CONCLUSION: A 10-d course of cefuroxime axetil offered no clinical benefit to children with an acute respiratory illness and imaging evidence of acute sinusitis.
53. Ward JI, Cherry JD, Chang SJ, et al.; APERT Study Group. Efficacy of an acellular pertussis vaccine among adolescents and adults. N Engl J Med. 2005 Oct 13;353(15):1555-63. (InfoPOEMs: An acellular pertussis vaccine reduces the risk of pertussis in adults and is well tolerated. (LOE = 1b))

TOP

54. Tiwari T, Murphy TV, Moran J; National Immunization Program, CDC. Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of **Pertussis**: 2005 CDC Guidelines. MMWR Recomm Rep. 2005 Dec 9;54(RR-14):1-16.
55. Jespersen CM, Als-Nielsen B, Damgaard M, et al. Randomised placebo controlled multicentre trial to assess short term **clarithromycin** for patients with stable coronary heart disease: **CLARICOR** trial. BMJ. 2005 Dec 8; [Epub ahead of print] (InfoPOEMs: The theory of a bacterial cause of heart disease is rapidly deflating. Using the antibiotic clarithromycin in patients with coronary heart disease (CHD) is not beneficial and may be harmful, with 1 additional death for every 50 patients who receive clarithromycin. Two other studies have also shown a slight increase in mortality with antibiotic therapy; taken together, these 3 studies show a 28% increase in mortality with clarithromycin (odds ratio = 1.28; 95% CI, 1.05 - 1.57). (LOE = 1b))
56. Schito GC, Felmingham D. Susceptibility of Streptococcus pneumoniae to penicillin, azithromycin and telithromycin (PROTEKT 1999-2003). Int J Antimicrob Agents. 2005 Dec;26(6):479-85. Epub 2005 Nov 9. Penicillin non-susceptibility rates were stable over the study period; overall, 21.8% of isolates were resistant. Azithromycin resistance increased from 31.0% in Year 1 to 36.3% in Year 4. Resistance rates for penicillin and azithromycin varied between countries and were highest in France, Spain, South Africa, USA and the Far East. Multidrug resistance in S. pneumoniae did not change significantly over the 4 years, with an overall rate of 38.6%. Telithromycin retained good activity against S. pneumoniae (0.1% of isolates resistant), including multidrug-resistant isolates.
57. Morganroth J, Dimarco JP, Anzueto A, Niederman MS, Choudhri S; CAPRIE Study Group. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. Chest. 2005 Nov;128(5):3398-406.
58. Health Canada Tequin hyper & hypoglycemic warning Dec/05 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/tequin_hpc-cps_e.pdf
Health Canada February, 2006 advises diabetic patients not to use the antibiotic Tequin http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_09_e.html
(Park-Wyllie LY, et al. Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults. N Engl J Med. 2006 Mar 1; [Epub ahead of print] Conclusions As compared with the use of other broad-spectrum oral antibiotics, including other fluoroquinolones, the use of gatifloxacin among outpatients is associated with an increased risk of in-hospital treatment for both hypoglycemia and hyperglycemia)
59. Shefet D, Robenshtok E, Paul M, Leibovici L. Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. Arch Intern Med. 2005 Sep 26;165(17):1992-2000.(InfoPOEMs: Treating community-acquired pneumonia with antibiotics effective against atypical organisms is no better and no worse than treating with a penicillin or cephalosporin alone. (LOE = 1a))
60. Fourcroy JL, Berner B, Chiang YK, Cramer M, Rowe L, Shore N. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. Antimicrob Agents Chemother. 2005 Oct;49(10):4137-43. (InfoPOEMs: A single dose of an extended-release version of ciprofloxacin (Cipro XR) is as effective as the immediate-release version taken twice daily for 3 days. The tiny reduction in the likelihood of gastrointestinal adverse effects (number needed to treat (NNT) = 60 - 80) is likely to be heavily promoted, and must be balanced against the higher cost of this formulation. As we are given more such options, it is important to remember the key elements in choosing a drug: its safety, tolerability, efficacy, price, and simplicity. Although extended-release ciprofloxacin is simpler, it is no more effective and will almost certainly cost more. (LOE = 1b))
61. Md SM, et al. Continuation of Antibiotics Is Associated With Failure of Metronidazole for Clostridium difficile-Associated Diarrhea. J Clin Gastroenterol. 2006 Jan;40(1):49-54.
62. FDA Jan/06 warns of **Ketek** increase **liver** toxicity case reports. http://www.fda.gov/cder/drug/advisory/telithromycin.htm (Clay KD, et al. Brief Communication: Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review. Ann Intern Med. 2006 Feb 15; [Epub ahead of print])
Health Canada Oct/06 http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/ketek_hpc-cps_e.html (see also Pharmacist's Letter: Ketek safety info. Dec/06)
63. Mitchell SJ, et al. **Azithromycin-resistant syphilis** infection: San Francisco, California, 2000-2004. Clin Infect Dis. 2006 Feb 1;42(3):337-45. Epub 2005 Dec 28.
64. Merenstein D, Diener-West M, Krist A, et al. An assessment of the shared-decision model in parents of children with acute otitis media. Pediatrics. 2005 Dec;116(6):1267-75. (InfoPOEMs: Presenting information about the pros and cons of antibiotic treatment for acute otitis media and letting parents decide whether and when to start treatment increases parents' satisfaction with their visit and could decrease antibiotic use. These results were found in wealthy, white, older parents and may not apply to other socioeconomic groups. (LOE = 2c))
65. Treatment of Community-Associated **MRSA**. Med Lett Drugs Ther. Feb 13, 2006.
66. Stevens DL, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406. Epub 2005 Oct 14.
67. Dupont HL. Travellers' Diarrhoea: Contemporary Approaches to Therapy and Prevention. Drugs. 2006;66(3):303-314.
68. Singh SM, Joyner CD, Alter DA. The importance of echocardiography in physicians' support of **endocarditis prophylaxis**. Arch Intern Med. 2006 Mar 13;166(5):549-53.
69. Poehling KA, et al. Invasive pneumococcal disease among infants before and after introduction of **pneumococcal conjugate vaccine**. JAMA. 2006 Apr 12;295(14):1668-74.
70. McFarland LV, et al. Meta-Analysis of **Probiotics** for the Prevention of Antibiotic Associated Diarrhea and the Treatment of Clostridium difficile Disease. Am J Gastroenterol. 2006 Apr;812-22. (InfoPOEMs: The probiotics Saccharomyces boulardii and Lactobacillus rhamnosus GG both prevent antibiotic-associated diarrhea (AAD), as does a combination of 2 or more probiotics. S. boulardii, given in addition to vancomycin or metronidazole, is also an effective treatment for Clostridium difficile disease (CDD). (LOE = 1a-))
71. Loo VG, et al. A predominantly clonal multi-institutional outbreak of **Clostridium difficile**-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005 Dec 8;353(23):2442-9. Epub 2005 Dec 1. Erratum in: N Engl J Med. 2006 May 18;354(20):2200.
72. Garbutt J, et al. Empiric first-line antibiotic treatment of acute otitis in the era of the heptavalent **pneumococcal conjugate vaccine**. Pediatrics. 2006 Jun;117(6):e1087-94.
73. Gordon RJ, Lowy FD. Bacterial infections in **drug users**. N Engl J Med. 2005 Nov 3;353(18):1945-54.
74. Samore MH, et al. **Clinical decision support** and appropriateness of antimicrobial prescribing: a randomized trial. JAMA. 2005 Nov 9;294(18):2305-14.
75. Slavin RG, et al. American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of **sinusitis**: a practice parameter update. J Allergy Clin Immunol. 2005 Dec;116(6 Suppl):S13-47. 75.
76. Linder JA, Bates DW, Lee GM, Finkelstein JA. Antibiotic treatment of children with **sore throat**. JAMA. 2005 Nov 9;294(18):2315-22.
77. Kyaw MH, et al.; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effect of introduction of the **pneumococcal conjugate vaccine** on drug-Resistant Streptococcus pneumoniae. N Engl J Med. 2006 Apr 6;354(14):1455-63.
78. Trautner BW, et al. Prospective evaluation of the risk of serious bacterial infection in children who present to the emergency department with **hyperpyrexia** (temperature of 106 degrees F or higher). Pediatrics. 2006 Jul;118(1):34-40.
79. Saha D, et al. Single-dose azithromycin for the treatment of **cholera** in adults. N Engl J Med. 2006 Jun 8;354(23):2452-62. (InfoPOEMs: While tetracycline (1 g to 2 g) or doxycycline (300 mg) in a single dose remains an effective and inexpensive treatment for cholera in older children and adults, azithromycin in a single 1-g dose is an effective (although somewhat more expensive) alternative. It has been shown in previous studies to be a good choice for younger children who cannot take tetracycline or doxycycline. (LOE = 1b))
80. Arroll B, Kenealy T. Are antibiotics effective for **acute purulent rhinitis**? Systematic review and meta-analysis of placebo controlled randomised trials. BMJ. 2006 Aug 5;333(7562):279. Epub 2006 Jul 21. Antibiotics are probably effective for acute purulent rhinitis. They can cause harm, usually in the form of gastrointestinal effects. Most patients will get better without antibiotics, supporting the current "no antibiotic as first line" advice. (InfoPOEMs: Antibiotic treatment of patients with purulent rhinitis

TOP

than 10 days duration increased the number of patients who had resolution of the rhinitis 5 days to 7 days later. On average, almost 60% of patients improved without treatment; antibiotics produced 1 more patient who benefited for every 6 patients who were treated. (LOE = 1a))
81. Canadian **STD** Guidelines. Pharmacist's Letter Sep 2006.
82. Barton N, et al. Guidelines for the prevention and management of community-associated **methicillin-resistant Staphylococcus aureus**: A perspective for Canadian health care practionioners. Can J Infect Dis Med Microbiol Vol 17 Suppl C Sept/Oct 2006. (At Risk: young, athletes, inmates, military, Iv drug users & aboriginal population. CMRSA 7 (USA400) from Minnesota; CMRSA10 (USA300) from California & BC.
83. Gilbert M, MacDonald J, et al. Outbreak in Alberta of community-acquired (**USA300**) **methicillin-resistant Staphylococcus aureus** in people with a history of drug use, homelessness or incarceration. CMAJ. 2006 Jul 18;175(2):149-54. Epub 2006 Jun 27.
84. Hogenauer C, Langner C, et al. **Klebsiella oxytoca** as a Causative Organism of **Antibiotic-Associated** Hemorrhagic Colitis. N Engl J Med. 2006 Dec 7;355(23):2418-2426.
85. Smeesters PR, et al. **Pharyngitis** in low-resources settings: a pragmatic **clinical approach** to reduce unnecessary antibiotic use. Pediatrics. 2006 Dec;118(6):e1607-11.
86. Leach AJ, Morris PS. Antibiotics for the **prevention of acute and chronic suppurative otitis media** in children. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004401. For children at risk, antibiotics given once or twice daily will reduce the probability of AOM while the child is on treatment. Antibiotics will reduce the number of episodes of AOM per year from around three to around 1.5. We believe that larger absolute benefits are likely in high-risk children. These conclusions were not affected by sensitivity analyses.
87. Hammerman C, Bin-Nun A, Kaplan M. Safety of **probiotics**: comparison of two popular strains. BMJ. 2006 Nov 11;333(7576):1006-8.
88. Kaye KS, et al. Differential effects of **levofloxacin & ciprofloxacin** on the risk for isolation of quinolone-resistant **Pseudomonas** aeruginosa. Antimicrob Agents Chemother. 2006 Jun;50(6):2192-6.
89. Segers P, et al. Prevention of Nosocomial Infection in Cardiac Surgery by Decontamination of the Nasopharynx and Oropharynx With **Chlorhexidine** Gluconate: A Randomized Controlled Trial. JAMA. 2006 Nov 22;296(20):2460-2466.
90. Fonseca SN, et al. Implementing **1-dose** antibiotic **prophylaxis** for prevention of surgical site infection. Arch Surg. 2006 Nov;141(11):1109-13.
91. Osguthorpe JD, Nielsen DR. **Otitis externa**: Review and clinical update.Am Fam Physician. 2006 Nov 1;74(9):1510-6.
92. Rosenfeld RM, et al. American Academy of Otolaryngology--Head and Neck Surgery Foundation. Clinical practice guideline: **acute otitis externa**. Otolaryngol Head Neck Surg. 2006 Apr;134(4 Suppl):S4-23.
93. Walter K, Tyler ME. Severe **corneal toxicity** after topical **fluoroquinolone** therapy: report of two cases. Cornea. 2006 Aug;25(7):855-7.
94. Ruohola A, et al. Microbiology of acute otitis media in children with **tympanostomy** tubes: prevalences of **bacteria & viruses**. Clin Infect Dis. 2006 Dec 1;43(11):1417-22. Epub 2006 Oct 31. In the great majority of children, AOM is a coinfection with bacteria and viruses. The patent tympanostomy tube does not change the spectrum of causative agents in AOM. A microbiological etiology can be established in practically all cases.
95. Auburtin M, et al. Detrimental role of **delayed antibiotic** administration & penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study. Crit Care Med. 2006 Nov;34(11):2758-65.
96. Qin X, et al. **Ciprofloxacin-resistant** gram-negative bacilli in the **fecal microflora** of children. Antimicrob Agents Chemother. 2006 Oct;50(10):3325-9. Thirteen (2.9%) of 455 stools yielded ciprofloxacin-resistant E. coli (seven children), Stenotrophomonas maltophilia (four children), and Achromobacter xylosoxidans and Enterobacter aerogenes (one child each).
97. Oosterheert JJ, et al. Effectiveness of **early** switch from **intravenous to oral antibiotics** in severe community acquired pneumonia: multicentre randomised trial. BMJ.2006Nov 7; [Epub ahead of print] Early switch from intravenous to oral antibiotics in patients with severe community acquired pneumonia is safe & decreases length of hospital stay by 2 days.
98. Orvidas LJ, St Sauver JL, Weaver AL. Efficacy of **Tonsillectomy** in Treatment of Recurrent Group A beta-Hemolytic Streptococcal Pharyngitis. Laryngoscope. 2006 Nov;116(11):1946-50.
99. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for **methicillin-resistant Staphylococcus aureus** infections: efficacy and toxicity. Arch Intern Med. 2006 Oct 23;166(19):2138-44.
100. Szajewska H, Ruszczynski M, et al. **Probiotics** in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. J Pediatr. 2006 Sep;149(3):367-372. Probiotics reduce the risk of AAD in children. For every 7 patients that would develop diarrhea while being treated with antibiotics, one fewer will develop AAD if also receiving probiotics. (InfoPOEMs: Probiotics appear to prevent antibiotic-associated diarrhea in children. However, the limited number of trials included in this study, their overall limited quality, and the potential for publication bias suggest that the data are too limited for certainty. (LOE = 1a-))
101. Rovers MM, et al. Antibiotics for **acute otitis media**: a meta-analysis with individual patient data. Lancet. 2006 Oct 21;368(9545):1429-35. Antibiotics seem to be most beneficial in children younger than 2 years of age with bilateral acute otitis media, and in children with both acute otitis media and otorrhoea. For most other children with mild disease an observational policy seems justified.
102. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for **sore throat**. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD000023. Antibiotics confer relative benefits in the treatment of sore throat. However, the absolute benefits are modest. Protecting sore throat sufferers against suppurative and non-suppurative complications in modern Western society can only be achieved by treating many with antibiotics, most of whom will derive no benefit. In emerging economies (where rates of acute rheumatic fever are high, for example), the number needed to treat may be much lower for antibiotics to be considered effective. Antibiotics shorten the duration of symptoms by about sixteen hours overall.
103. Fernandez J, et al. Norfloxacin vs Ceftriaxone in the Prophylaxis of Infections in Patients With **Advanced Cirrhosis** & Hemorrhage. Gastroenterology. 2006Oct;131(4):1049-56.
104. Huang SS, Datta R, Platt R. Risk of acquiring antibiotic-resistant bacteria from **prior room occupants**. Arch Intern Med. 2006 Oct 9;166(18):1945-51.
105. Pharmacist's Letter Oct 2006. Alternative or **Off-label** Routes of Drug Administration. (Oral administration of: vancomycin)

TOP

106. Clement A, et al. Long term effects of **azithromycin** in patients with **cystic fibrosis**: a double blind, placebo controlled trial. Thorax. 2006 Oct;61(10):895-902.Epub 2006Jun 29.
107. Pharmacist's Letter Oct 2006. Community-acquired Methicillin-Resistant S. aureus (**CA-MRSA**).
108. Moran GJ, et al. EMERGEncy ID Net Study Group. Methicillin-resistant S. aureus infections among patients in the emergency department. N Engl J Med. 2006 Aug 17;355(7):666-74. (InfoPOEMs: Methicillin-resistant Staphylococcus aureus (**MRSA**) is the most common bacteria isolated from purulent skin and soft-tissue infections. It is most sensitive to trimethoprim-sulfamethoxazole, rifampin, clindamycin, and tetracycline. (LOE = 1b))
109. Dhalla IA, et al. Are broad-spectrum **fluoroquinolones** more likely to cause **Clostridium difficile**-associated disease? Antimicrob Agents Chemother. 2006 Sep;50(9):3216-9.
110. Clegg HW, et al. Treatment of streptococcal **pharyngitis** with **once-daily** compared with twice-daily amoxicillin: a noninferiority trial. Pediatr Infect Dis J. 2006Sep;25(9):761-7.
111. Grijalva CG, et al. National impact of universal childhood immunization with **pneumococcal conjugate vaccine** on outpatient medical care visits in the United States. Pediatrics. 2006 Sep;118(3):865-73.
112. Bergman M, et al. Macrolide and Azithromycin Use Are Linked to Increased **Macrolide Resistance** in Streptococcus pneumoniae. Antimicrob Agents Chemother. 2006 Aug 28; [Epub ahead of print]
113. Spiro DM, et al. **Wait-and-see prescription** for the treatment of acute otitis media: a randomized controlled trial. JAMA. 2006Sep13;296(10):1235-41. (InfoPOEMs:A wait-and-see approach of asking parents of children given a diagnosis of acute otitis media (AOM) in the emergency department to delay filling a prescription significantly reduces unnecessary antibiotic use. Parents of children in the delayed group reported otalgia slightly, if any, more often than the parents of children in the standard group. All parents received explicit instructions to provide both ibuprofen & otic analgesic drops to their kids. Children in the standard treatment group were more likely to have diarrhea.(LOE = 1b))
114. Hasin T, et al. Postexposure treatment with doxycycline for the prevention of **tick-borne** relapsing fever. N Engl J Med. 2006 Jul 13;355(2):148-55. (InfoPOEMs: Doxycycline at an initial dose of 200 mg followed by 4 days of 100 mg daily effectively prevents tick-borne relapsing fever (TBRF) in patients in a TBRF-endemic area who have evidence of a tick bite. (LOE = 1b))
115. Mangione-Smith R, et al. Ruling **out the need for antibiotics**: are we sending the right message? Arch Pediatr Adolesc Med. 2006 Sep;160(9):945-52.
116. Poehling KA, et al. Invasive pneumococcal disease among infants before and after introduction of **pneumococcal conjugate vaccine**. JAMA. 2006 Apr 12;295(14):1668-74.
117. Kyaw MH, et al. Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effect of introduction of the **pneumococcal conjugate vaccine** on drug-resistant Streptococcus pneumoniae. N Engl J Med. 2006 Apr 6;354(14):1455-63. Erratum in: N Engl J Med. 2006 Aug 10;355(6):638.
118. Ross JD, et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated **pelvic inflammatory disease**: results of a multicentre, double-blind, randomised trial. Sex Transm Infect. 2006 Jun 28; [Epub ahead of print]
119. Miller KE. Diagnosis and treatment of **Neisseria gonorrhoeae** infections. Am Fam Physician. 2006 May 15;73(10):1779-84.
120. Lieberthal AS. **Acute otitis** media guidelines: review and update. Curr Allergy Asthma Rep. 2006 Jul;6(4):334-41.
121. Marra F, et al. Does antibiotic exposure during infancy lead to development of **asthma**?: a systematic review and metaanalysis. Chest. 2006 Mar;129(3):610-8.
122. Everitt HA, Little PS, Smith PW. A randomised controlled trial of management strategies for **acute infective conjunctivitis** in general practice. BMJ. 2006 Aug 12;333(7563):321. Epub 2006 Jul 17. (InfoPOEMs: Treatment with an antibiotic, either immediately or after 3 days without symptom improvement, shortened the duration of acute conjunctivitis but did not decrease the severity of symptoms. Delaying the antibiotic reduced the need for antibiotics by almost 50% with similar symptom control and no more repeat visits than immediate antibiotic use. These results were the same for conjunctivitis with and without an identified bacterial cause. (LOE = 1b))
123. Dohar J, et al. Topical **Ciprofloxacin/Dexamethasone** Superior to Oral Amoxicillin/Clavulanic Acid in Acute **Otitis Media** With Otorrhea Through Tympanostomy Tubes. Pediatrics. 2006 Jul 31; [Epub ahead of print]
124. Camilleri M. Clinical practice. **Diabetic gastroparesis**. N Engl J Med. 2007 Feb 22;356(8):820-9.
125. CDC: Fluoroquinolones No Longer Recommended for Treatment of **Gonococcal** Infections MMWR April 2007 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5614a3.htm (Pharmacist's Letter. May 2007. Fluoroquinolones no longer recommended for Gonococcal infections.)
126. April/07 NEJM: In the face of Congressional subpoenas and unfavorable publicity, reviewers at the FDA were warned at a June 2006 meeting by Andrew von Eschenbach, then the acting FDA commissioner, not to discuss **Ketek** outside the agency. By this time, 23 cases of acute severe liver injury and 12 cases of acute liver failure, 4 of them fatal, had been linked to Ketek. By the end of 2006, Ketek had been implicated in 53 cases of hepatotoxic effects. The FDA did not relabel Ketek to indicate its possible severe hepatotoxicity until 16 months after the first liver-failure cases became public. The withdrawal of approval for two indications, acute bacterial sinusitis and acute exacerbation of chronic bronchitis, for which Ketek's efficacy had never been demonstrated, did not occur until February 12, 2007 — only a day before the Congressional hearing on Ketek.
127. Wilson W, Taubert KA, Gewitz M, et al. **Prevention of infective endocarditis guidelines** from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007. DOI:10.1161/CIRCULATIONAHA.106.183095. Available at: http://circ.ahajournals.org. (see also Pharmacist's Letter. May 2007. Guidelines for infective endocarditis. Recommended if: artificial heart valve, history of infective endocarditis, specific congenital heart conditions, or if a heart transplant that develops a problem in a heart valve)
American Academy of Pediatric Dentistry Clinical Affairs Committee, American Academy of Pediatric Dentistry Council on Clinical Affairs. Guideline on antibiotic prophylaxis for **dental** patients at risk for infection. Pediatr Dent 2008-2009;30(7 Suppl):215-8. http://www.aapd.org/media/Policies_Guidelines/G_AntibioticProphylaxis.pdf
128. Medical Letter: Treatment Guidelines. **Choice of Antibacterial Drugs**. May 2007.
129. Health Canada Sept/07 Sanofi-aventis Canada, Inc. is informing Canadians that the antibiotic Ketek (telithromycin), should no longer be used to treat sinusitis, bronchitis, tonsillitis or pharyngitis. Ketek can still be used to treat certain types of pneumonia. (only for CAP)

TOP

130. Dimopoulos G, Siempos II, Korbila IP, et al. Comparison of first-line with second-line antibiotics for **acute exacerbations of chronic bronchitis**: a metaanalysis of randomized controlled trials. Chest. 2007 Aug;132(2):447-55. Epub 2007 Jun 15. Compared to first-line antibiotics, second-line antibiotics are more effective, but not less safe, when administered to patients with AECB.
131. Pichichero ME, Casey JR. Emergence of a multiresistant serotype **19A pneumococcal strain** not included in the 7-valent conjugate vaccine as an otopathogen in children. JAMA. 2007 Oct 17;298(15):1772-8. In the years following introduction of PCV7, a strain of S pneumoniae has emerged in the United States as an otopathogen that is **resistant** to all FDA-approved antibiotics for treatment of AOM in children.
132. Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. BMJ. 2007 Oct 18; [Epub ahead of print] **Antibiotics are not justified** to reduce the risk of serious **complications for upper respiratory tract infection, sore throat, or otitis media**. Antibiotics substantially reduce the risk of pneumonia after chest infection, particularly in elderly people in whom the risk is highest.
133. Ramakrishnan K, Sparks RA, Berryhill WE. Diagnosis and treatment of **otitis media**. Am Fam Physician. 2007 Dec 1;76(11):1650-8.
134. Slapak I, Skoupá J, et al Efficacy of **isotonic nasal seawater wash** in the treatment & prevention of rhinitis in children. Arch Otolaryngol Head Neck Surg. 2008 Jan;134(1):67-74.
135. Monaghan T, Boswell T, Mahida YR. Recent advances in **Clostridium difficile**-associated disease. Gut. 2008 Feb 5; [Epub ahead of print]
136. Young J, De Sutter A, Merenstein D, et al. Antibiotics for adults with clinically diagnosed **acute rhinosinusitis**: a meta-analysis of individual patient data. Lancet. 2008 Mar 15;371(9616):908-14. Common clinical signs and symptoms cannot identify patients with rhinosinusitis for whom treatment is clearly justified. Antibiotics are not justified even if a patient reports symptoms for longer than 7-10 days.
137. Williamson IG, Rumsby K, Benge S, et al. **Antibiotics and topical nasal steroid** for treatment of **acute maxillary sinusitis**: a randomized controlled trial. JAMA. 2007 Dec 5;298(21):2487-96. Neither an antibiotic nor a topical steroid alone or in combination was effective as a treatment for acute sinusitis in the primary care setting.
138. Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, et al. Fluoroquinolones compared with beta-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials. CMAJ. 2008 Mar 25;178(7):845-54. In the treatment of **acute bacterial sinusitis**, newer fluoroquinolones conferred no benefit over beta-lactam antibiotics. The use of fluoroquinolones as first-line therapy cannot be endorsed.
139. Rajendran PM, Young D, Maurer T, Chambers H, Perdreau-Remington F, Ro P, Harris H. randomized, double-blind, placebo-controlled trial of cephalexin for treatment of **uncomplicated skin abscesses** in a population at risk for community-acquired methicillin-resistant Staphylococcus aureus infection. Antimicrob Agents Chemother. 2007 Nov;51(11):4044-8. Epub 2007 Sep 10. Simply incising and draining a superficial skin abscess is sufficient treatment and results in a very high cure rate. Adding a beta-lactam antibiotic does not improve outcomes. This is not the final word on this subject -- it is possible, although unlikely, that use of an antibiotic effective against community-acquired methicillin resistant staph aureus (CA-MRSA) would have increased the cure rate, or that this result may not apply in populations with a lower rate of CA-MRSA -- but it supports the increasingly common practice of not prescribing antibiotics following incision and drainage of a superficial skin abscess. (LOE = 1b-)
140. Lennon DR et al. Once-daily Amoxicillin vs Twice-daily Penicillin V in Group A {beta}-Hemolytic **Streprococcus Pharyngitis**. Arch Dis Child. 2008 Mar 12; [Epub ahead of print] This adequately-powered study, **once-daily oral amoxicillin** is not inferior to twice-daily penicillin V for the treatment & eradication of GABHS in children with pharyngitis.
141. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, Varonen H, Rautakorpi UM, Williams JW Jr, Mäkelä M. Antibiotics for acute maxillary sinusitis. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD000243. Antibiotics have a small treatment effect in patients with uncomplicated **acute sinusitis** in a primary care setting with symptoms for more than seven days. However, 80% of participants treated without antibiotics improve within two weeks. Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level.
142. Pennesi M, et al. Is antibiotic prophylaxis in children with **vesicoureteral reflux** effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics. 2008 Jun;121(6):e1489-94. Epub 2008 May 19. Continuous antibiotic prophylaxis was ineffective in reducing the rate of pyelonephritis recurrence and the incidence of renal damage in children who were younger than 30 months and had vesicoureteral reflux grades II through IV.
143. Nishimura RA, Carabello BA, Faxon DP, Freed MD, Lytle BW, O'Gara PT, O'Rourke RA, Shah PM. ACC/AHA 2008 Guideline update on valvular heart disease: focused update on **infective endocarditis**: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.J Am Coll Cardiol. 2008 Aug 19;52(8):676-85.
144. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: **adult sinusitis**. Otolaryngol Head Neck Surg. 2007 Sep;137(3 Suppl):S1-31.
145. Haider BA, Saeed MA, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005976. The evidence of this review suggests that a short course (three days) of antibiotic therapy is as effective as a longer treatment (five days) for non-severe pneumonia in children under five years of age.
146. Pegler S, Healy B. In patients **allergic to penicillin**, consider second and third generation cephalosporins for life threatening infections. BMJ. 2007 Nov 10;335(7627):991.
147. Kelly CP, LaMont JT. **Clostridium difficile**--more difficult than ever. N Engl J Med. 2008 Oct 30;359(18):1932-40.
148. Muzi F, Gravante G, Tati E, Tati G. **Fluoroquinolones-induced tendinitis** and tendon rupture in kidney transplant recipients: 2 cases and a review of the literature. Transplant Proc. 2007 Jun;39(5):1673-5.
149. Chalasani N et al. for the **Drug Induced Liver** Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008 Dec; 135:1924. The most commonly implicated drug classes were antibiotics (46% of cases) and central nervous system agents, such as antiseizure or psychotropic drugs (15%). The most commonly implicated single agent was amoxicillin/clavulanate (23 cases); nitrofurantoin, isoniazid, and trimethoprim/sulfamethoxazole were implicated in 13 cases each.

TOP

150. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United kingdom general practice research database. Pediatrics. 2009 Feb;123(2):424-30.
151. Ota KV, Jamieson F, Fisman DN, et al. Prevalence of and risk factors for quinolone-resistant Neisseria gonorrhoeae infection in Ontario. CMAJ. 2009 Feb 3;180(3):287-90. During 2006 in Ontario, 28% of N. gonorrhoeae isolates were resistant to quinolones. Infections in heterosexual men appear to have contributed significantly to the quinolone resistance rate. Medical practitioners should be aware of the widespread prevalence of quinolone-resistant N. gonorrhoeae and avoid quinolone use for empiric therapy.
152. Gerber M, Baltimore R, Eaton C, et al. Prevention of **rheumatic fever** and diagnosis and treatment of acute **streptococcal pharyngitis**. American Heart Association (AHA) Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics & Translational Biology, & Interdisciplinary Council on Quality of Care & Outcomes Research. Circulation. 2009; DOI: 10.1161/CIRC-AHA.109.191959.
153. Choby BA. Diagnosis and treatment of **streptococcal pharyngitis**. Am Fam Physician. 2009 Mar 1;79(5):383-90.
154. Kelly CP. A 76-year-old man with recurrent **Clostridium difficile**-associated diarrhea: review of C. difficile infection. JAMA. 2009 Mar 4;301(9):954-62. Epub 2009 Feb 3.
155. Nduba VN, Mwachari CW, Magaret AS, et al. Placebo found equivalent to amoxicillin for treatment of **acute bronchitis** in Nairobi, Kenya: a triple blind, randomised, equivalence trial. Thorax. 2008 Nov;63(11):999-1005. Epub 2008 Jun 17. Amoxicillin is not effective for acute productive bronchitis, even in patients with HIV infection. (LOE = 1b)
156. Dupont HL. Systematic review: the epidemiology and clinical features of **travellers' diarrhoea**. Aliment Pharmacol Ther. 2009 Apr 21.
157. Hwang PH. A 51-year-old woman with acute onset of facial pressure, rhinorrhea, and tooth pain: review of acute **rhinosinusitis**. JAMA. 2009 May 6;301(17):1798-807.
158. Noblett SE, Welfare M, Seymour K. The role of surgery in **Clostridium difficile** colitis. BMJ. 2009 May 6;338:b1563. doi: 10.1136/bmj.b1563.
159. Leffler DA, Lamont JT. Treatment of **Clostridium difficile**-associated disease. Gastroenterology. 2009 May;136(6):1899-912. Epub 2009 May 7.
160. Butler C C, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with **acute cough** in primary care: prospective study in 13 countries. BMJ 2009;338:b2242, doi: 10.1136/bmj.b2242 (Published 23 June 2009)
161. Bezáková N, et al. Recurrence up to 3.5 years **after antibiotic treatment** of acute otitis media in very young Dutch children: survey of trial participants. BMJ. 2009 Jun 30;338:b2525. doi: 10.1136/bmj.b2525.
162. Aspinall SL, Good CB, et al. Severe **Dysglycemia** with the Fluoroquinolones: A Class Effect? Clin Infect Dis. 2009 Jun 22. [Epub ahead of print] The odds of severe hypo- and hyperglycemia were significantly greater with **gatifloxacin and levofloxacin**, but not ciprofloxacin, than with azithromycin. Thus, the risk of a clinically relevant dysglycemic event appears to vary among the fluoroquinolones.
163. Oduyebo OO, Anorlu RI, et al. The effects of antimicrobial therapy on **bacterial vaginosis** in non-pregnant women. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006055.
164. Oehler RL, Velez AP, Mizrachi M, Lamarche J, Gompf S. Bite-related and septic syndromes caused by **cats and dogs**. Lancet Infect Dis. 2009 Jul;9(7):439-47.
165. Raja AS, et al. The use of **penicillin skin testing** to assess the prevalence of penicillin allergy in an emergency department setting. Ann Emerg Med. 2009 Jul;54(1):72-7.
166. Grijalva Carlos G.; Nuorti J. Pekka; et al. **Antibiotic Prescription Rates** for Acute Respiratory Tract Infections in US Ambulatory Settings. JAMA. 2009;302(7):758-766.
167. Kwong JC, Maaten S, Upshur RE, Patrick DM, Marra F. The effect of **universal** influenza immunization on antibiotic prescriptions: an ecological study. Clin Infect Dis. 2009 Sep 1;49(5):750-6. Universal influenza immunization is associated with reduced influenza-associated antibiotic prescriptions.
168. Lynch Michael F.; Blanton Elizabeth M.; Bulens Sandra; et al. **Typhoid Fever** in the United States, 1999-2006 JAMA. 2009;302(8):859-865. Infection with antimicrobial-resistant S Typhi strains among US patients with typhoid fever is associated with travel to the Indian subcontinent, and an increasing proportion of these infections are due to S Typhi strains with decreased susceptibility to fluoroquinolones.
169. Schuetz Philipp; Christ-Crain Mirjam; Thomann Robert; et al.; for the ProHOSP Study Group. Effect of **Procalcitonin**-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial. JAMA. 2009;302(10):1059-1066.
170. Forgie S, Zhanel G, RobinsonJ; Canadian Paediatric Society (**CPS**). Management of **acute otitis media**. Paediatr Child Health 2009;14(7):457-60.
171. Crider Krista S.; Cleves Mario A.; Reefhuis Jennita; et al. Antibacterial Medication Use During **Pregnancy and Risk of Birth Defects**: National Birth Defects Prevention Study. Arch Pediatr Adolesc Med. 2009;163(11):978-985.
172. Centor RM. Expand the **pharyngitis** paradigm for adolescents and young adults. Ann Intern Med. 2009 Dec 1;151(11):812-5.
173. Lowy, IM, DC., Leav, BA., et al. Treatment with **Monoclonal Antibodies against Clostridium** difficile Toxins.N Engl J Med 2010 362: 197-205.
174. Patel RA, Gallagher JC. **Drug Fever**. Pharmacotherapy. 2010 Jan;30(1):57-69.
175. Shannon-Lowe J, Matheson N J, Cooke F J, Aliyu S H. Prevention and medical management of **Clostridium difficile** infection. BMJ 2010;340:c1296, doi: 10.1136/bmj.c1296
176. Jarlier Vincent; Trystram David; Brun-Buisson Christian; et al.; for the Collegiale de Bacteriologie-Virologie-Hygiene des Hopitaux Universitaires de l'Ile de France **Curbing Methicillin-Resistant Staphylococcus aureus** in 38 French Hospitals Through a 15-Year Institutional Control Program. Arch Intern Med. 2010;170(6):552-559.
177. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. Clinical practice guidelines for **Clostridium difficile** infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (**IDSA**). Infect Control Hosp Epidemiol. 2010 May;31(5):431-55.
178. Saiman Lisa; Anstead Michael; Mayer-Hamblett Nicole; et al. for the AZ0004 **Azithromycin** Study Group Effect of Azithromycin on Pulmonary Function in Patients With **Cystic Fibrosis** Uninfected With Pseudomonas aeruginosa: A Randomized Controlled Trial. JAMA. 2010;303(17):1707-1715.
179. Deleo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated **methicillin-resistant Staphylococcus aureus**. Lancet. 2010 May 1;375(9725):1557-68.
180. Costelloe Céire, Metcalfe Chris, Lovering Andrew, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010;340:c2096
181. Medical Letter. Treatment Guidelines. **Drugs for Bacterial Infections**. June 2010.

TOP

182. Antoniou Tony; Gomes Tara; Juurlink David N.; Loutfy Mona R.; et al. Trimethoprim-Sulfamethoxazole-**Induced Hyperkalemia** in Patients Receiving Inhibitors of the **Renin-Angiotensin System**: A Population-Based Study. Arch Intern Med. 2010;170(12):1045-1049.
183. Chang B, Knowles SR, Weber E. Immediate **hypersensitivity** to **moxifloxacin** with tolerance to ciprofloxacin: report of three cases and review of the literature. Ann Pharmacother 44 (4): 740-5, 2010.
184. Blomberg J, Lagergren P, Martin L, Mattsson F, Lagergren J. 9 Novel approach to antibiotic prophylaxis (Bactrim/Co-trimoxazole 20ml soln) in percutaneous endoscopic gastrostomy (**PEG**): randomised controlled trial. BMJ 2010;340:c3115.
185. Jahanfar S, Ng CJ, Teng CL. Antibiotics for **mastitis** in breastfeeding women. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD005458.
186. Dhiwakar M, Clement WA, Supriya M, McKerrow W. Antibiotics to reduce post-tonsillectomy morbidity. Cochrane Database Syst Rev. 2010 Jul 7;7:CD005607.
The present systematic review, including meta-analyses for select outcomes, suggests that although individual studies vary in their findings, there is no evidence to support a consistent, clinically important impact of antibiotics in reducing the main morbid outcomes following tonsillectomy (i.e. pain, need for analgesia and secondary haemorrhage rates). Limited benefit apparent with antibiotics may be a result of positive bias introduced by several important methodological shortcomings in the included trials. Based on existing evidence therefore, we would advocate against the routine prescription of antibiotics to patients undergoing tonsillectomy. Whether a subgroup of patients who might benefit from selective administration of antibiotics exists is unknown and needs to be explored in future trials.
187. Zhang Yuting; Lee Bruce Y.; Donohue Julie M.. **Ambulatory** Antibiotic Use and Prescription Drug Coverage in Older Adults. Arch Intern Med. 2010;170(15):1308-1314.
188. Stahlmann R, Lode H. Safety considerations of **fluoroquinolones in the elderly**: an update. Drugs Aging 27 (3): 193-209, 2010.
189. Khan S, Sharrack B, Sewell WA. **Metronidazole-induced aseptic meningitis** during Helicobacter pylori eradication therapy. Ann Intern Med 146 (5): 395-6, 2007.
190. Wilson Jennifer F. In the Clinic: **Acute Sinusitis**. *Ann Intern Med* September 7, 2010 153:ITC3-1. September 7, 2010.
191. Kozyrskyj A, Klassen TP, Moffatt M, et al. **Short-course antibiotics for acute otitis media**. Cochrane Database Syst Rev. 2010 Sep 8;9:CD001095. Clinicians need to evaluate whether the minimal short-term benefit from longer treatment of antibiotics is worth exposing children to a longer course of antibiotics.
192. Dalton Bruce R, Zuege Danny J, Shahpori Reza, et al. Concomitant **Ceftriaxone** and High-Concentration Intravenous **Calcium** Therapy in Adult Critical Care Patients: A Matched Cohort Study. Ahead of Print on 1 July 2010, DOI 10.1345/aph.1M745. Ann Pharmacother ;44:1158-1163.
193. Minson Q, Gentry CA. Analysis of **linezolid**-associated **hematologic** toxicities in a large veterans affairs medical center. Pharmacotherapy 30 (9): 895-903, 2010.
194. Hessen Margaret Trexler. In the Clinic: ***Clostridium difficile*** **Infection**. *Ann Intern Med* October 5, 2010 153:ITC4-1; doi:10.1059/0003-4819-153-7-201010050-01004.
195. Oake N; Taljaard M; van Walraven C; et al. The Effect of **Hospital-Acquired Clostridium difficile** Infection on In-Hospital Mortality. Arch Intern Med. 2010;170(20):1804-1810.
196. Coker Tumaini R.; Chan Linda S.; Newberry Sydne J.; et al. Diagnosis, Microbial Epidemiology, and Antibiotic Treatment of **Acute Otitis Media** in Children: A Systematic Review. JAMA. 2010;304(19):2161-2169.
197. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: Results of a U.S. multicenter, prospective study. Hepatology. 2010 Dec;52(6):2065-76.
Antimicrobial agents were found to be the most common cause of DILI ALF cases and included anti-tuberculosis drugs (25), sulphur-containing drugs (12), nitrofurantoin (12), other antibiotics (7), antifungal agents (6), and anti-retroviral drugs (4).
198. Skalet AH, Cevallos V, Ayele B, Gebre T, Zhou Z, et al. 2010 Antibiotic Selection Pressure and **Macrolide Resistance (azithromycin)** in Nasopharyngeal Streptococcus pneumoniae: A Cluster-Randomized Clinical Trial. PLoS Med 7(12): e1000377. doi:10.1371/journal.pmed.1000377
199. Hoberman Alejandro, Paradise Jack L., Rockette Howard E., et al. Treatment of **Acute Otitis Media** in Children under 2 Years of Age. N Engl J Med 2011; 364:105-115.
200. Tähtinen Paula A., Laine Miia K., Huovinen Pentti, et al. A Placebo-Controlled Trial of Antimicrobial Treatment for **Acute Otitis Media**. N Engl J Med 2011; 364:116-126.
201. Hatchette TF, Farina D. **Infectious diarrhea**: when to test and when to treat. CMAJ. 2010 Dec 20.
202. Wessels Michael R, **Streptococcal Pharyngitis**. N Engl J Med 2011; 364:648-655.
203. Kim NH, Kim M, Lee S, et al. Routine **Sterile Gloving on Contamination Rates** in Blood Culture: A Cluster Randomized Trial. *Ann Intern Med* Feb 1, 2011 154:145-151.
204. Chen AE, Carroll KC, Diener-West M, et al. Randomized controlled trial of **cephalexin versus clindamycin for uncomplicated pediatric skin infections**. Pediatrics. 2011 Mar;127(3):e573-80.
205. Seltz LB, Smith J, Durairaj VD, Enzenauer R, Todd J. Microbiology and antibiotic management of **orbital cellulitis**. Pediatrics. 2011 Mar;127(3):e566-72.
206. Chiappini E, Regoli M, Bonsignori F, et al. Analysis of different recommendations from international guidelines for the management of **acute pharyngitis in adults and children**. Clin Ther. 2011 Jan;33(1):48-58.
207. van Zuuren EJ, Kramer S, Carter B, et al. **Interventions for rosacea**. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD003262.
208. Li M, Al-Sarraf A, Sinclair G, Frohlich J. **Fish odour syndrome**. CMAJ. 2011 Mar 21.
209. Nambiar S, Rellosa N, Wassel RT, et al. **Linezolid-Associated Peripheral and Optic Neuropathy** in Children. Pediatrics. 2011 May 9.
210. Paul I. M., Maselli J. H., Hersh A. L., et al. Antibiotic Prescribing During Pediatric Ambulatory Care **Visits for Asthma**. *Pediatrics*, 2011; DOI: 10.1542/peds.2011-0218
211. Copp HL, Shapiro DJ, et al. National Ambulatory Antibiotic Prescribing Patterns for Pediatric **Urinary Tract Infection**,1998-2007.*Pediatrics*, 2011; DOI: 10.1542/peds.2010-3465
212. Vons C et al. **Amoxicillin plus clavulanic acid versus appendicectomy** for treatment of acute uncomplicated appendicitis: An open-label, non-inferiority, randomised controlled trial. Lancet 2011 May 7; 377:1573.
213. Van den Bruel A, Thompson M, Haj-Hassan T, Stevens R, Moll H, Lakhanpaul M, et al. **Diagnostic value of laboratory tests** in identifying serious infections in febrile children: systematic review. BMJ 2011;342:d3082.
214. Morgan DJ, Okeke IN, Laxminarayan R, et al. **Non-prescription (OTC) antimicrobial** use worldwide: a systematic review. Lancet Infect Dis. 2011 Jun 7.
215. Jenkins TC; et al. Decreased Antibiotic Utilization After Implementation of a Guideline for Inpatient **Cellulitis & Cutaneous Abscess**. Arch Intern Med. 2011;171(12):1072-1079.
216. Di Pierdomenico A, Borgia SM, Richardson D, Baqi M. **Brucellosis** in a returned traveller. CMAJ. 2011 Jul 12;183(10):E690-2.
217. FDA July/11 has received reports of serious central nervous system (CNS) reactions when the antibacterial drug **linezolid** (Zyvox) is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications.
218. Weiss K, Blais R, Fortin A, Lantin S, Gaudet M. Impact of a Multipronged **Education Strategy** on Antibiotic Prescribing in Quebec, Canada. Clin Infect Dis. 2011 Ju

TOP

219. Albert RK, Connett J, Bailey WC, et al. **Azithromycin** (up to 1yr) for prevention of exacerbations of COPD. N Engl J Med 2011;365: 689-98.
220. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. **Ciprofloxacin safety in paediatrics**: a systematic review. Arch Dis Child. 2011 Sep;96(9):874-80.
221. Antoniou T, Gomes T, Mamdani MM, et al. **Trimethoprim-sulfamethoxazole induced hyperkalaemia** in elderly patients receiving **spironolactone**: nested case-control study. BMJ. 2011 Sep 12;343:d5228.
222. Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, et al. Antibiotics for **preventing meningococcal infections**. Cochrane Database Syst Rev. 2011 Aug 10;(8):CD004785. Using rifampin during an outbreak may lead to the circulation of resistant isolates. Use of ciprofloxacin, ceftriaxone or penicillin should be considered. All four agents were effective for up to two weeks follow up, though more trials comparing the effectiveness of these agents for eradicating N. meningitidis would provide important insights.
223. Mullane KM, Miller MA, Weiss K, et al. Efficacy of **fidaxomicin versus vancomycin** as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. Clin Infect Dis. 2011 Sep;53(5):440-7.
224. Arias CA, Panesso D, McGrath DM, et al. Genetic basis for in vivo **daptomycin resistance** in enterococci. N Engl J Med. 2011 Sep 8;365(10):892-900.
225. Cooper MR, Durand CR, Beaulac MT, Steinberg M. Single-agent, broad-spectrum **fluoroquinolones** for the outpatient treatment of low-risk **febrile neutropenia**. Ann Pharmacother. 2011 Sep;45(9):1094-102.
226. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in **infants and children older than 3 months of age**: clinical practice guidelines by the pediatric infectious diseases society and the Infectious Diseases Society of America. (IDSA)Clin Infect Dis. 2011 Oct;53(7):e25-76.
227. Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/
228. Ho JM, Juurlink DN. Considerations when prescribing **trimethoprim-sulfamethoxazole**. CMAJ. 2011 Oct 11.
229. Kees MG, Weber S, Kees F, Horbach T. Pharmacokinetics of **moxifloxacin** in plasma and tissue of morbidly **obese** patients. J Antimicrob Chemother. 2011;66(10):2330-5.
230. Cook AM, Martin C, et al. Pharmacokinetics of intravenous **levofloxacin** administered at 750 milligrams in **obese** adults. Antimicrob Agents Chemother 2011;55(7):3240-3.
231. Luque S, Grau S, Valle M, et al. **Levofloxacin** weight-adjusted dosing and pharmacokinetic disposition in a morbidly **obese** patient. J Antimicrob Chemother 2011;66(7):1653-4.
232. American Academy of Pediatrics (AAP) Committee on Infectious Diseases. The Use of **Systemic and Topical Fluoroquinolones**. Pediatrics. 2011 Oct;128(4):e1034-e1045.
233. Health Canada Nov/11 **Fluoroquinolone** antibiotics: patients with **myasthenia gravis** may risk increased muscle weakness.
234. Loo VG et al. Host and pathogen factors for **Clostridium difficile infection** and colonization. N Engl J Med 2011 Nov 3; 365:1693.
235. Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.
234. Cadena J et al. Dose of **trimethoprim-sulfamethoxazole** to treat skin and skin structure infections caused by **methicillin-resistant Staphylococcus aureus**. Antimicrob Agents Chemother 2011: 55: 5430-2.
235. Liu Catherine, Bayer Arnold, Cosgrove Sara E., et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) for the Treatment of **Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children.** Clin Infect Dis. ciq146 Jan 4, 2011.
236. Ivers Noah, Arroll Bruce, Allan G. Michael. **Delayed antibiotic prescriptions** for URTIs. Can Fam Physician November 2011 57: 1287.
237. van den Aardweg MT, Boonacker CW, Rovers MM, Hoes AW, Schilder AG. Effectiveness of **adenoidectomy** in children with recurrent upper respiratory tract infections: open randomised controlled trial. BMJ. 2011 Sep 6;343:d5154.
238. Finkelstein Y, Soon GS, Acuna P, et al. Recurrence and outcomes of **stevens-johnson syndrome** and toxic epidermal necrolysis in children. Pediatrics. 2011 Oct;128(4):723-8.
239. Kamboj M et al. **Relapse** versus reinfection: Surveillance of **Clostridium difficile infection**. Clin Infect Dis 2011 Nov 15; 53:1003.
240. Forster AJ, Taljaard M, Oake N, et al. The effect of **hospital acquired** infection with **Clostridium dificile** on length of stay in hospital. CMAJ 2012;184:37-42.
241. Rajan S**. Skin and soft-tissue infections**: Classifying and treating a spectrum. Cleve Clin J Med. 2012 Jan;79(1):57-66.
242. Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections. Gonococcal infections. Updated January 2010. www.phac-aspc.gc.ca/std-mts/sti-its/pdf/506gonococcal-eng.pdf
Public Health Agency of Canada. Important notice – public health information update on the treatment for **gonococcal infection**. Public Health Agency of Canada issued important notice on gonococcal infection. **December 21, 2011**. www.phac-aspc.gc.ca/std-mts/sti-its/alert/2011/alert-gono-eng.php (accessed December 21, 2011).
243. Lin E, Bhusal Y, Horwitz D, Shelburne III SA, Trautner BW. **Overtreatment of enterococcal bacteriuria**. Arch Intern Med. 2012;172(1):33-38.
244. Hersh AL et al. **Antibiotic prescribing in ambulatory pediatrics** in the United States. Pediatrics. 2011 Dec;128(6):1053-61.
245. Mitjà O, Hays R, Ipai A, et al. Single-dose **azithromycin versus benzathine benzylpenicillin for treatment of yaws** in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. Lancet 2012; published online Jan 11
246. Desrosiers M, Evans GA, et al. **Canadian** clinical practice guidelines for acute and **chronic rhinosinusitis**. J Otolaryngol Head Neck Surg. 2011 May;40 Suppl 2:S99-193.
247. Kassam Z, Hundal R, Marshall JK, Lee CH. **Fecal Transplant** via Retention Enema for Refractory or Recurrent Clostridium difficile Infection. Arch Intern Med. 2012 Jan 23;172(2):191-3.
248. Di Pentima MC, Chan S, Hossain J. Benefits of a **Pediatric Antimicrobial Stewardship Program** at a Children's Hospital. Pediatrics. 2011 Dec;128(6):1062-70.
249. Butler CC, Simpson SA, Dunstan F, et al. Effectiveness of multifaceted **educational programme** to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. BMJ 2012.344:d8173.
250. Imamura H, KurokawaY, Tsujinaka T, et al. **Intraoperative versus extended antimicrobial prophylaxis** after gastric cancer surgery: a phase 3, open-label, randomised controlled, non-inferiority trial. Lancet Infect Dis 2012; published online Jan 31.
251. Tan IL, Polydefkis MJ, Ebenezer GJ, et al. Peripheral nerve toxic effects of **nitrofurantoin**. Arch Neurol. 2012 Feb;69(2):265-8.

TOP

252. Garbutt Jane M, Banister Christina, Spitznagel E, et al. **Amoxicillin for Acute Rhinosinusitis**: A Randomized Controlled Trial. *JAMA*. 2012;307(7):685-692. (not effective)
253. Mattila E, Uusitalo-Seppälä R, Wuorela M et al. **Fecal Transplantation**, Through Colonoscopy, Is Effective Therapy for Recurrent Clostridium difficile Infection. Gastroenterology. 2012 Mar;142(3):490-6.
254. Logan LK, McAuley JB, Shulman ST. **Macrolide treatment** failure in streptococcal pharyngitis resulting in acute **rheumatic fever**. Pediatrics. 2012 Mar;129(3):e798-802.
255. Frassetto L, Kohlstadt I. Treatment and prevention of **kidney stones**: an update. Am Fam Physician. 2011 Dec 1;84(11):1234-42.
256. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet. 2012 Mar 10;379(9819):953-64.
257. Nitschke M, Sayk F, Härtel C et al. Association between **azithromycin** therapy and duration of bacterial shedding among patients with Shiga toxin-producing enteroaggregative **Escherichia coli O104:H4**. JAMA. 2012 Mar 14;307(10):1046-52. (lower frequency of carriage)
258. Smith SR, Montgomery LG, Williams JW Jr. Treatment of **mild to moderate sinusitis**. Arch Intern Med. 2012 Mar 26;172(6):510-3. Antibiotics should not be prescribed for mild to moderate sinusitis within the first week of the illness.
259. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of **antibiotics compared with appendicectomy** for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. BMJ. 2012 Apr 5;344:e2156.
260. Fraser CL, Biousse V, Newman NJ. **Minocycline-Induced Fulminant Intracranial Hypertension**. Arch Neurol. 2012 Apr 9.
261. Breda L, et al. Population-based study of incidence and clinical characteristics of **rheumatic Fever** in abruzzo, central Italy, 2000-2009. J Pediatr. 2012 May;160(5):832-836.e1.
262. Fraser TN, Avellaneda AA, Graviss EA, Musher DM. **Acute kidney injury associated with trimethoprim/sulfamethoxazole**. J Antimicrob Chemother. 2012 May;67(5):1271-7.
263. Walkey AJ, Wiener RS. Macrolide antibiotics and survival in patients with acute lung injury. Chest. 2012 May;141(5):1153-9.
264. Stone SP, Fuller C, Savage J, et al. Evaluation of the national **Cleanyourhands** campaign to reduce Staphylococcus aureus bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. BMJ. 2012 May 3;344:e3005.
265. Ganske CM, Horning KK. **Levofloxacin-induced tendinopathy** of the hip. Ann Pharmacother. 2012 May;46(5):e13.
266. Ray WA, Murray KT, Hall K, et al. **Azithromycin and the risk of cardiovascular death**. N Engl J Med 2012; 366:1881-90.
267. Romøren M, Lindbaek M, et al. Pregnancy outcome after **gestational exposure to erythromycin-**a population-based register study from Norway. Br J Clin Pharmacol.2012Mar 30.
268. Wu JY, et al. Use of serum **procalcitonin** to detect bacterial infection in patients with autoimmune diseases: A systemic review and meta-analysis. Arthritis Rheum. 2012 May 17.
269. Fine AM, Nizet V, Mandl KD. **Large-Scale Validation of the Centor and McIsaac Scores to Predict Group A Streptococcal Pharyngitis.** Arch Intern Med. 2012 May 7.
270. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America-**IDSA** clinical practice guideline for the diagnosis and treatment of **diabetic foot infections**. Clin Infect Dis. 2012 Jun;54(12):e132-73.
271. Schuetz P, Amin DN, Greenwald JL. Role of **procalcitonin** in managing adult patients with respiratory tract infections. Chest. 2012 Apr;141(4):1063-73.
272. **WHO**-Global action plan to control the spread and impact of antimicrobial resistance in **Neisseria gonorrhoeae**. 2012 http://whqlibdoc.who.int/publications/2012/9789241503501_eng.pdf
273. Katz AR et al. **Neisseria gonorrhoeae** with high-level **resistance to azithromycin**: Case report of first isolate identified in the United States. Clin Infect Dis 2012 Mar 15; 54:841.
274.

[i] D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ. 2002;324:1361.
Clarification: *Saccharomyces cerevisiae (including S boulardii)*

[ii] McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea & treatment of Clostridium difficile disease. Am J Gastroenterol. 2006 Apr;101(4):812-22. (see also Pharmacist's Letter July'06 and Zocco MA, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 2006 Jun 1;23(11):1567-74. InfoPOEMs: Lactobacillus rhamnosus GG (LGG) was as effective as a mesalazine product in preventing recurrence in patients with ulcerative colitis. However, the study was unblinded and a confirmatory study would be helpful. (LOE = 1b-)).(Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. Lancet Infect Dis. 2006 Jun;6(6):374-82. InfoPOEMs: Probiotics reduce the risk of antibiotic-associated diarrhea and other types of acute diarrhea, but not the risk of traveler's diarrhea, in both children and adults. The protective effect does not vary among different probiotic strains nor by mode of delivery. (LOE = 1a).

TOP

(Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. BMJ. 2007 Jun 29; [Epub ahead of print] Consumption of a probiotic drink containing L casei, L bulgaricus, and S thermophilus can reduce the incidence of antibiotic associated diarrhoea and C difficile associated diarrhoea. This has the potential to decrease morbidity, healthcare costs, and mortality if used routinely in patients aged over 50.) (Canani RB, Cirillo P, Terrin G, Cesarano L, Spagnuolo MI, De Vincenzo A, Albano F, Passariello A, De Marco G, Manguso F, Guarino A. Probiotics for treatment of acute diarrhoea in children: randomised clinical
trial of five different preparations. BMJ. 2007 Aug 18;335(7615):340. Epub 2007 Aug 9. One day after the first probiotic administration, the daily number of stools was significantly lower (P<0.001) in children who received L rhamnosus strain GG and in those who received the probiotic mix than in the other groups. Not all commercially available probiotic preparations are effective in children with acute diarrhoea.)(Medical Letter. Probiotics. Aug 13,2007.)
Besselink MG, van Santvoort HC, et al.; Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised,
double-blind, placebo-controlled trial. Lancet. 2008 Feb 23;371(9613):651-9. Epub 2008 Feb 14. In patients with severe pancreatitis, probiotics were no more effective than placebo in preventing infectious complications. Furthermore, there were significantly more deaths in patients receiving probiotics. One would only need to administer probiotics to 11 patients to have 1 extra death. (LOE = 1b)
Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML. Probiotics for treating **eczema**. *Cochrane Database Syst Rev*. 2008;(4):CD006135.
Beausoleil M, Fortier N, Guénette S, L'ecuyer A, Savoie M, Franco M, Lachaine J, Weiss K. Effect of a fermented milk combining Lactobacillus acidophilus Cl1285 and Lactobacillus casei in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. Can J Gastroenterol. 2007 Nov;21(11):732-6. The daily administration of a lactobacilli-fermented milk was safe and effective in the prevention of antibiotic-associated diarrhea in hospitalized patients.
Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Long-term safety and impact on infection rates of
postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. Pediatrics. 2008 Jul;122(1):8-12. Administering probiotics to newborns for 6 months is safe but does not reduce colic. The probiotics produced a decrease in antibiotic use and a decrease in respiratory infections in the 18 months following the course of administration, but both effects were small. (LOE = 1b)
Conen Anna, Zimmerer Stefan, Frei Reno, Et al. A Pain in the Neck: Probiotics for Ulcerative Colitis. Ann Intern Med December 15, 2009 151:895-897.
Tung JM, Dolovich LR, Lee CH. Prevention of Clostridium difficile infection with Saccharomyces boulardii: A systematic review. Can J Gastroenterol. 2009 Dec;23(12):817-21.
Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy. 2010 Feb;30(2):119-26. The probiotic Lactobacillus is effective in preventing antibiotic-associated diarrhea (AAD) in adults, though perhaps not in children. (LOE = 1a-)
Hojsak I, Abdovic S, Szajewska H, Milosevic M, Krznaric Z, Kolacek S. Lactobacillus GG in the Prevention of Nosocomial Gastrointestinal and Respiratory Tract Infections. Pediatrics. 2010 Apr 19. [Epub ahead of print]
Deshpande G, Rao S, Patole S, et al. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics. 2010 May;125(5):921-30. Epub 2010 Apr 19
Dugoua JJ, Machado M, Zhu X, et al. Probiotic safety in pregnancy: a systematic review and meta-analysis of randomized controlled trials of Lactobacillus, Bifidobacterium, and Saccharomyces spp. Journal of Obstetrics and Gynaecology Canada 2009; 31(6): 542-552.
Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub3. Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.
Bernaola Aponte G, Bada Mancilla CA, Carreazo Pariasca NY, Rojas Galarza RA. Probiotics for treating persistent diarrhoea in children. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD007401. DOI: 10.1002/14651858.CD007401.pub2. There is limited evidence suggesting probiotics may be effective in treating persistent diarrhoea in children.
Thomas, Dan W., Greer, Frank R., Committee on Nutrition; Section on Gastroenterology, Hepatology, and Nutrition, Clinical Report--Probiotics and Prebiotics in Pediatrics. Pediatrics 2010 0: peds.2010-2548.
Lin HC, Hsu CH, Chen HL, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics. 2008 Oct;122(4):693-700.
Riquelme AJ, Calvo MA, Guzmán AM, et al. Saccharomyces cerevisiae fungemia after Saccharomyces boulardii treatment in immunocompromised patients. J Clin Gastroenterol. 2003 Jan;36(1):41-3.
Elias, Jackie, Bozzo, Pina, Einarson, Adrienne. Are probiotics safe for use during pregnancy and lactation? Can Fam Physician 2011 57: 299-301.
Hao Q, Lu Z, Dong BR, Huang CQ, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD006895. DOI: 10.1002/14651858.CD006895.pub2. Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTIs, the rate ratio of episodes of acute URTI and reducing antibiotic use. This indicates that probiotics may be more beneficial than placebo for preventing acute URTIs.
Guillemard E, Tondu F, Lacoin F, Schrezenmeir J. Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled
trial. Br J Nutr. 2010 Jan;103(1):58-68.
Bailey JL, Yeung SY. Probiotics for disease prevention: a focus on ventilator-associated pneumonia. Ann Pharmacother. 2011 Nov;45(11):1425-32.
Johnston BC, Goldenberg JZ, Vandvik PO, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea.Cochrane Database Syst Rev. 2011 Nov 9;11:CD004827. Despite heterogeneity in probiotic strain, dose, and duration, as well as in study quality, the overall evidence suggests a protective effect of probiotics in preventing AAD.
Wanke M, Szajewska H. Lack of an Effect of Lactobacillus reuteri DSM 17938 in Preventing Nosocomial Diarrhea in Children: A Randomized, Double-Blind, Placebo-Controlled Trial. J Pediatr. 2012 Feb 3. (no effect)
Butler CC, Duncan D, Hood K. Does taking probiotics routinely with antibiotics prevent antibiotic associated diarrhoea? BMJ. 2012 Feb 21;344:e682.
Pozzoni P, Riva A, Bellatorre AG, et al. Saccharomyces boulardii for the Prevention of Antibiotic-Associated Diarrhea in Adult Hospitalized Patients: A Single-Center, Randomized, Double-Blind, Placebo-Controlled Trial. Am J Gastroenterol. 2012 Apr 3. In elderly hospitalized patients, S. boulardii was not effective in preventing the development of AAD.
Agustina R, Kok FJ, van de Rest O, et al. Randomized trial of probiotics and calcium on diarrhea and respiratory tract infections in Indonesian children. Pediatrics. 2012 May;129(5):e1155-64. RC milk, alone or with L casei, did not reduce diarrhea or ARTIs in indonesian children.
L reuteri may prevent diarrhea, especially in children with lower nutritional status.
Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA. 2012 May 9;307(18):1959-69.
[iii] Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004 Mar 4;350(10):1013-22.

TOP

Additional articles:

Abbas Z, Khan MA, Salih M, et al. **Interferon alpha for chronic hepatitis D**. Cochrane Database Syst Rev. 2011 Dec 7;12:CD006002. Interferon alpha does not seem to cure hepatitis D in most patients. The agent seems effective in suppressing viral and liver disease activity in some patients, but this improvement is not sustained in the majority of patients.

Arora S, Thornton K, Murata G, et al. Outcomes of **treatment for hepatitis C infection by primary care providers**. N Engl J Med 2011;364:2199-2207

Chayama K, Takahashi S, Toyota J, et al. Dual therapy with the **NS5A inhibitor BMS-790052 and the NS3 protease inhibitor BMS-650032** in HCV genotype 1b-infected null responders. Hepatology 2011;55:742–748.

El-Serag Hashem B., **Hepatocellular Carcinoma**. N Engl J Med 2011;365:1118-27.

Kamar N, Bendall R, Legrand-Abravanel F, et al. **Hepatitis E**. Lancet. 2012 Apr 27.

Liao MT, Chang MH, Lin FG, et al. **Universal Hepatitis B Vaccination** Reduces Childhood Hepatitis B Virus-Associated Membranous Nephropathy. Pediatrics. 2011 Aug 22.

Lin ZH, Xin YN, et al. Performance of the **aspartate aminotransferase-to-platelet ratio index** for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 2011;53:726-736

Lo Re V 3rd, Teal V, Localio AR, et al. Relationship between **adherence to hepatitis C virus therapy** and virologic outcomes: a cohort study. Ann Intern Med. 2011 Sep 20;155(6):353-60.

Starr SP, Raines D. **Cirrhosis**: diagnosis, management, and prevention. Am Fam Physician. 2011 Dec 15;84(12):1353-9.

Tseng TC, Liu CJ, Yang HC, et al. High levels of **hepatitis B surface antigen increase risk of hepatocellular carcinoma** in patients with low HBV load. Gastroenterology 2012;142:1140–1149.

Wai CT, Greenson JK, Fontana RJ, et al. A **simple noninvasive index** can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology2003;38:518-526 (**APRI** scores)

HEPATITIS B REFERENCES:

1. Sherman M, Shafran S, Burak K, et al. Management of chronic hepatitis B: **consensus guidelines**. Can J Gastroenterol. 2007 Jun;21 Suppl C:5C-24C.
2. Lok AS, McMahon BJ. **American Association for the Study of Liver Diseases**. Chronic hepatitis B: update 2009. Hepatology. 2009 Sep;50(3):661-2.
3. European Association For The Study Of The Liver. EASL **Clinical Practice Guidelines**: management of chronic hepatitis B. J Hepatol. 2009 Feb;50(2):227-42.
4. Yang HI, Yuen MF, Chan HL, et al; REACH-B Working Group. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol. 2011 Jun;12(6):568-74.
5. Launay O, van der Vliet D, Rosenberg AR, et al; ANRS HB03 VIHVAC-B Trial. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA. 2011 Apr 13;305(14):1432-40.
6. Rapti IN, Hadziyannis SJ. Treatment of special populations with chronic hepatitis B infection. Expert Rev Gastroenterol Hepatol. 2011 Jun;5(3):323-39.
7. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology. 2009 Dec;50(6):2001-6.

Pregnancy References:

8. Pan CQ, Duan ZP, Bhamidimarri KR, Zou HB, Liang XF, Li J, Tong MJ. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. Clin Gastroenterol Hepatol. 2012 May;10(5):452-9.
9. Bzowej NH. Optimal Management of the Hepatitis B Patient Who Desires Pregnancy or Is Pregnant. Curr Hepat Rep. 2012 Jun;11(2):82-89.
10. Lam NC, Gotsch PB, Langan RC. Caring for pregnant women and newborns with hepatitis B or C. Am Fam Physician. 2010 Nov 15;82(10):1225-9.
11. Dusheiko G. Interruption of mother-to-infant transmission of hepatitis B: time to include selective antiviral prophylaxis? Lancet. 2012 May 26;379(9830):2019-21.
12. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat. 2009 Feb;16(2):94-103.
13. van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat. 2003 Jul;10(4):294-7.
14. ter Borg MJ, Leemans WF, de Man RA, Janssen HL. Exacerbation of chronic hepatitis B infection after delivery. J Viral Hepat. 2008 Jan;15(1):37-41.
15. Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol. 2011 Apr 15.
16. Lee C, Gong Y, Brok J, et al. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD004790. DOI: 10.1002/14651858.CD004790.pub2
17. Yang J, Zeng XM, Men YL, Zhao LS. Elective caesarean section versus vaginal delivery for preventing mother to child transmission of hepatitis B virus—a systematic review. Virol J. 2008 Aug 28;5:100.

Pediatric References:

18. Haber BA, Block JM, Jonas MM, et al; Hepatitis B Foundation. Recommendations for screening, monitoring, and referral of pediatric chronic hepatitis B. Pediatrics. 2009 Nov;124(5):e1007-13.
19. Lim SG, Ng TM, Kung N, et al; Emtricitabine FTCB-301 Study Group. A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B. Arch Intern Med. 2006 Jan 9;166(1):49-56.

Other References:

20. Canadian Liver Foundation. LIVERight: Healthy Living With Viral Hepatitis. March 2010. Accessed via http://www.liver.ca/files/PDF/Eng_Viral_Hep_WEB.pdf on August 9, 2011.
21. Cholongitas E, Goulis J, Akriviadis E, Papatheodoridis GV. Hepatitis B immunoglobulin and/or nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: A systematic review. Liver Transpl. 2011 Jun 7. doi: 10.1002/lt.22354.
22. Cooke GS, Main J, Thursz MR. Treatment for hepatitis B. BMJ. 2010 Jan 5;340:b5429. doi: 10.1136/bmj.b5429. Review.
23. Dienstag JL. Hepatitis B virus infection. N Engl J Med. 2008 Oct 2;359(14):1486-500. Review. Erratum in: N Engl J Med. 2010 Jul 15;363(3):298.
24. e-CPS. 2011.
25. Gish RG. Hepatitis B treatment: Current best practices, avoiding resistance. Cleve Clin J Med. 2009 May;76 Suppl 3:S14-9.
26. Holness G, Carriero DC, Dieterich DT. Hepatitis B therapies and antiviral resistance detection and management. Expert Rev Gastroenterol Hepatol. 2009 Dec;3(6):693-9. Review.
27. Janssen HL, van Zonneveld M, Senturk H, et al; HBV 99-01 Study Group; Rotterdam Foundation for Liver Research. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet. 2005 Jan 8-14;365(9454):123-9.

TOP

28. Janssen HL, Buster EH. Comments on the EASL practice guidelines for the management of chronic hepatitis B: controversies in interferon-based therapy. J Hepatol. 2009 Jul;51(1):224-6.
29. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. Clin Gastroenterol Hepatol. 2008 Dec;6(12):1315-41; quiz 1286. Epub 2008 Aug 23. Review.
30. Kumar M, Sarin SK. Systematic review: combination therapies for treatment-naïve chronic hepatitis B. Aliment Pharmacol Ther. 2008 Jun;27(12):1187-209. Review.
31. Lai CL, Yuen MF. Chronic hepatitis B--new goals, new treatment. N Engl J Med. 2008 Dec 4;359(23):2488-91.
32. Lai CL, Gane E, Hsu CW, et al. Two-year results from the **GLOBE trial** in patients with hepatitis B: greater clinical and antiviral efficacy for telbivudine (LdT) vs. lamivudine. [Abstract] HEPATOLOGY 2006;44:222A
33. Liaw YF, Sheen IS, Lee CM, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology. 2011 Jan;53(1):62-72. doi: 10.1002/hep.23952.
34. Lok AS, McMahon BJ. American Association for the Study of Liver Diseases. Chronic hepatitis B. Hepatology. 2007 Feb;45(2):507-39. Erratum in: Hepatology. 2007 Jun;45(6):1347.
35. Lam NC, Gotsch PB, Langan RC. Caring for pregnant women and newborns with hepatitis B or C. Am Fam Physician. 2010 Nov 15;82(10):1225-9. Review.
36. Martín-Carbonero L, Teixeira T, Poveda E, et al. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. AIDS. 2011 Jan 2;25(1):73-9.
37. Pascarella S, Negro F. Hepatitis D virus: an update. Liver Int. 2011 Jan;31(1):7-21. doi: 10.1111/j.1478-3231.2010.02320.x. Review.
38. Paul N, Han SH. Combination Therapy for Chronic Hepatitis B: Current Indications. Curr Hepat Rep. 2011 Jun;10(2):98-105.
39. Public Health Agency of Canada: Hepatitis G Fact Sheet. 2003. Accessed via http://www.phac-aspc.gc.ca/hcai-iamss/bbp-pts/hepatitis/hep_g-eng.php on August 9, 2011.
40. Roque-Afonso AM, Desbois D, Dussaix E. Hepatitis A Virus: Serology and Molecular Diagnostics. Future Virology. 2010;5(2):233-242. Accessed via http://www.medscape.com/viewarticle/719977 on Aug 8, 2011.
41. Shamliyan TA, MacDonald R, Shaukat A, et al. Antiviral therapy for adults with chronic hepatitis B: a systematic review for a National Institutes of Health Consensus Development Conference. Ann Intern Med. 2009 Jan 20;150(2):111-24.
42. Singh AE, Plitt SS, Osiowy C, et al. Factors associated with vaccine failure and vertical transmission of hepatitis B among a cohort of Canadian mothers and infants. J Viral Hepat. 2011 Jul;18(7):468-73. doi: 10.1111/j.1365-2893.2010.01333.x.
43. Sorrell MF, Belongia EA, Costa J, et al. **National Institutes of Health consensus development conference statement: management of hepatitis B.** Hepatology. 2009 May;49(5 Suppl):S4-S12.
44. Standring DN, Seifer M, Patty A, et al. HBV resistance determination from the telbivudine globe registration trial. J Hepatol 2006;44:S191.
45. Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther. 2008 Nov 1;28(9):1067-77.
46. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. Hepatology. 2009 May;49(5):1503-14.
47. Tong MJ, Hsu L, Chang PW, Blatt LM. Evaluation of current treatment recommendations for chronic hepatitis B: a 2011 update. J Gastroenterol Hepatol. 2011 May;26(5):829-35. doi: 10.1111/j.1440-1746.2011.06623.x.
48. Wakim-Fleming J. Hepatic encephalopathy: Suspect it early in patients with cirrhosis. Cleveland Clinic Journal of Medicine 2011; 78(9):597-605.
49. WHO. Hepatitis E Fact Sheet No. 280(Revised January 2005). Accessed via http://www.who.int/mediacentre/factsheets/fs280/en/ on August 9, 2011.
50. Wilkins T, Zimmerman D, Schade RR. Hepatitis B: diagnosis and treatment. Am Fam Physician. 2010 Apr 15;81(8):965-72.
51. Gish R, Jia JD, Locarnini S et al. Selection of chronic hepatitis B therapy with high barrier to **resistance**. Lancet Infect Dis. 2012 Feb 8.
52. Lok AS, Ward JW, Perrillo RP, et al. **Reactivation of hepatitis B** during immunosuppressive therapy: potentially fatal yet preventable. Ann Intern Med. 2012 May 15;156(10):743-5.

REFERENCES –HEPATITIS C

1. Myers RP, Ramji A, Bilodeau M, Wong S et al. An update on the management of hepatitis C: **Consensus guidelines from the Canadian Association for the Study of the Liver**. Can J Gastroenterol. 2012 Jun;26(6):359-75.
2. European Association for the Study of the Liver. **EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.** J Hepatol. 2011 Aug;55(2):245-64.
3. Ghany MG, Strader DB, Thomas DL, Seeff LB; **American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update.** Hepatology. 2009 Apr;49(4):1335-74.
4. Sulkowski MS, Cooper C, Hunyady B, et al. Management of adverse effects of Peg-IFN and ribavirin therapy for hepatitis C. Nat Rev Gastroenterol Hepatol. 2011 Apr;8(4):212-23
5. Koirala J, Gandotra SD, Rao S, et al. Granulocyte colony-stimulating factor dosing in pegylated interferon alpha-induced neutropenia and its impact on outcome of anti-HCV therapy. J Viral Hepat. 2007 Nov;14(11):782-7.
6. FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease. 2011 June 24. Accessed via http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm#table on August 10, 2011.
7. Bloom RD, Lake JR. Emerging issues in hepatitis C virus-positive liver and kidney transplant recipients. Am J Transplant. 2006 Oct;6(10):2232-7.
8. Guitard J, Rostaing L, Kamar N. New-onset diabetes and nephropathy after renal transplantation. Contrib Nephrol. 2011;170:247-55.
9. Fabrizi F, Messa P, Martin P, Takkouche B. Hepatitis C virus infection and post-transplant diabetes mellitus among renal transplant patients: a meta-analysis. Int J Artif Organs. 2008 Aug;31(8):675-82. Review.
10. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. Hepatology. 2010 Apr;51(4):1176-84.
11. Afdhal NH, Dieterich DT, Pockros PJ, et al; Proactive Study Group. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology. 2004 May;126(5):1302-11.
12. Aghemo A, Rumi MG, Colombo M. Pegylated interferons alpha2a and alpha2b in the treatment of chronic hepatitis C. Nat Rev Gastroenterol Hepatol. 2010 Sep;7(9):485-94. Review.
13. Albeldawi M, Ruiz-Rodriguez E, Carey WD. Hepatitis C virus: Prevention, screening, and interpretation of assays. Cleve Clin J Med. 2010 Sep;77(9):616-26. Review.
14. Alberti A, Clumeck N, Collins S, et al; ECC Jury. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol. 2005 May;42(5):615-24. Review. Erratum in: J Hepatol. 2005 Dec;43(6):1098.
15. Ascione A, De Luca M, Tartaglione MT, et al. **Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection.** Gastroenterology. 2010 Jan;138(1):116-22.

TOP

16. Bacon BR, Gordon SC, Lawitz E, et al; **HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection.** N Engl J Med. 2011 Mar 31;364(13):1207-17.
17. Buxton JA, Kim JH. Hepatitis A and hepatitis B vaccination responses in persons with chronic hepatitis C infections: A review of the evidence and current recommendations. Can J Infect Dis Med Microbiol. 2008 Mar;19(2):197-202.
18. e-CPS. 2011.
19. Ferguson MC. Current therapies for chronic hepatitis C. Pharmacotherapy. 2011 Jan;31(1):92-111. Review.
20. Freedman ND, Curto TM, Lindsay KL, et al; **HALT-C** TRIAL GROUP. Coffee consumption is associated with response to peginterferon and ribavirin therapy in patients with chronic hepatitis C. Gastroenterology. 2011 Jun;140(7):1961-9.
21. Freedman ND, Everhart JE, Lindsay KL et al; **HALT-C** Trial Group. Coffee intake is associated with lower rates of liver disease progression in chronic hep C. Hepatology. 2009 Nov;50(5):1360-9.
22. Hadigan C, Kottilil S. Hepatitis C virus infection and coinfection with human immunodeficiency virus: challenges and advancements in management. JAMA. 2011 Jul 20;306(3):294-301.
23. Jacobson IM, McHutchison JG, Dusheiko G, et al; **ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection.** N Engl J Med. 2011 Jun 23;364(25):2405-16.
24. Jou JH, Muir AJ. In the clinic. Hepatitis C. Ann Intern Med. 2008 Jun 3;148(11):ITC6-1-ITC6-16. Review.
25. Mauss S, Hueppe D, John C, et al. Estimating the likelihood of sustained virological response in chronic hepatitis C therapy. J Viral Hepat. 2011 Apr;18(4):e81-90. doi: 10.1111/j.1365-2893.2010.01372.x.
26. McHutchison JG, Lawitz EJ, Shiffman ML, et al; **IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.** N Engl J Med. 2009 Aug 6;361(6):580-93. Erratum in: N Engl J Med. 2009 Sep 3;361(10):1027.
27. Muir AJ, Hu KQ, Gordon SC, et al. Hepatitis C treatment among racial and ethnic groups in the IDEAL trial. J Viral Hepat. 2011 Apr;18(4):e134-43. doi: 10.1111/j.1365-2893.2010.01402.x.
28. Nash KL, Bentley I, Hirschfield GM. Managing hepatitis C virus infection. BMJ. 2009 Jun 26;338:b2366. doi: 10.1136/bmj.b2366. Review.
29. Poordad F, McCone J Jr, Bacon BR, et al; **SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection.** N Engl J Med. 2011 Mar 31;364(13):1195-206.
30. Rosen HR. Clinical practice. Chronic hepatitis C infection. N Engl J Med. 2011 Jun 23;364(25):2429-38. Review.
31. Rosenberg P, Hagen K. Serum B12 levels predict response to treatment with interferon and ribavirin in patients with chronic HCV infection. J Viral Hepat. 2011 Feb;18(2):129-34. doi: 10.1111/j.1365-2893.2010.01288.x.
32. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology. 2010 Jan;138(1):108-15.
33. Sherman M, Cohen L, Cooper MA, et al. Clinical recommendations for the use of recombinant human erythropoietin in patients with hepatitis C virus being treated with ribavirin. Can J Gastroenterol. 2006 Jul;20(7):479-85. Review.
34. Sherman M, Shafran S, Burak K, et al. **Management of chronic hepatitis C: consensus guidelines.** Can J Gastroenterol. 2007 Jun;21 Suppl C:25C-34C.
35. Sockalingam S, Abbey SE. Managing depression during hepatitis C treatment. Can J Psychiatry. 2009 Sep;54(9):614-25. Review.
36. Sockalingam S, Links PS, Abbey SE. Suicide risk in hepatitis C and during interferon-alpha therapy: a review and clinical update. J Viral Hepat. 2011 Mar;18(3):153-60. doi: 10.1111/j.1365-2893.2010.01393.x.
37. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV co-infection. AIDS. 2004 Jan 2;18(1):1-12. Review.
38. Spradling PR, Richardson JT, Buchacz K, et al; HIV Outpatient Study Investigators. Trends in hepatitis C virus infection among patients in the HIV Outpatient Study, 1996-2007. J Acquir Immune Defic Syndr. 2010 Mar 1;53(3):388-96.
39. Stravitz RT, Chung H, Sterling RK, et al. Antibody-mediated pure red cell aplasia due to epoetin alfa during antiviral therapy of chronic hepatitis C. Am J Gastroenterol. 2005 Jun;100(6):1415-9.
40. Sulkowski MS. Anemia in the treatment of hepatitis C virus infection. Clin Infect Dis. 2003;37 Suppl 4:S315-22.
41. Teshale EH. Hepatitis B. CDC Yellow Book. Accessed via <http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.htm> on August 29, 2011.
42. Vellozzi C, Buchacz K, Baker R, et al; HOPS Investigators. Treatment of hepatitis C virus (HCV) infection in patients coinfected with HIV in the HIV Outpatient Study (HOPS), 1999-2007. J Viral Hepat. 2011 May;18(5):316-24. doi: 10.1111/j.1365-2893.2010.01299.x.
43. Vezali E, Aghemo A, Colombo M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis. Clin Ther. 2010 Dec;32(13):2117-38. Review.
44. Vezali E, Aghemo A, Colombo M. Interferon in the treatment of chronic hepatitis C: a drug caught between past and future. Expert Opin Biol Ther. 2011 Mar;11(3):301-13.
45. Wakim-Fleming J. Hepatic encephalopathy: Suspect it early in patients with cirrhosis. Cleveland Clinic Journal of Medicine 2011; 78(9):597-605.
46. Zeuzem S, Andreone P, Pol S, et al; **REALIZE** Study Team. **Telaprevir** for retreatment of HCV infection**.** N Engl J Med. 2011 Jun 23;364(25):2417-28.
47. Sherman KE, Flamm SL, Afdhal NH, et al. **ILLUMINATE** Study Team. Response-guided **telaprevir** combination treatment for hepatitis C virus infection. N Engl J Med. 2011 Sep 15;365(11):1014-24.
48. Di Bisceglie AM, Stoddard AM, Dienstag JL, et al. **HALT-C** Trial Group. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. Hepatology. 2011 Apr;53(4):1100-8. doi:10.1002/hep.24169.
49. Morgan TR, Ghany MG, Kim HY, et al. **HALT-C** Trial Group. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010 Sep;52(3):833-44.
50. Di Bisceglie AM, Shiffman ML, Everson GT, et al. **HALT-C** Trial Investigators. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med. 2008 Dec 4;359(23):2429-41.
51. Foote BS, Spooner LM, Belliveau PP. **Boceprevir**: a protease inhibitor for the treatment of chronic hepatitis C. Ann Pharmacother. 2011 Sep;45(9):1085-93.
52. Rowe IA, Mutimer DJ. **Protease inhibitors** for treatment of genotype 1 hepatitis C virus infection. BMJ. 2011 Nov 10;343:d6972. doi: 10.1136/bmj.d6972.
53. Lok AS et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med 2012 Jan 19; 366:216. (60 mg daily of daclatasvir (an NS5A replication complex inhibitor) and 600 mg twice daily of asunaprevir (an NS3 protease inhibitor)).
54. FDA Feb/12 notified healthcare professionals and patients that drug interactions between the hepatitis C virus (HCV) protease inhibitor Victrelis (**boceprevir**) and certain **ritonavir-boosted** human immunodeficiency virus (HIV) protease inhibitors (atazanavir, lopinavir, darunavir) can potentially reduce the effectiveness of these medicines when they are used together.
55. Centers for Disease Control and Prevention (CDC). Transmission of hepatitis C virus through **transplanted organs and tissue**--Kentucky and Massachusetts, 2011. MMWR Morb Mortal Wkly Rep. 2011 Dec 23;60(50):1697-700.
56. FDA Mar/12 notified healthcare professionals of updates to the prescribing information concerning interactions between protease inhibitors (HIV & HCV) and certain **statin drugs**. Protease inhibitors and statins taken together may raise the blood levels of statins and increase the risk for muscle injury (myopathy/ rhabdomyolysis).
57. Alkhouri N, Zein NN. **Protease inhibitors**: Silver bullets for chronic hepatitis C infection? Cleve Clin J Med. 2012 Mar;79(3):213-22.
58. Ly KN, Xing J, Klevens RM et al. The increasing burden of **mortality** from viral **hepatitis** (**esp C**) in the United States between 1999 and 2007. Ann Intern Med. 2012 Feb 21;156(4):271-8.
59. Liu S, Cipriano LE, Holodniy M, Owens et al. New **protease inhibitors** for the treatment of chronic hepatitis C: a **cost-effectiveness** analysis. Ann Intern Med. 2012 Feb 21;156(4):279-90.
60. Rein DB, Smith BD, Wittenborn JS, et al. The cost-effectiveness of **birth-cohort screening** for hepatitis C antibody in U.S. primary care settings. Ann Intern Med. 2012;156:263-70.

TOP

61. Hoofnagle JH, Seeff LB. **Peginterferon and ribavirin** for chronic hepatitis C. N Engl J Med. 2006;355:2444-51.
62. Hadigan C, Kottilil S. **Hepatitis C** virus infection **and** coinfection with **human immunodeficiency virus (HIV)**: challenges and advancements in management. JAMA. 2011 Jul 20;306(3):294-301.
63. Sterling RK, Wright EC, et al. Frequency of elevated hepatocellular carcinoma-HCC **biomarkers** (AFP-fetoprotein) in patients with advanced hepatitis C. Am J Gastroenterol. 2012 Jan;107(1):64-74.
64. FDA notified healthcare professionals that the Victrelis drug label has been revised to state that co-administration of Victrelis (**boceprevir**), a hepatitis C virus (HCV) protease inhibitor, along with certain **ritonavir**-boosted human immunodeficiency virus (HIV) protease inhibitors, is not recommended. The findings of a drug-drug interaction study and clinical trial showed that co-administration increased of the possibility of reducing the effectiveness of the medicines, permitting the amount of HCV or HIV virus in the blood to increase. Ritonavir-boosted HIV protease inhibitors include ritonavir-boosted Reyataz (atazanavir), ritonavir-boosted Prezista (darunavir), and Kaletra (lopinavir/ritonavir).
65. Spaulding AC, Thomas DL. **Screening for HCV infection in jails**. JAMA. 2012 Mar 28;307(12):1259-60.
66. McGilvray I, et al. **Hepatic Cell-Type Specific Gene Expression** Better Predicts HCV Treatment Outcome Than **IL28B Genotype**. Gastroenterology. 2012 May;142(5):1122-1131.e1.
67. Levitsky J, Fiel MI, Norvell JP, et al. Risk for immune-mediated **graft dysfunction in liver transplant** recipients with recurrent HCV infection treated with pegylated interferon. Gastroenterology. 2012 May;142(5):1132-1139.e1.
68. El-Serag HB. Epidemiology of viral hepatitis and **hepatocellular carcinoma (HCC)**. Gastroenterology. 2012 May;142(6):1264-1273.e1.
69. Naggie S, et al. Management of Patients **Coinfected With HCV and HIV**: A Close Look at the Role for Direct-Acting Antivirals. Gastroenterology. 2012 May;142(6):1324-1334.e3.
70. Crespo G, Mariño Z, Navasa M, Forns X. Viral hepatitis in **liver transplantation**. Gastroenterology. 2012 May;142(6):1373-1383.e1.
71. Grebely J, Prins M, Hellard M, et al. on behalf of the International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC(3)). Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of **injecting drug users**: towards a vaccine. Lancet Infect Dis. 2012 May;12(5):408-414.
72. CDC: All baby boomers should be tested for hepatitis C, according to draft guidelines proposed by the CDC. The CDC estimates that 1 in 30 boomers, those born from 1945 through 1965, is infected with hepatitis C and most are unaware of their infection status. http://www.cdc.gov/nchhstp/newsroom/HepTestingRecsPressRelease2012.html
73. Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of **general population screening for hepatitis C**. Clin Infect Dis. 2012 May;54(9):1259-71.
74. Pearlman BL. **Protease inhibitors** for the treatment of chronic hepatitis C genotype-1 infection: the new standard of care. Lancet Infect Dis. 2012 May 28.
75. Pol S, Ghalib RH, Rustgi VK, et al. **Daclatasvir** for previously untreated chronic hepatitis C genotype-1 infection: a randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. Lancet Inf Dis 2012.
76. Lok A, Gardiner D, Hézode C, et al. Confi rmation that quadruple therapy with **daclatasvir** (NS5A inhibitor), **asunaprevir** (NS3 inhibitor) and peginterferon/ribavirin results in a high rate of SVR4 in HCV genotype 1 null responders. J Hepatol 2012; 56 (suppl 2): S557.
77. Suzuki F, Ikeda K, Toyota J, et al. Dual oral therapy with the NS5A inhibitor daclatasvir (BMS-790052) and NS3 protease inhibitor asunaprevir (BMS-650032) in HCV genotype 1b-I infected null responders or ineligible/ intolerant to peginterferon/ribavirin. J Hepatol 2012; 56 (suppl 2): S7–S8.
78. Clark PJ, Muir AJ. Overcoming barriers to care for hepatitis C. N Engl J Med. 2012 Jun 28;366(26):2436-8.
79. Rumi M, Aghemo A, Prati GM. Comparative trials of peginterferon α2a and peginterferon α2b for chronic hepatitis C. J Viral Hepat. 2012 Jan;19 Suppl 1:37-41.
80. Brennan BJ, Xu ZX, Grippo J. Effect of peginterferon alfa-2a (40KD) on cytochrome P450 isoenzyme activity. Br J Clin Pharmacol. 2012 Jul 6.
81. Centers for Disease Control and Prevention. Updated recommendations on managing HBV-infected providers, students.. MMWR 2012;61(No. RR-3):pg1-10.
82. Pol S, Ghalib RH, Rustgi VK, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection:a randomised, parallel-group, double-blind, placebo-controlled, dose-finding,phase 2a trial. Lancet Infect Dis. 2012 Jun 15.
83. Welzel TM, Zeuzem S. NS5A inhibitors to treat hepatitis C virus infection. Lancet Infect Dis. 2012 Jun 15.

TOP

Acknowledgements: Contributors & Reviewers: M. Foisy Pharm D, L. Sulz Pharm D, Dr. K Williams, Dr. S Skinner, Dr. T Penrod
Tessa Laubscher (CCFP, College of Medicine, U of S, Saskatoon) & the RxFiles Advisory Committee.
Prepared by: *Shannon Stone BSP (RxFiles / Positive Living Program - Saskatoon Health Region)*

Extras

Combos to Avoid: Early virologic failure: abacavir + lamivudine (or emtricitabine) + tenofovir ; didanosine + lamivudine (or emtricitabine) + tenofovir; didanosine + tenofovir + NNRTI; didanosine + emtricitabine(lamivudine) + atazanavir; Caution: emtricitabine(or lamivudine) + tenofovir + nevirapine [69] (early virologic failure in small clinical trials; ARTEN [70] trial: may be okay)

↑SE: Didanosine + stavudine (peripheral neuropthy, pancreatitis & lactic acidosis); ATV + IDV ↑bilirubin; 2 NNRTI regimen Antagonism: stavudine + zidovudine

- Oral contraceptives + non-ritonavir boosted atazanavir (may ↑ hormone levels; ⇨use lowest dose OC)[71] or indinavir (will maintain hormone levels)

{Refractory large volume diarrhea, HIV related: octreotide (50-500mcg sc tid)[$$$] }[72,73]

References – HIV Drug Treatment – www.RxFiles.ca

[1] Micromedex. 2011.
[2] Association CP. Compendium of Pharmaceuticals and Specialties; 2009.
[3] Briggs G, Freeman, Roger, Yaffe, Sumner, ed. *Drugs in Pregnancy and Lactation.* 9th ed: TechBooks
[4] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1-128. Available at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf . Accessed Nov 6, 2008
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1–166. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf . Accessed 10 Jan 2011
[5] Hammer SM, Eron JJ, Reiss P, et al. Antiretroviral treatment if adult HIV infection 2008 Recommendations of the International AIDS society-USA panel. JAMA. 2008; 300(5):555-70. ; Thompson MA;. Aberg JA; Cahn P, et al. Antiretroviral Treatment of Adult HIV Infection: 2010 Recommendations of the International AIDS Society-USA Panel JAMA. 2010;304(3):321-333.
[6] Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. July 8, 2008. 1-103. Avalaible at http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf . Accessed May 29, 2008
[7] Borra´s-Blasco1 J, Navarro-Ruiz A, Borra´s C and Castera´ E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J of Antimic Chem. Advanced access published July23, 2008
[8] Clay PG. The abacavir hypersensitivity reaction: a review. Clin Ther 2002; 24: 1502–14.
[9] Mallal S, Phillips E, Giampiero C, Molina J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-79
[10] Hughes CA, Foisy MM, Dewhurst N, et al. Abacavir hypersensitivity reaction: An update. Ann Pharmacoth 2008;42:387-96 {Note, if 2 symptoms from 2 symptom groups , most likely HSR rx}
[11] Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. Ann Pharmacother 1997;31: 633–5.
[12] Briggs G, Freeman, Roger, Yaffe, Sumner, ed. Drugs in Pregnancy and Lactation. 9th ed: TechBooks
[13] Micromedex. 2008
[14] Friis-Medler N, Reiss P, Sabin CA, Weber R et al. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356:1723-35. 15 D:A:D Study Group, Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, D'Arminio Monforte A, Friis-Møller N, Kirk O, Pradier C, Weller I, Phillips AN, Lundgren JD.Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008 Apr 26;371(9622):1417-26. Epub 2008 Apr 2. Erratum in: Lancet. 2008 Jul 26;372(9635):292.
[16] Medical Letter Inc. Drugs for HIV infection. Treat Guidel Med Lett. 2006 Oct;4(50):67-76. (Updated Feb 2009 & June 2011.)
[17] De Wit S, Sabin CA, Weber R, et al. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Diabetes Care. 2008 Jun;31(6):1224-9. Epub 2008 Feb 11.
[18] Boyd M, Reiss P. The long-term consequences of antiretroviral therapy: a review. J HIV Ther. 2006 Jun;11(2):26-35.
[19] Sax PE, Tierney C, Collier AC, et al. Aabacavir-lamivudine versus tenofovir-emtricitabine fo initial HIV-1 therapy. N Engl J Med 2009;361 :2230-40.
[20] Madruga JVR, Cassetti I, Suleiman JMAH, Zhong L, Enejosa J, Cheng AK. Improvement in lipoatrophy and lipid abnormalities following switch from stavudine (d4T) to tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in HIV-infected patients: a 48 week follow up from Study 903e. Program and abstracts of the 3rd International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract TuPe2.2B12.
[21] Moyle G, Sabin C, Cartledge J, Reilly G, et al. Factors associated with limb fat recovery in a prospective randomised comparative study of thymidine replacement with either tenofovir DF or abacavir in persons with clinical lipoatrophy. Program and abstracts of the 10th European AIDS Conference; November 17-20, 2005; Dublin, Ireland. Abstract PE9.3/2.
[22] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1-128. Available at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf . Accessed May 29, 2008
[23] Yakiwchuk EM, Foisy MM, Hughes CA. Complexity of interactions between voriconazole and antiretroviral agents. Ann pharmacoth. 2008 May;42(5):698-703(Epub 2008 Apr 15)
[24] Torti C, Costarelli S, De Silvestri A, et al. Analysis of severe hepatic events associated with nevirapine-containing regimens: CD4+ T-cell count and gender in hepatitis C seropositive and seronegative patients. Drug Saf 2007; 30: 1161–9
[25] Medical Letter inc. Etravirine(Intelence) for HIV infection. Med Lett Drugs Ther. 2008 Jun 16;50(1288):47-8
[26] Kiser JK. Pharmacologic characteristics of investigational and recently approved agents for the treatment of HIV. Curr Opin HIV AIDS 2008, 3:330-41
[27] Sheehan NL, Kelly DV, Tseng AL, van Heeswijk RPG, Beique LC, Hughes CA. Evaluation of HIV drug interaction websites. Ann Pharmacoth 2003;37:1577-86

TOP

[28] Malan DR, Krantz E, David N, Wirtz V, Hammond J, McGrath D; 089 Study Group. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. J Acquir Immune Defic Syndr. 2008 Feb 1;47(2):161-7.
[29] Boyd M, Reiss P. The long-term consequences of antiretroviral therapy: a review. J HIV Ther. 2006 Jun;11(2):26-35.
[30] Foisy MM; Yakiwchuk EMK; Chiu I; Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Medicine. 9(6) July 2008 , 389-96
[31] Agarwala S, Eley TVC, Child M, et al. Pharmacokinetic effect of famotidine on atazanavir with and without ritonavir in healthy subjects (abstract 11). Presented at: 6th International Annual Workshop on Clinical Pharmacology on HIV Therapy, April 28-30,2005.
[32] Agarwala S, Gray K, Wang Y, Grasela D. Pharmacokinetic effect of omeprazole on atazanavir co-administered with ritonavir in healthy subjects (abstract 658). Presented at: 12th Conference on Retroviruses and Opportunistic Infections, Boston, February 22-25, 2005
[33] Eley T, Zhu L, Dragone J, Persson A, Filoramo D, Li T, et al. Effect of omeprazole 20 mg daily on the bioavailability of multiple-dose atazanavir with ritonavir in healthy subjects [abstract 66]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.
[34] Khanlou H, Allavena C, Billaud E, et al. Development of hepatic cytolysis after switching from enfuvirtide to raltegravir in virologically suppressed patients treated with tipranavir/ritonavir. XVII International AIDS Conference. August 3-8, 2008. Mexico City. Abstract TUPE0087.
[35] CB Hicks et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment –experienced HIV-1 infected pateients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. Lancet 2006; 368: 466
[36] Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 2010 Feb 1;201(3):318-30.
[37] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1-128. Available at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf . Accessed May 29, 2008
[38] Dicenzo R, Luque A, Larppanichpoonphol P, et al. Association of total bilirubin with indinavir and lopinavir plasma concentrations in HIV-infected patients receiving three double-boosted dosing regimens. J Antimicrob chemother 2006 Aug: 58(2):393-400
[39] New drug: Celsentri(maraviroc). Pharmacist's Letter/Prescriber's Letter 2007; 23(11):231118
[40] Ndegwa S. Maraviroc (Celsentri®) for multidrug-resistant human immunodeficiency virus (HIV)-1. [Issues in emerging health technologies issue 110]. Canadian Agency for Drugs and Technologies in Health; 2007.
[41] New HIV drug: Isentress (raltegravir). Pharmacist's Letter/Prescriber's Letter 2008; 24(1):240177.
[42] Yazdanpanah Y, Fagard C, Descamps D, et al. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV: results of the ANRS 139 TRIO trial. Clin Infect Dis. 2009 Nov 1;49(9):1441-9.
[43] El-Ibiary, Shareen Y. and Cocohoba, Jennifer M. (2008) 'Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives', The European Journal of Contraception & Reproductive Health Care, 1-10 To link to this article: http://dx.doi.org/10.1080/13625180701829952.
Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives (esp injectables) & risk of HIV-1 transmission: a prospective cohort study. Lancet Infect Dis 2011; online Oct 4, 2011.
44 Heikinheimo O, Lehtovirta P, Aho I, Ristola M, Paavonen J. The levonorgestrel-releasing intrauterine system in human immunodeficiency virus-infected women: a 5-year follow-up study. Am J Obstet Gynecol. 2010 Oct 28.[Epub ahead of print]
[45] Law MG, Friis-Moller N, El-Sadr WM, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D study. HIV Med. 2006;7:218-30.
[46] Martinez E, Leyes P, Ros E. Effectiveness of lipid lowering therapy in HIV patients. Curr Opin HIV AIDS 2008; 3:240-6.
[47] Burger D, Stroes E, Reiss P. Drug interactions between statins and antiretroviral agents. Curr Opin HIV AIDS 2008; 3:247-51.
[48] Calza L, Manfredo R, Colangeli V, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidemaemia. AIDS 2005;19:1051-58.
[49] Kiser JJ, Gerber JG, Predhomme JA, et al, Drug/drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. J Acquir Immune Defic Syndr 2008;47:570-8.
[50] Wohl D, Hsue P, Richard P, et al. Ezetimibe's effects on the LDL cholesterol levels of HIV-infected patients receiving HAART. Abstracts and posters of the 14th Conference on Retroviruses and Opportunistic Infections, February 25-28, 2007; Los Angeles, CA.
Singh S, Willig JH, Mugavero MJ, et al. Comparative Effectiveness and Toxicity of Statins Among HIV-Infected Patients. Clin Infect Dis. 2010 Dec 28.
[51] Wohl DA, Tien HC, Busby M, et al. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counseling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. Clin Infect Dis. 2005 Nov 15;41(10):1498-504. Epub 2005 Oct 11.
[52] Calza L, Manfredi R, Colangeli V, et al. Substitution for nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidemia. AIDS 2005; 19:1051-58.
[53] Busse KH, Hadigan C, Chairez C, et al. Gemfibrozil Concentrations Are Significantly Decreased in the Presence of Lopinavir–Ritonavir. J Acquir Immune Defic Syndr 2009;52:235–239)
[54] Pecora Fulco P, Vora UB, Bearman GML. Acid suppressive therapy and the effects on protease inhibitors. Ann Pharmacoth 2006;40:1974-83.
[55] Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. N Engl J Med. 2000 May 11;342(19):1416-29.
56 Mast EE, Weinbaum CM, Fiore AE, et al. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: Immunization of Adults. 2006. 55(RR16);1-25
[57] Morse Caryn G, Kovacs Joseph A. Metabolic and skeletal complications of HIV infection: The price of success. JAMA. 2006;296(7):844-854. Available at http://jama.ama-assn.org/cgi/content/full/296/7/844
[58] Bruera D, Luna N, David DO, Bergoglio LM, Zamudio J. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS. 2003:17:1917-1923
[59] McComsey GA, Kendall MA, Tebas P, Swindells S, Hogg E, Alston-Smith B, et al. Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV. AIDS 2007; 21(18):2473-2482.
[60] Mondy K, Powderly WG, Claxton SA, et al. Alendronate, Vitamin D, and Calcium for the treatment of osteopenia/osteoporosis associated with HIV infection. J Acquir Immune Defic Syndr 2005;38(4):426-431
[61] Negredo E, Martinez-Lopez E, Paredes R, Rosales J, Perez-Alvarez N, Holgado S, et al. Reversal of HIV-1-associated osteoporosis with once-weekly alendronate. AIDS 2005;19(3):343-5
McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010 Oct 15;51(8):937-46.
[62] Clay P, Voss LE, Williams C, Daume EC. Valid treatment options for osteoporosis and osteopenia in HIV-infected persons. Ann Pharmacother 2008;42:670-9
[63] Sande MA, Eliopoulous GM, Moellering RC Jr, Gilbert DN. The Sanford guide to HIV/AIDS therapy 2008, 16th edition: Antimicrobial Therapy Inc.
[64] Gilbert DN, Moellering RC Jr, Eliopoulous GM, Sande MA. The Sandford guide to antimicrobial therapy 2008, 38th edition: Antimicrobial therapy Inc.
[65] Recommendations of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. June 18, 2008; 1-286. Available at: http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf Accessed July 22, 2008
[66] Recommendations of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. June 18, 2008; 1-286. Available at: http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf Accessed July 22, 2008

TOP

[67] The Strategies for Management of Antiretroviral Therapy (SMART) study group. CD4+ count-guided interruption of antiretroviral treatment. N Engl J med 2006;355:2283-96.

[68] Devesh J. Dhasmana,1 Keertan Dheda,2,3 Pernille Ravn,4 Robert J. Wilkinson5, Graeme Meintjes. Immune Reconstitution Inflammatory Syndrome in HIV-Infected Patients Receiving Antiretroviral Therapy: Pathogenesis, Clinical Manifestations and Management. Drugs 2008; 68 (2): 191-208.

[69] Rey D, Schmitt M, Meyer P, et al. Early virologic non-response to once daily combination of lamivudine, tenofovir, and nevirapine in antiretroviral naïve HIV-infected patients: Preliminary results of the DAUFIN study. Abstracts and posters of the Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 503, 2007.

70 Soriano V, Koppe S, Migrono H, et al. Prospective randomized comparison of nevirapine and atazanavir/ritonavir both combined with tenofovir DF/emtricitabine in treatment-naïve HIV-1 infected patients: ARTEN Study week 48 results. Paper presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; July 19-22, 2009; Cape Town, South Africa. Abstract LBPEB07

[71] Toronto general hospital – Immunodeficiency clinic website-Drug interactions. Accessed 14July, 2008

[72] Garcia Compean D, Ramos Jimenez J, et al. Octreotide therapy of large-volume refractory AIDS-associated diarrhea: a randomized controlled trial. AIDS. 1994 Nov;8(11):1563-7.

[73] Simon DM, Cello JP, Valenzuela J, et al. Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome-associated diarrhea. Gastroenterology. 1995 Jun;108(6):1753-60. Erratum in: Gastroenterology 1995 Sep;109(3):1024.

Other articles of interest:

1. McCabe S, Ma Q, Slish J, Catanzaro L, Sheth N, DiCenzo R, et al. Antiretroviral Therapy Pharmacokinetic Considerations in Patients with Renal or Hepatic Impairment. Clin Pharmacokinet 2008; 47(3)153-172.
2. Spray J, Willett K, Chase D, Sindelar R, Connelly S; Dosage adjustment for hepatic dysfunction based on Child-Pugh score. Am J Health-Syst Pharm 2007; 64: Apr; 690,692
3. Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection.N Engl J Med. 2000 May 11;342(19):1416-29.
4. Lopez Bernaldo de Quiros JC, Miro JM, et al. Grupo de Estudio del SIDA 04/98. A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. N Engl J Med. 2001 Jan 18;344(3):159-67.
5. Feldman, Charles. Pneumonia associated with HIV infection. Curr Opin Infect Dis 18:165–170
6. Croxtall JD, Lyseng-Williamson KA, Perry CM. Raltegravir. Drugs 2008: 68(1):131-138
7. Dhasmana DJ, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients receiving antiretroviral therapy: Pathogenesis, clinical manifestations and management. Drugs;68(2)191-208.
8. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ. 2009 Jan 26;338:a3172. doi: 10.1136/bmj.a3172.
9. Kitahata MM, Gange SJ, Abraham AG, et al.; the NA-ACCORD Investigators. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. N Engl J Med. 2009 Apr 1. [Epub ahead of print]
10. Health Canada June/09 is Warning Canadians Not to Use Clean Testing HIV Home Test Kit, or Any Home HIV Test Kit
11. Kovacs JA, Masur H. Evolving health effects of Pneumocystis: one hundred years of progress in diagnosis and treatment. JAMA. 2009 Jun 24;301(24):2578-85.
12. Health Canada July/09: Association of TELZIR (fosamprenavir) with a potential increased risk of myocardial infarction. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/telzir_hpc-cps-eng.php
13. Gutiérrez-Valencia A, et al. for the Sociedad Andaluza de Enfermedades Infecciosas. Stepped-Dose vs. Full-Dose Efavirenz for HIV Infection and Neuropsychiatric Adverse Events: A Randomized Trial. Ann Intern Med. 2009 Jul 6. [Epub ahead of print]
14. Kredo T, Van der Walt JS, Siegfried N, et al. Therapeutic drug monitoring of antiretrovirals for people with HIV. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007268.
15. Rerks-Ngarm S et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009 Oct 20; [e-pub ahead of print].
16. Aslangul E, Assoumou L, Bittar R, et al. Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients (n=88) receiving protease inhibitors: a randomized trial. AIDS. 2009 Oct 15.
17. Landovitz, Raphael J., Currier, Judith S. Postexposure Prophylaxis for HIV Infection. N Engl J Med 2009 361: 1768-1775.
18. Centers for Disease Control and Prevention (CDC). Updated interim recommendations — HIV-infected adults and adolescents: Considerations for clinicians regarding 2009 H1N1 influenza. Oct 21 , 2009. (http://www.cdc.gov/h1n1flu/guidance_HIV.htm)
19. Silverberg MJ, Leyden W, Hurley L, et al. Response to Newly Prescribed Lipid-Lowering Therapy in Patients With and Without HIV Infection. Ann Intern Med. 2009;150:301-313.
20. Pollack TM, McCoy C, Stead W. Clinically significant adverse events from a drug interaction between quetiapine and atazanavir-ritonavir in two patients. Pharmacotherapy. 2009 Nov;29(11):1386-91.
21. Romanelli F, Matheny SC. HIV infection: the role of primary care. Am Fam Physician. 2009 Nov 1;80(9):946-52.
22. Bera E, McCausland K, Nonkwelo R, et al. Birth defects following exposure to efavirenz-based antiretroviral therapy during pregnancy: a study at a regional South African hospital. AIDS. 2009 Oct 27.
23. Sax PE, Tierney C, et al. the AIDS Clinical Trials Group Study A5202. Abacavir-Lamivudine vs Tenofovir-Emtricitabine for Initial HIV-1 Therapy. N Engl J Med. 2009 Dec 3;361(23):2230-2240. Epub 2009 Dec 1.
24. WHO Guidelines 2009: Adults & adolescents http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf Pregnant women and preventing HIV Infection in infants http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf
HIV and infant feeding http://www.who.int/child_adolescent_health/documents/hiv_if_principles_recommendations_112009.pdf
25 . Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf Accessed 7December, 2009
26. French, Neil, Gordon, Stephen B., Mwalukomo, Thandie, et al. A Trial of a 7-Valent Pneumococcal Conjugate Vaccine (Prevnar) in HIV-Infected Adults. N Engl J Med 2010 362: 812-822
27. Lingappa JR, Baeten JM, Wald A, et al. Partners in Prevention HSV/HIV Transmission Study Team. Daily aciclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. Lancet. 2010 Mar 6;375(9717):824-33. (acyclovir)
28. Mathers BM, Degenhardt L, Ali H, et al. for the 2009 Reference Group to the UN on HIV and Injecting Drug Use. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010 Feb 26.
29. Hill A, Sawyer W, Gazzard B. Effects of first-line use of nucleoside analogues, efavirenz, and ritonavir-boosted protease inhibitors on lipid levels. HIV Clin Trials 2009;10(1):1-12.
30. Sturt AS, Dokubo EK, Sint TT. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. Cochrane Database Syst Rev. 2010 Mar 17;3:CD008440. In ART-eligible pregnant women with HIV infection, ART is a safe and effective means of providing maternal virologic suppression, decreasing infant mortality, and reducing MTCT. Specifically, AZT/3TC/NVP, AZT/3TC/LPV-r, and AZT/3TC/ABC have been shown to decrease MTCT.
31. Del Romero J, Castilla J, Hernando V, et al. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. BMJ. 2010 May 14.
32. Shapiro RL et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med 2010 Jun 17; 362:2282.
33. Chasela CS et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med 2010 Jun 17; 362:2271.
34. Perry CM. Maraviroc: a review of its use in the management of CCR5-tropic HIV-1 infection. Drugs. 2010 Jun 18;70(9):1189-213.
35. Severe, Patrice, Jean Juste, Marc Antoine, et al. Early versus Standard Antiretroviral Therapy for HIV-Infected Adults in Haiti N Engl J Med 2010 363: 257-265.
36. Mar Pujades-Rodriguez; Suna Balkan; Line Arnould; et al.; for the AIDS Working Group of MSF. Treatment Failure and Mortality Factors in Patients Receiving Second-Line HIV Therapy in Resource-Limited Countries JAMA. 2010;304(3):303-312.
37. Thompson MA, Aberg JA, Cahn P, et al. International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA. 2010 Jul 21;304(3):321-33.
38. Bateganya M, Abdulwadud OA, Kiene SM. Home-based HIV voluntary counselling and testing (VCT) for improving uptake of HIV testing. Cochrane Database Syst Rev. 2010 Jul 7;7:CD006493. Although hom based HIV VCT has the potential to enhance VCT uptake in developing countries, insufficient data exist to recommend large-scale implementation of home-based HIV testing. Further studies are needed to

TOP

determine if home-based VCT is better than facility-based VCT in improving VCT uptake.
39. Welz T, Childs K, Ibrahim F, Poulton M, Taylor CB, Moniz CF, Post FA. Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. AIDS. 2010 Jul 31;24(12):1923-8.
40. Lang S, Mary-Krause M, Cotte L, et al. Impact of Individual Antiretroviral Drugs on the Risk of Myocardial Infarction in Human Immunodeficiency Virus-Infected Patients: A Case-Control Study Nested Within the French Hospital Database on HIV ANRS Cohort CO4. Arch Intern Med. 2010 Jul 26;170(14):1228-1238.
41. Spaulding A, Rutherford GW, Siegfried N. Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naive individuals. Cochrane Database Syst Rev. 2010 Aug 4;8:CD008651. While ideally future research would focus on direct comparison of standard therapeutic combinations of d4T+3TC+an NNRTI and AZT+3TC+an NNRTI to compare these regimens more directly, it is unlikely that additional trials will be mounted. Observational studies should focus on understanding outcomes, including toxicity and tolerability, in low- and middle-income countries.
42. O`Brien K, Nixon S, Tynan AM, et al. Aerobic exercise interventions for adults living with HIV/AIDS. Cochrane Database Syst Rev. 2010 Aug 4;8:CD001796. Aerobic exercise appears to be safe and may be beneficial for adults living with HIV.
43. Altice FL, Kamarulzaman A, Soriano VV, et al. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet. 2010 Jul 31;376(9738):367-87.
44. Lockman S, Hughes MD, McIntyre J, et al. OCTANE A5208 Study Team. Antiretroviral therapies in women after single-dose nevirapine exposure. N Engl J Med. 2010 Oct 14;363(16):1499-509.
45. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. N Engl J Med. 2010 Oct 14;363(16):1510-20.
46. Lavae-Mokhtari M, Mohammad-Khani S, Schmidt RE, Stoll M. [Acute renal failure and hypercalcemia in an AIDS patient on tenofovir and low-dose vitamin D therapy with immune reconstitution inflammatory syndrome]. Med Klin (Munich). 2009 Oct 15;104(10):810-3. Epub 2009 Oct 25.
47. Grant Robert M., Lama Javier R., Anderson Peter L., et al. for the iPrEx Study Team. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. Nov, 2010 (10.1056/NEJMoa1011205)
48. WHO-Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained setting-WHO-2010 http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf
49. Pienaar ED, Young T, Holmes H. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. Cochrane Database Syst Rev. 2010 Nov 10;11:CD003940.
50. Spaulding A, Rutherford GW, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor & one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naïve individuals. Cochrane Database Syst Rev. 2010 Oct 6;10:CD008740. We conclude that for the critical outcomes of virologic response and serious adverse events, initial ART regimens containing TDF are equivalent to those containing AZT. However, TDF is superior to AZT in terms of immunologic response and adherence and less frequent emergence of resistance.
51. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin No. 117: Gynecologic care for women with human immunodeficiency virus. Obstet Gynecol. 2010 Dec;116(6):1492-509.
52. Allers K, Hütter G, Hofmann J, Loddenkemper C, Rieger K, Thiel E, Schneider T. Evidence for the cure of HIV infection by CCR5{Delta}32/{Delta}32 stem cell transplantation. Blood. 2010 Dec 8.
53. Humphrey JH, Marinda E, Mutasa K, et al. on behalf of the ZVITAMBO study group. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. BMJ. 2010 Dec 22;341:c6580. doi: 10.1136/bmj.c6580.
54. Grant Robert M., Lama JR., Anderson PL., et al. for the iPrEx Study Team. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med 2010; 363:2587-2599.
55. Long EF, Brandeau ML, Owens DK. Cost-Effectiveness and Population Outcomes of Expanded HIV Screening and Antiretroviral Treatment in the United States. Ann Intern Med. 2010 Dec 21;153(12):778-89.
56. Singh S, Willig JH, Mugavero MJ, et al. Comparative Effectiveness and Toxicity of Statins Among HIV-Infected Patients. Clin Infect Dis. 2011 Feb;52(3):387-95.
57. Wawer MJ, Tobian AA, Kigozi G, et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. Lancet. 2011 Jan 6.
58. Jones CE., Naidoo S, De Beer C, et al. Maternal HIV Infection and Antibody Responses Against Vaccine-Preventable Diseases in Uninfected Infants. JAMA. 2011;305(6):576-584.doi:10.1001/jama.2011.100.
59. Chu C, Selwyn PA. Diagnosis and initial management of acute HIV infection. Am Fam Physician. 2010 May 15;81(10):1239-44.
60. Chu C, Selwyn PA. Complications of HIV Infection: A Systems-Based Approach. Am Fam Physician. 2011 Feb 15;83(4):395-406.
61. Taege A. Seek and treat: HIV update 2011. *Cleveland Clinic Journal of Medicine* 2011; 78(2):95-100; doi:10.3949/ccjm.78gr.10003
62. Kaufmann GR, Elzi L, Weber R, et al. Swiss HIV Cohort Study. Interruptions of cART limits CD4 T-cell recovery and increases the risk for opportunistic complications and death. AIDS.2011Feb 20;25(4):441 451.
63. FDA Mar/11: serious health problems that have been reported in premature babies receiving Kaletra (lopinavir/ritonavir) oral solution. Kaletra oral solution contains alcohol & propylene glycol.
64. Garvey L, Winston A, Walsh J, et al; For the UK Collaborative HIV Cohort (CHIC) Study. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. Neurology. 2011 Feb 22;76(8):693-700.
65. Young B, Dao CN, Buchacz K, Baker R, Brooks JT; the HIV Outpatient Study (HOPS) Investigators. Increased Rates of Bone Fracture among HIV-Infected Persons in the HIV Outpatient Study (HOPS) Compared with the US General Population, 2000-2006. Clin Infect Dis. 2011 Mar 10.
66. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010 Oct 15;51(8):937-46.
67. Koblic, Paul M., Gold, Wayne L., la Porte, Charles J.L., Lee, Todd C. Medication-based urolithiasis and atazanavir. CMAJ 2011 0: cmaj.100019
68. Daar Eric S., Tierney Camlin, Fischl Margaret A., et al. and for the AIDS Clinical Trials Group Study A5202 Team. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV Type-1: A Randomized Trial. Ann Intern Med E-316published ahead of print February 14, 2011.
69. Launay Odile, van der Vliet Diane, Rosenberg Arielle R., et al. Safety and Immunogenicity of 4 Intramuscular Double Doses and 4 Intradermal Low Doses vs Standard Hepatitis B Vaccine Regimen in Adults With HIV-1: A Randomized Controlled Trial. for the ANRS HB03 VIHVAC-B Trial. JAMA. 2011;305(14):1432-1440.doi:10.1001/jama.2011.351
70. Jansman FG, Reyners AK, van Roon EN, et al; Scientific Institute for Dutch Pharmacists (WINAp), the Dutch Society for Medical Oncology (NVMO); Dutch Society of Clinical Pharmacology and Biopharmacy (NVKF&B). Consensus-Based Evaluation of Clinical Significance and Management of Anticancer Drug Interactions. Clin Ther. 2011 Apr 1.
71. Mussini C, Cossarizza A, Sabin C, et al, of CASCADE Collaboration. Decline of CD4+ T cell count before start of therapy and immunological response to treatment in antiretroviral-naive individuals. AIDS. 2011 Mar 15.
72. Kalichman SC, Cherry C, Kalichman MO, et al. Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission. Am J Public Health. 2011 Mar;101(3):531-8.
73. El-Bassel Nabila; Jemmott III John B., Landis J Richard; et al. for the National Institute of Mental Health Multisite HIV/STD Prevention Trial for African-American Couples Group. Intervention to Influence Behaviors Linked to Risk of Chronic Diseases: A Multisite Randomized Controlled Trial With African-American HIV-Serodiscordant Heterosexual Couples. Arch Intern Med. 2011;171(8):728-736.
74. Butt AA.; Chang Chung-Chou; Kuller L; et al. Risk of Heart Failure With Human Immunodeficiency Virus in the Absence of Prior Diagnosis of Coronary Heart Disease. Arch Intern Med. 2011;171(8):737-743.
75. Rudek MA, Flexner C, Ambinder RF. Use of **antineoplastic agents in patients with cancer who have HIV**/AIDS. Lancet Oncol. 2011 May 12.
76. Cohen Myron S, Shaw George M., McMichaelet Andrew J. al. **Acute HIV-1 Infection**. N Engl J Med 2011; 364:1943-1954.
77. Zhang F, Dou Z, Ma Y, et al. Effect of **earlier initiation of antiretroviral treatment** and increased treatment coverage on HIV-related mortality in China: a national observational cohort study. Lancet Infect Dis 2011: published online May 19. DOI:10.1016/S1473-3099(11)70097-4.
78. Venter W.D. Francois, Ndung'u Thumbi, Karim QA. Case 15-2011 — A 19-Year-Old South African Woman with Headache, Fatigue, and Vaginal Discharge. (Acute HIV & SDT) N Engl J Med 2011; 364:1956-1964.
79. Sutcliffe CG, Moss WJ. Do children infected with **HIV receiving HAART need to be revaccinated**? Lancet Infect Dis. 2010 Sep;10(9):630-42.
80. Dieffenbach CW, Fauci AS. **Thirty Years of HIV** and AIDS: Future Challenges and Opportunities. Ann Intern Med. 2011 May 31.
81. Anglemyer A, et al. Antiretroviral therapy for **prevention of HIV transmission in HIV discordant couples**. Cochrane Database of Systematic Reviews 2011, Issue 5. Art.No.:CD009153.
82. Reust CE. **Common Adverse Effects** of Antiretroviral Therapy for HIV Disease. Am Fam Physician. 2011 Jun 15;83(12):1443-1451.

TOP

83. Bhattacharya Sangeeta Das, Bhattacharyya Subhasish, Do children receiving **HAART need to be revaccinated**?, The Lancet Infectious Diseases, Volume 11, Issue 6, June 2011.
84. Costello Daniel J., Gonzalez R. Gilberto, Frosch Matthew P.. Case 18-2011 — A 35-Year-Old HIV-Positive Woman with Headache and Altered Mental Status. (**Neuro-IRIS: Immune reconstitution Inflammatory syndrome**). N Engl J Med 2011; 364:2343-2352.
85. **WHO 2011**: Prevention and Treatment of HIV and Other Sexually Transmitted Infections (STIs) among **Men who have Sex with Men and Transgender** People: Recommendations for a Public Approach is at www.who.int/hiv/pub/guidelines/msm_guidelines2011/en . http://whqlibdoc.who.int/publications/2011/9789241501750_eng.pdf
86. Flateau Clara, Le Loup Guillaume, Pialoux Gilles. Consequences of **HIV infection on malaria** and therapeutic implications: a systematic review. Lancet Infect Dis 2011; 11: 541–56.
87. Simon Albane, Warszawski Josiane, Kariyawasam Dulanjalee, et al., for the ANRS French Perinatal Cohort Study Group. Association of Prenatal and Postnatal Exposure to **Lopinavir-Ritonavir and Adrenal Dysfunction Among Uninfected Infants** of HIV-Infected Mothers. JAMA. 2011;306(1):70-78.doi:10.1001/jama.2011.915
88. de BM, Viechtbauer W, Schaalma HP, Kok G, Abraham C, Hospers HJ. Standard care impact on effects of highly active antiretroviral therapy **adherence interventions**: A meta-analysis of randomized controlled trials. Arch Intern Med. 2010 Feb 8;170(3):240-50.
89. Cohen MS, Chen YQ, McCauley M, et al. **Prevention** of HIV-1 infection with early antiretroviral therapy (**HPTN 052**). N Engl J Med 2011. DOI: 10.1056/NEJMoa1105243.
90. Molina J-M, Cahn P, Grinsztejn B, et al, on behalf of the ECHO study group. **Rilpivirine** versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (**ECHO**): a phase 3 randomised double-blind active-controlled trial. Lancet 2011; 378: 238–46.
91. Cohen CJ, Andrade-Villanueva J, Clotet B, et al, on behalf of the THRIVE study group. **Rilpivirine** versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (**THRIVE**): a phase 3, randomised, non-inferiority trial. Lancet 2011; 378: 229–37.
92. Allers K, Hütter G, Hofmann J, et al. Evidence for the cure of HIV infection by **CCR5Δ32/Δ32 stem cell transplantation**. Blood. 2011 Mar 10;117(10):2791-9.
93. Tanser F, Bärnighausen T, Hund L, et al. Effect of **concurrent sexual partnerships** on rate of new HIV infections in a high-prevalence, rural South African population: a cohort study. Lancet. 2011 Jul 16;378(9787):247-55.
94. Powers KA, Ghani AC, Miller WC, et al. The role of **acute and early HIV infection** in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. Lancet. 2011 Jul 16;378(9787):256-68.
95. Abdool Karim SS, Kashuba A, Werner L, Abdool Karim Q. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. Lancet 2011; 378: 279–81.
96. Rackal JM, Tynan AM, Handford CD, et al. **Provider training and experience for people living with HIV/AIDS**. Cochrane Database Syst Rev. 2011 Jun 15;6:CD003938. The results demonstrate improved medical outcomes when treated by a provider with more training/expertise in HIV/AIDS care in the outpatient (clinic) setting.
97. Sigaloff KC, Calis JC, Geelen SP, et al. **HIV-1-resistance**-associated mutations after failure of first-line antiretroviral treatment among **children** in resource-poor regions: a systematic review. Lancet Infect Dis. 2011 Aug 25.
98. Royal College of Obstetricians and Gynaecologists (RCOG). Management of **HIV in pregnancy**. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Jun. http://www.rcog.org.uk/files/rcog-corp/GT39HIVPregnancy0610.pdf
99. Health Canada Sep/11 **ACCU-METRICS, has been advertising HIV home test kits** for sale via their website, Health Canada would like to remind Canadians that there are currently no HIV test kits that have been authorized for home use in Canada.
100. Sacktor N, Miyahara S, Deng L, et al. On behalf of ACTG A5235 team. Minocycline treatment for HIV-associated cognitive impairment: Results from a randomized trial. Neurology. 2011 Sep 7.
101. Marine L, Castro P, Enriquez A, et al. **Four-limb acute ischemia induced by ergotamine** in an AIDS patient treated with protease inhibitors. Circulation. 2011 Sep 20;124(12):1395-7.
102. Libman H. **Screening for HIV** infection: a healthy, "low-risk" 42-year-old man. JAMA. 2011 Aug 10;306(6):637-44.
103. Eron JJ Jr, Rockstroh JK, Reynes J, et al, for the QDMRK Investigators. **Raltegravir once daily or twice daily** in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. Lancet Infect Dis 2011; published online Sept 19.
104. Writing Committee for the **CASCADE** Collaboration. **Timing of HAART initation** and clinical outcomes in human immunodeficiency virus type 1 seroconverters. Arch Intern Med. 2011;171(17):1560-1569.
105. Laurent C, Kouanfack C, Laborde-Balen G, et al, for the Stratall ANRS 12110/ESTHER study group. **Monitoring of HIV viral loads, CD4 cell counts, and clinical assessments versus** clinical **monitoring alone** for antiretroviral therapy in rural district hospitals in Cameroon (Stratall ANRS 12110/ESTHER): a randomised non-inferiority trial. Lancet Infect Dis 2011
106. Jani IV, Sitoe NE, Alfai ER, et al. Effect of **point-of-care CD4 cell count tests** on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study. Lancet. 2011 Sep 23.
107. In the Clinic. **Management of Newly Diagnosed HIV Infection**. Annals of Internal Medicine 4 October 2011.
108. Heffron R, Donnell D, Rees H, et al. Use of **hormonal contraceptives** (esp injectables) **& risk of HIV-1 transmission**: a prospective cohort study. Lancet Infect Dis 2011; online Oct 4, 2011.
109. Wainberg MA, Zaharatos GJ, Brenner BG. Development of **antiretroviral drug resistance**. N Engl J Med. 2011 Aug 18;365(7):637-46.
110. Hamers RL, Wallis CL, Kityo C, et al.for PharmAccess African Studies to Evaluate Resistance (PASER). **HIV-1 drug resistance** in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. Lancet Infect Dis. 2011 Oct;11(10):750-9.
111. Burgard M, Blanche S, Jasseron C, et al. Agence Nationale de Recherche sur le SIDA et les Hepatites virales French Perinatal Cohort. Performance of HIV-1 DNA or HIV-1 RNA Tests for **Early Diagnosis of Perinatal** HIV-1 Infection during Anti-Retroviral Prophylaxis. J Pediatr. 2011 Aug 23.
112. Mills EJ, Bakanda C, Birungi J, et al. **Life expectancy** of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. Ann Intern Med. 2011 Aug 16;155(4):209-16.
113. HIV services--what role for **primary care**? Drug Ther Bull. 2011 Aug;49(8):85.
114. May M, Gompels M, Delpech V, et al. Impact of **late diagnosis** and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. BMJ 2011;343:d6016.
115. Berretta Massimiliano, Garlassi Elisa, Cacopardo Bruno,et al. **Hepatocellular Carcinoma** in HIV-Infected Patients: Check Early, Treat Hard. The Oncologist 2011; 16:1258-1269.
116. Parkes-Ratanshi R, Wakeham K, Levin J, et al, on behalf of the **Cryptococcal** Trial Team. Primary prophylaxis of cryptococcal disease with fl uconazole in HIV-positive Ugandan adults: a double-blind, randomised, placebo-controlled trial. Lancet Infect Dis 2011; published online Oct 7. DOI:10.1016/S1473-3099(11)70245-6.
117. Pursuing Later Treatment Options II (**PLATO II**) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). Risk of **triple-class virological failure** in children with HIV: a retrospective cohort study. Lancet 2011; 377: 1580–87.
118. van Lunzen J, Maggiolo F, Arribas JR, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis 2011; online Oct 21/11.
119. Abdool Karim SS et al. Integration of antiretroviral therapy with **tuberculosis** treatment. N Engl J Med 2011 Oct 20; 365:1492.
120. Havlir DV et al. Timing of antiretroviral therapy for HIV-1 infection and **tuberculosis**. (A5221) N Engl J Med 2011 Oct 20; 365:1482.

TOP

121. Blanc F-X et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with **tuberculosis**. (**Camelia**) N Engl J Med 2011 Oct 20; 365:1471.
122. Török ME and Farrar JJ. When to start antiretroviral therapy in HIV-associated **tuberculosis**. N Engl J Med 2011 Oct 20; 365:1538.
123. Rekart ML, Macintosh J. **Acute primary HIV** infection. CMAJ. 2011 Aug 9;183(11):1280.
124. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. (**SAPIT**) N Engl J Med 2010;362:697-706.
125. Ng Marie, Gakidou Emmanuela, Levin-Rector Alison, et al, Assessment of **population-level effect of Avahan**, an HIV-prevention initiative in India, The Lancet, Available online 10 October 2011
126. Marti-Carvajal AJ, Sola I, Pena-Marti GE, et al. Treatment for **anemia** in people with **AIDS**. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004776.
127. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. **Guidelines** for the use of antiretroviral agents in **pediatric HIV** infection. Bethesda (MD): U.S. Department of Health and Human Services; 2011 Aug 11. http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf
128. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of **antiretroviral drugs in pregnant HIV-1-infected women** for maternal health & interventions to reduce perinatal HIV-1 transmission in United States. Rockville: Public Health Service Task Force; 2011Sep14. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf
129. Hazra R, Cohen RA, Gonin R, et al. for the NISDI **Pediatric** Study Group 2011. **Lipid Levels** in the Second Year of Life among HIV-infected and HIV-exposed Uninfected Latin American Children. AIDS. 2011 Oct 15.
130. Mermin J, Ekwaru JP, Were W, et al. **Utility of routine viral load, CD4 cell count, and clinical monitoring** among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial. BMJ. 2011 Nov 9
131. Kahn JG, Marseille E, Moore D, et al. **CD4 cell count and viral load monitoring** in patients undergoing antiretroviral therapy in Uganda: cost effectiveness study. BMJ. 2011 Nov 9;343:d6884.
132. Bärnighausen T, Chaiyachati K, Chimbindi N, et al. Interventions to **increase antiretroviral adherence** in sub-Saharan Africa: a systematic review of evaluation studies. Lancet Infect Dis. 2011 Oct 24.
133. Uyei J, Coetzee D, Macinko J, et al. **Integrated delivery of HIV and tuberculosis** services in sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2011 Nov;11(11):855-67.
134. Committee on Pediatric AIDS. Adolescents and HIV Infection: The Pediatrician's Role in Promoting **Routine Testing**. Pediatrics. 2011 Nov;128(5):1023-9.
135. Kakalia S, Sochett EB, Stephens D, et al. **Vitamin d supplementation** and CD4 count in children infected with human immunodeficiency virus. J Pediatr. 2011 Dec;159(6):951-7.
136. Hamers RL, Schuurman R, Sigaloff KCE, et al. Effect of **pretreatment HIV-1 drug resistance** on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. Lancet Infect Dis 2011 online Oct 28.
137. Whitmore SK et al. Correlates of **Mother-to-Child Transmission** of HIV in the United States and Puerto Rico. Pediatrics. 2011 Dec 5.
138. Ota E, Wariki WM, Mori R, et al. Behavioral interventions to reduce the transmission of **HIV infection among sex workers** and their clients in high-income countries. Cochrane Database Syst Rev. 2011 Dec 7;12:CD006045. There is limited evidence from randomised controlled trials for the effectiveness of behavioural interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries.
139. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. Lancet. 2011 Dec 22.
140. d'Almeida KW, Kierzek G, de Truchis P, et al. Modest public health impact of nontargeted human immunodeficiency virus screening in 29 emergency departments [published online October 24, 2011]. Arch Intern Med. 2012;172(1):12-20.
141. Birbeck GL, French JA, Perucca E, et al. Evidence-based guideline: **Antiepileptic drug selection for people with HIV/AIDS**: Report of the Quality Standards Subcommittee of the American Academy of Neurology (**AAN**) and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy.Neurology. 2012 Jan 10;78(2):139-45.
142. Pant Pai N, Balram B, Shivkumar S, et al. Head-to-head comparison of accuracy of a **rapid point-of-care HIV test** with oral versus whole-blood specimens: a systematic review and meta-analysis. Lancet Infect Dis 2012.
143. Henderson DK. Management of **needlestick injuries**: a house officer who has a needlestick. JAMA. 2012 Jan 4;307(1):75-84.
144. Wawer MJ, Makumbi F, Kigozi G, et al. **Circumcision** in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. Lancet. 2009;374(9685):229-237.
145. Tobian AA, Kong X, Wawer MJ, et al. **Circumcision** of HIV-infected men and transmission of human papillomavirus to female partners: analyses of data from a randomised trial in Rakai, Uganda. Lancet Infect Dis. 2011;11(8):604-612.
146. Patel SM, Patel SS, Myers R. A 37-year-old man with a chronic cough. **(HIV & Coccidioides**). Cleveland Clinic Journal of Medicine 2012; 79(2):141-150;doi:10.3949/ccjm.79a.11010.
147. Berg K, Litwin A, Li X, et al. Lack of sustained improvement in **adherence** or viral load following a directly observed antiretroviral therapy intervention. Clin Infect Dis. 2011Nov;53(9):936-43.
148. FDA Feb/12 notified healthcare professionals and patients that drug interactions between the hepatitis C virus (HCV) protease inhibitor Victrelis (**boceprevir**) and certain **ritonavir-boosted** human immunodeficiency virus (HIV) protease inhibitors (atazanavir, lopinavir, darunavir) can potentially reduce the effectiveness of these medicines when they are used together.
149. Spooner LM, Olin JL. **Tesamorelin**: A Growth Hormone-Releasing Factor Analogue for HIV-Associated Lipodystrophy (February). Ann Pharmacother. 2012 Jan 31.
150. WHO 2012: **Hormonal contraceptivion** & HIV http://www.who.int/reproductivehealth/topics/family_planning/Hormonal_contraception_and_HIV.pdf
151. Mugo NR et al. Increased risk of HIV-1 transmission in pregnancy: A prospective study among African HIV-1-**serodiscordant couples**. *AIDS* 2011 Sep 24; 25:1887.
152. Baird SJ, Garfein RS, McIntosh CT, et al. Effect of a **cash transfer** programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. Lancet 2012.
153. Frassetto L, Kohlstadt I. Treatment and prevention of **kidney stones**: an update. Am Fam Physician. 2011 Dec 1;84(11):1234-42.
154. Horvath T, Azman H, Kennedy GE, Rutherford GW. **Mobile phone text messaging** for promoting **adherence** to antiretroviral therapy in patients with HIV infection. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No.: CD009756. DOI: 10.1002/14651858.CD009756. There is high-quality evidence from the two RCTs that mobile phone text-messaging at weekly intervals is efficacious in enhancing adherence to ART, compared to standard care. There is high quality evidence from one trial that weekly mobile phone text-messaging is efficacious in improving HIV viral load suppression.
155. Kuhn L, Coovadia A, Strehlau R, et al. **Switching children** previously exposed to **nevirapine** to nevirapine-based treatment after initial suppression with a protease-inhibitor-based regimen: long-term follow-up of a randomised, open-label trial. Lancet Infect Dis 2012
156. Reynolds SJ, Makumbi F, Newell K, et al. Effect of daily **acyclovir** on HIV disease progression in individuals in Rakai, Uganda, **co-infected with HIV-1 and herpes simplex virus type 2**: a randomised, double-blind placebo-controlled trial. Lancet Infect Dis 2012; online March 19.
157. Ludema C, Cole SR, Poole C, Chu H, Eron JJ. Meta-analysis of randomized trials on the association of prophylactic acyclovir and HIV-1 viral load in individuals coinfected with herpes simplex virus-2. AIDS 2011; 25: 1265–69.
158. Mugwanya K, Baeten JM, Mugo NR, Irungu E, Ngure K, Celum C. High-dose valacyclovir HSV-2 suppression results in greater reduction in plasma HIV-1 levels compared with standard dose acyclovir among HIV-1/HSV-2 coinfected persons: a randomized, crossover trial. J Infect Dis 2011; 204: 1912–17.
159. Mayer KH et al. **Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis** to prevent the sexual transmission of HIV: Safety, tolerability and adherence. J Acquir Immune Defic Syndr 2012 Apr 1; 59:354.
160. Baral S, Beyrer C, et al. Burden of **HIV among female sex workers** in low-income and middle-income countries: systematic review and meta-analysis. Lancet Infect Dis 2012: online March 1
161. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an **HIV-1 vaccine** efficacy trial. N Engl J Med 2012;366:1275-86.

TOP

162. Horwood C, Vermaak K, Butler L, et al. Elimination of paediatric HIV in KwaZulu-Natal, South Africa: large-scale assessment of **interventions for the prevention of mother-to-child** transmission. Bull World Health Organ. 2012 Mar 1;90(3):168-75.
163. Grijsen ML, Steingrover R, Wit FWNM, et al. **No Treatment versus 24 or 60 Weeks** of Antiretroviral Treatment during Primary HIV Infection: The Randomized **Primo-SHM** Trial. 2012 PLoS Med 9(3): e1001196.
164. Jamieson DJ, Chasela CS, Hudgens MG, et al, for the **BAN** study team. **Maternal and infant antiretroviral regimens** to prevent postnatal HIV-1 transmission: 48-week follow-up of the BAN randomised controlled trial. Lancet 2012
165. Siberry GK, Williams PL, Mendez H, et al. for the Pediatric HIVAIDS Cohort Study (PHACS). Safety of **tenofovir use during pregnancy**: early growth outcomes in HIV-exposed uninfected infants. AIDS. 2012 Feb 29.
166. Kenyon C, Mfolozi S, Croxford R, et al. Severe **efavirenz-induced vacuolar axonopathy** complicated by fatal aspiration pneumonia. Br J Clin Pharmacol. 2012 Apr 18.
167. Juusola JL, Brandeau ML, Owens DK, Bendavid E. The Cost-Effectiveness of **Preexposure Prophylaxis for HIV** Prevention in the United States in **Men Who Have Sex With Men**. Ann Intern Med. 2012 Apr 17;156(8):541-50.
168. Walker NF, Clark SO, Oni T, et al. **Doxycycline** and HIV Infection Suppress Tuberculosis-induced Matrix Metalloproteinases. Am J Respir Crit Care Med. 2012 May 1;185(9):989-97.
169. Khalili H, Farasatinasab M, et al. **Efavirenz severe hypersensitivity** reaction: case report and rapid desensitization protocol development. Ann Pharmacother. 2012 May;46(5):e12.
170. Nielsen-Saines K, Komarow L, Cu-Uvin S, et al; for the ACTG 5190/PACTG 1054 Study Team. **Infant Outcomes After Maternal** Antiretroviral Exposure in Resource-Limited Settings. Pediatrics. 2012 May 14.
171. Simms V, Higginson IJ, Harding R. **Integration of palliative care** throughout HIV disease. Lancet Infect Dis. 2012 Jun 8.
172. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for Improving Entry Into and Retention in Care and Antiretroviral **Adherence** for Persons With HIV: Evidence-Based Recommendations From an International Association of Physicians in AIDS Care Panel. Ann Intern Med. 2012 Jun5;156(11):817-833.
173. Nielsen-Saines K, Komarow L, Cu-Uvin S, et al; for the ACTG 5190/PACTG 1054 Study Team. **Infant Outcomes After Maternal Antiretroviral Exposure** in Resource-Limited Settings. Pediatrics. 2012 Jun;129(6):e1525-e1532.
174. Bogoch II, Scully EP, Zachary KC. Antiretroviral medication for **preventing** HIV infection in **nonoccupational settings**. CMAJ. 2012 May 28.
175. Bendavid E, Holmes CB, Bhattacharya J, Miller G. **HIV Development Assistance** and Adult Mortality in Africa HIV Aid and Adult Mortality in Africa. JAMA. 2012 May 16;307(19):2060-7.
176. Robb ML, Rerks-Ngarm S, Nitayaphan S, et al. Risk behaviour and time as covariates for efficacy of the **HIV vaccine regimen ALVAC-HIV** (vCP1521) and AIDSVAX B/E: a post-hoc analysis of the Thai phase 3 eff cacy trial RV 144. Lancet Infect Dis 2012; online May 30.
177.

TOP

Extras:

1) Clinical Decision Rule for Point of Care Testing of Influenza Patients: *fever* (2 points), *myalgia* (2 points), *symptoms <48hrs* (1 point), *chills/sweats* (1 point). **0-2points** = 8%; **3 points** = 30%; **4-6 points** = 59%.

Rx Files – Drugs for Influenza
References

[1] Adapted from the National Advisory Committee on Immunization's Statement on Influenza Vaccination for the 2000-2001 Season. Health Protection Branch - Laboratory Centre for Disease Control (Ottawa, Canada), Vol 26 (ACS-2), June 1, 2000.

NACI: National Advisory Committee on Immunization. Statement on seasonal trivalent inactivated influenza vaccine (TIV) for **2010-2011**. CCDR 2010;36(ACS-6):1-49. www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php (accessed August 30, 2010).

NACI: Statement on Seasonal Influenza vaccine for **2011-2012**. CCDR Sept 2011 (ACS-5) Vol 37. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php

NACI 2011: Recommendations on the use of **intradermal trivalent inactivated influenza vaccine** (TIV-ID). http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-4/index-eng.php

[2] McGeer A, Sitar D, Tamblyn S, et al. Use of antiviral prophylaxis in influenza outbreaks in long term care facilities. Can J Infect Dis 2000; 11(4): 187-192.

[3] Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. BMJ. 2003 Jun 7;326(7401):1235.

[4] Stiver G. The treatment of influenza with antiviral drugs. CMAJ. 2003 Jan 7;168(1):49-56.

[5] Influenza Prevention 2002-2003. Med Lett Drugs Ther. 2002 Sep 2;44(1138):75-6.

[6] Kiso M., Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004; 364: 759-65. (9 of 50 treated kids had resistant gene mutations, but transmissibility unknown)

Physician's First Watch: Feb/08 A common influenza virus has developed a mutation resistant to oseltamivir (Tamiflu) has been found in U.S., Canada, & 4 European nations, the *New York Times* reports. A small percentage of **influenza A/H1N1** — the predominant flu virus infecting people this season — is affected by the **H274Y mutation**. Norway appears to be hardest hit, with 75% (12 of 16) of the isolated viruses showing **resistance to oseltamivir**. In the U.S., Britain, Denmark, and France, roughly 3% to 5% of tested viruses showed resistance (data on Canada were not provided, but reported in Pharmacy Bulletin Board Feb 4/08 at **10%**). "We don't know right now if this is a trend on the upswing or just a small blip," the CDC's chief of epidemiology and prevention told the Associated Press. Officials from the U.S. and World Health Organization told the *Times* they do not currently advise changes in Tamiflu use. In addition, the flu vaccine is still effective against the mutant virus.

Dec/08: Clinicians should remain alert for changes in recommendations that might occur as the 2008--09 influenza season progresses. Recommendations regarding the use of antiviral medications might be revised if surveillance data indicate a substantial and widespread increase in the prevalence of oseltamivir-resistant influenza viruses in the United States. In fact, the interim CDC guidance provides advice for clinicians on how to treat patients with influenza antiviral medications this season. Clinicians can use influenza test results and information, if available, about which viruses are circulating, to help decide which antiviral(s) should be used. If H1N1 viruses are circulating in the community, or it's not clear which viruses are circulating, health care providers are recommended to use an alternative antiviral, zanamivir (Relenza®), or to use combination therapy of oseltamivir and rimantadine. Use of zanamivir or dual therapy with oseltamivir and rimantadine would provide effective treatment against all circulating influenza viruses. In some instances, oseltamivir alone can still be used, such as when influenza B is diagnosed, or H1N1 viruses are not circulating.

Dharan NJ, Gubareva LV, Meyer JJ, et al. for the Oseltamivir-Resistance Working Group. Infections With Oseltamivir-Resistant Influenza A(H1N1) Virus in the United States. JAMA. 2009 Mar 2. [Epub ahead of print] Oseltamivir-resistant A(H1N1) viruses circulated widely in the United States during the 2007-2008 influenza season, appeared to be unrelated to oseltamivir use, and appeared to cause illness similar to oseltamivir-susceptible A(H1N1) viruses. Circulation of oseltamivir-resistant A(H1N1) viruses will continue, with a higher prevalence of resistance, during the 2008-2009 season.

Van der Vries Erhardl Emergence of a **Multidrug-Resistant Pandemic Influenza A (H1N1)** Virus. N Engl J Med 2010; 363:1381-1382.

[7] Orr P; National Advisory Committee on Immunization. An Advisory Committee Statement (ACS). National Advisory Committee on Immunization (NACI). Statement on influenza vaccination for the 2004-2005 season. Can Commun Dis Rep. 2004 Jun 15;30:1-32. (Canada Communicable Disease Report,Volume 31 • ACS-6,15 June **2005** ,An Advisory Committee Statement (ACS), National Advisory Committee on Immunization (NACI)*† , Statement on Influenza Vaccination, for the 2005-2006 Season, http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05pdf/acs-dcc3106.pdf)

NACI: National Advisory Committee on Immunization. Statement on seasonal trivalent inactivated influenza vaccine (TIV) for **2010-2011**. CCDR 2010;36(ACS-6):1-49. www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php (accessed August 30, 2010).

NACI: Statement on Seasonal Influenza vaccine for **2011-2012**. CCDR Sept 2011 (ACS-5) Vol 37. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php

TOP

8 Schmidt AC. Antiviral therapy for influenza : a clinical and economic comparative review. Drugs. 2004;64(18):2031-46.
Shun-Shin Matthew, Thompson Matthew, Heneghan Carl, et al. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials**.** BMJ 2009;339:b3172, doi: 10.1136/bmj.b3172 (Published 10 August 2009)

Additional sources:

Acosta EP, Jester P, Gal P, et al. Oseltamivir dosing for influenza infection in premature neonates. J Infect Dis. 2010 Aug 15;202(4):563-6.

Alves Galvão MG, et al. **Amantadine and rimantadine for influenza A in children and the elderly**. Cochrane Database Syst Rev. 2008;1:CD002745 Our conclusions about effectiveness of both antivirals for the treatment of influenza A in children were limited to a proven benefit of RMT in the abatement of fever on day three of treatment. Due to the small number of available studies we could not reach a definitive conclusion on the safety of AMT or the effectiveness of RMT in preventing influenza in children and the elderly.

Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. **Amantadine and rimantadine** for influenza A in children and the elderly. Cochrane Database Syst Rev. 2012 Jan 18;1:CD002745. AMT is effective in preventing influenza A in children but the NNTB is high (NNTB: 12 (95% CI 9 to 17). RMT probably helps the abatement of fever on day three of treatment, but the quality of the evidence is poor. Due to the small number of available studies, we could not reach a definitive conclusion on the safety of AMT or the effectiveness of RMT in preventing influenza in children and the elderly.

American Academy of Pediatrics Committee on Infectious Diseases. **Antiviral therapy and prophylaxis for influenza in children. Pediatrics. 2007** Apr;119(4):852-60.

American Academy of Pediatrics Committee on Infectious Diseases. Prevention of influenza: recommendations for influenza immunization of children, 2006-2007. Pediatrics. 2007 Apr;119(4):846-51.

American Academy of Pediatrics Committee on Infectious Diseases. Prevention of influenza: recommendations for influenza immunization of children, 2008-2009. Pediatrics. 2008 Nov;122(5):1135-41. http://pediatrics.aappublications.org/cgi/reprint/122/5/1135

American Academy of Pediatrics (AAP) Committee on Infectious Diseases, Policy Statement--Recommendations for the **Prevention and Treatment of Influenza in Children**, **2009-2010**. Pediatrics 2009 124: 1216-1226 http://pediatrics.aappublications.org/cgi/reprint/124/4/1216

American Academy of Pediatrics. Committee on Infectious Diseases. Policy statement--recommendations for prevention and control of influenza in children, 2010-2011. Pediatrics 2010 Oct;126(4):816-26. http://aappolicy.aappublications.org/cgi/reprint/pediatrics;126/4/816.pdf

American Academy of Pediatrics (AAP). Committee on Infectious Diseases. Recommendations for **prevention and control of influenza in children, 2011-2012**. Pediatrics. 2011 Oct;128(4):813-25. http://pediatrics.aappublications.org/content/128/4/813.long

Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/

Antiviral Drugs for Prophylaxis and Treatment of Influenza. **Med Lett Drugs Ther**. 2005 Novt 21;47(1222):93-5. (Influenza vaccine Oct 9**,2006** & also Updated Oct 23,2006 & **Oct 22, 2007**)

Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ **ECMO**) Influenza Investigators. Extracorporeal Membrane Oxygenation for 2009 Influenza A(**H1N1**) Acute Respiratory Distress Syndrome. *JAMA*. 2009;0(2009):2009.1535.

Bardage C, Persson I, Ortqvist A, et al. **Neurological and autoimmune disorders** after vaccination against pandemic influenza A (**H1N1**) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. BMJ. 2011 Oct 12;343:d5956. doi: 10.1136/bmj.d5956.

Barry M. Anita. A 29-Year-Old Woman With Flu-like Symptoms: Review of Influenza **Diagnosis and Treatment**. JAMA. 2010;304(6):671-678.

Beigel JH, Farrar J, Han AM, et al.; Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. N Engl J Med. 2005 Sep 29;353(13):1374-85.

Bhat N, Wright JG, Broder KR, et al. Influenza-Associated Deaths among Children in the United States, 2003-2004. N Engl J Med. 2005 Dec 15;353(24):2559-2567.
RESULTS: One hundred fifty-three influenza-associated deaths among children were reported by 40 state health departments

Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet. 2005 Oct 1;366(9492):1175-81. Epub 2005 Sep 22. FINDINGS: More than 7000 influenza A field isolates were screened for specific aminoacid substitutions in the M2 gene known to confer drug resistance. During the decade of surveillance a significant increase in drug resistance was noted, from 0.4% in 1994-1995 to 12.3% in 2003-2004. This increase in the proportion of resistant viruses was weighted heavily by those obtained from **Asia** with 61% of resistant viruses isolated since 2003 being from people in Asia. INTERPRETATION: Our data raise concerns about the appropriate use of adamantanes & draw attention to the importance of tracking the emergence and spread of drug-resistant influenza A viruses.

Bright RA, et al. Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. JAMA. 2006 Feb 22;295(8):891-4. Epub 2006 Feb 2. RESULTS: A total of 209 influenza A(H3N2) viruses isolated from patients in 26 states were screened, of which 193 (92.3%) contained a change at amino acid 31 (serine to asparagine [S31N]) in the M2 gene known to be correlated with adamantane resistance. Two of 8 influenza A(H1N1) viruses contained the same mutation. Drug-resistant viruses were distributed across the United States. CONCLUSIONS: The high proportion of influenza A viruses currently circulating in the United States demonstrating adamantane resistance highlights the clinical importance of rapid surveillance for antiviral resistance. Our results indicate that these drugs should not be used for the treatment or prophylaxis of influenza in the United States until susceptibility to adamantanes has been reestablished among circulating influenza A isolates.

Briggs GE, et al **Drugs in Pregnancy & Lactation**, 9th Ed. Wilkins; Baltimore, MD.2011.

TOP

Brun-Buisson C, Richard JCM, Mercat A, et al. REVA-SRLF A/H1N1v 2009 Registry Group. Early **corticosteroids** in severe influenza A/H1N1 pneumonia and acute respiratory Distress syndrome. Am J Respir Crit Care Med 2011;183:1200–1206.

Burch J, Corbett M, Stock C, et al.. **Prescription of anti-influenza drugs** for healthy adults: a systematic review and meta-analysis. Lancet Infect Dis. 2009 Sep;9(9):537-45. Epub 2009 Aug 7.

Campitelli MA, Inoue M, Calzavara AJ, et al. Low Rates of Influenza Immunization in Young Children Under **Ontario's Universal Influenza** Immunization Program. Pediatrics. 2012 May 14.

Campos MA, Alazemi S, Zhang G, et al. Influenza Vaccination in Subjects With **Alpha-1 Antitrypsin Deficiency**. Chest. 2007 Oct 1; [Epub ahead of print] Subjects with AATD in the United States receive adequate influenza vaccination regardless of age. However, we did not observe a significant impact of the vaccination on disease exacerbations and other respiratory outcomes during the 2003-2004 influenza season.

Canadian Society of Allergy and Clinical Immunology ADMINISTRATION OF H1N1 AND SEASONAL INFLUENZA **VACCINE TO EGG ALLERGIC** INDIVIDUALS http://www.csaci.ca/include/files/CSACI_H1N1_Statement.pdf

Cates CJ, Jefferson TO, Rowe BH. Vaccines for preventing influenza in people with **asthma**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD000364. Uncertainty remains about the degree of protection vaccination affords against asthma exacerbations that are related to influenza infection. Evidence from recently published trials indicates that there is no significant increase in asthma exacerbations immediately after vaccination (at least with inactivated influenza vaccination). There is concern regarding possible increased wheezing and hospital admissions in infants given live intranasal vaccination.

CDC Jan 2006 CDC Recommends against the Use of Amantadine and Rimantadine for the Treatment or Prophylaxis of Influenza in the United States during the 2005–06 Influenza Season http://www.cdc.gov/flu/han011406.htm (Recommendations against amantadine for influenza in 2005-06. Pharmacist's Letter/Prescriber's Letter 2006;22(2):220216)

CDC July 2009 Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), **2009** http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0724a1.htm ; http://www.cdc.gov/flu/

CDC Centers for Disease Control and Prevention. Updated interim recommendations — **HIV**-infected adults and adolescents: Considerations for clinicians regarding 2009 **H1N1** influenza. Oct 21 , 2009. (http://www.cdc.gov/h1n1flu/guidance_HIV.htm)

CDC data strengthen the evidence that the risk for **Guillain-Barré syndrome (GBS)** associated with the 2009 H1N1 vaccine is similar to the risk seen with seasonal flu vaccines, according to an *MMWR* report. The CDC's analysis of data from October 2009 through March 2010 found that the incidence of GBS was 1.92 per 100,000 person-years among vaccinated individuals and 1.21 per 100,000 person-years among the unvaccinated. If final data confirm this finding, the CDC says, then this would translate to 0.8 excess GBS cases for every 1 million vaccinations — a rate comparable to that found with seasonal flu vaccination. *MMWR* article (Free)

CDC **Prevention and Control of Influenza with Vaccines**. Recommendations of the Advisory Committee on Immunization Practices (ACIP), **2010**. http://www.cdc.gov/mmwr/pdf/rr/rr59e0729.pdf

CDC Preliminary Results: Surveillance for **Guillain-Barré Syndrome** After Receipt of Influenza A (H1N1) 2009 Monovalent Vaccine — United States, 2009–2010 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm59e0602a1.htm Preliminary results from an analysis in EIP comparing GBS patients hospitalized through March 31, 2010, who did and did not receive 2009 H1N1 vaccination showed an estimated age-adjusted rate ratio of 1.77 (GBS incidence of 1.92 per 100,000 person-years among vaccinated persons and 1.21 per 100,000 person-years among unvaccinated persons). If end-of-surveillance analysis confirms this finding, this would correspond to 0.8 excess cases of GBS per 1 million vaccinations, similar to that found in seasonal influenza vaccines.[2,3] No other federal system to date has detected a statistically significant association between GBS and 2009 H1N1 vaccination. Surveillance and further analyses are ongoing. The 2009 H1N1 vaccine safety profile is similar to that for seasonal influenza vaccines, which have an excellent safety record. Vaccination remains the most effective method to prevent serious illness and death from 2009 H1N1 influenza infection; illness from the 2009 H1N1 influenza virus has been associated with a hospitalization rate of 222 per 1 million and a death rate of 9.7 per 1 million population.

CDC Aug/10 Estimates of **Deaths** Associated with Seasonal Influenza --- United States, 1976—2007 http://www.cdc.gov/mmwr/pdf/wk/mm5933.pdf

CDC: Interim Guidance on the Use of Influenza Antiviral Agents During the **2010-2011 Influenza Season** Nov 2010. **http://www.cdc.gov/flu/professionals/antivirals/guidance/**

CDC: Antiviral Agents for Treatment and **Chemoprophylaxis of Influenza Recommendations** of the Advisory Committee on Immunization Practices (ACIP) Recommendations and Reports **January 21, 2011** / 60(RR01);1-24 **http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm?s_cid=rr6001a1_x**

CDC: Update: Influenza Activity — United States, **2010–11 Season, and Composition of the 2011–12 Influenza Vaccine** http://www.cdc.gov/mmwr/pdf/wk/mm6021.pdf

CDC Sep/11 Maternal and Infant Outcomes Among Severely Ill **Pregnant and Postpartum Women with 2009 Pandemic Influenza A (H1N1)** --- United States, April 2009—August 2010 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6035a2.htm

CDC: Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among **pregnant women** - 29 States and New York City, 2009-10 season. MMWR Morb Mortal Wkly Rep. 2012 Feb 24;61(7):113-8.

Chartrand C, Leeflang MM, Minion J, et al. **Accuracy of Rapid Influenza Diagnostic Tests**: A Meta-analysis. Ann Intern Med. 2012 Feb 27.

Chen XY, Wu TX, Liu GJ, et al. **Chinese medicinal herbs** for influenza. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD004559. The present evidence is too weak to support or reject the use of Chinese medicinal herbs for preventing and treating influenza.

Chen Mark I. C.; Lee Vernon J. M.; Lim Wei-Yen; et al. 2009 Influenza A(H1N1) **Seroconversion** Rates and Risk Factors Among Distinct Adult Cohorts in Singapore. JAMA.

TOP

2010;303(14):1383-1391.
Chung, Erica Y., Huang, Lin, Schneider, Lynda. Safety of Influenza Vaccine Administration in **Egg-Allergic** Patients. Pediatrics 2010 125: e1024-e1030.
Ciszewski A, Bilinska ZT, Brydak LB, et al. Influenza vaccination in secondary prevention from **coronary ischaemic events** in coronary artery disease: FLUCAD study. Eur Heart J. 2008 Jun;29(11):1350-8. Epub 2008 Jan 10. In optimally treated CAD patients influenza vaccination improves the clinical course of CAD and reduces the frequency of coronary ischaemic events. Large-scale studies are warranted to evaluate the effect of influenza vaccination on cardiovascular mortality.
Coffin SE, Leckerman K, Keren R, et al. **Oseltamivir** shortens **hospital stays of critically ill children** hospitalized with seasonal influenza: a retrospective cohort study. Pediatr Infect Dis J. 2011 Nov;30(11):962-6.
Cohen D. Complications: tracking down the **data on oseltamivir**. BMJ 2009;339:b5387.
Cohen Steven A., Chui Kenneth K.H., Naumova Elena N. Influenza Vaccination in Young **Children Reduces Influenza-Associated Hospitalizations in Older Adults**, 2002–2006. Journal of the American Geriatrics Society. Article first published online: 28 JAN 2011. DOI: 10.1111/j.1532-5415.2010.03271.x.
Corti D, Voss J, Gamblin SJ, et al. A **neutralizing antibody** selected from plasma cells that binds to group 1 and group 2 **influenza** A hemagglutinins. Science 2011;333:850-6.
Cowling BJ, Chan KH, et al. **Facemasks and hand hygiene** to prevent influenza transmission in households: a cluster randomized trial. Ann Intern Med. 2009 Oct 6;151(7):437-46.
Cowling, BJ., Chan, KH, Fang, VJ. et al; Comparative **Epidemiology of Pandemic and Seasonal Influenza A** in Households N Engl J Med 2010 362: 2175-2184.
Crowe SR, Merrill JT, Vista ES, Dedeke AB, et al. Influenza vaccination responses in human systemic **lupus erythematosus**: impact of clinical and demographic features. Arthritis Rheum. 2011 May 19. doi: 10.1002/art.30388.
Dawood FS et al. Emergence of a novel swine-origin influenza A (**H1N1**) virus in humans. N Engl J Med 2009 May 7.
Dawood Fatimah S., Kamimoto Laurie, D'Mello Tiffany A., et al. and the Emerging Infections Program Network. Children With **Asthma** Hospitalized With Seasonal or Pandemic Influenza, 2003–2009. Pediatrics 2011; 128:1 e27-e32; ahead of print June 6, 2011
de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med. 2005 Dec 22;353(25):2667-72.
Diaz E, Rodriguez A, Martin-Loeches I, Lorente L, del Mar MM, Pozo JC, et al. Impact of **obesity** in patients infected with 2009 influenza A(H1N1). Chest. 2011 Feb;139(2):382-6.
Dieleman J, Romio S, Johansen K, et al. **Guillain-Barré syndrome** and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ 2011;343:d3908.
Diggle L, et al. Effect of **needle size** on immunogenicity and reactogenicity of vaccines in infants: randomised controlled trial. BMJ. 2006 Sep 16;333(7568):571. Epub 2006 Aug 4. Long (25 mm) needles for infant immunisations can significantly reduce vaccine reactogenicity at each dose while achieving comparable immunogenicity to that of short (16 mm) needles. (InfoPOEMs: Using a 25-mm needle to inject the combined diptheria, pertussis, tetanus, and Haemophilus influenzae type B vaccine (ACT-Hib DTP) will result in significantly fewer injection site reactions and those that occur will be of less severe. The World Health organization recommends use of a 25-mm needle, although most physicians in the United States use the shorter 16-mm needle. (LOE = 1b))
Dominguez-Cherit Guillermo; Lapinsky Stephen E.; Macias Alejandro E.; et al. Critically Ill Patients With 2009 Influenza A(**H1N1**) in **Mexico**. JAMA. 2009;0(2009):2009.1536.
Donner B, Niranjan V, Hoffmann G. Safety of **oseltamivir in pregnancy**: a review of preclinical and clinical data. Drug Saf. 2010 Aug 1;33(8):631-42.
Doshi P, Jefferson T, Del Mar C. The imperative to **share clinical study reports**: recommendations from the **tamiflu** experience. PLoS Med. 2012 Apr;9(4):e1001201.
Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of **oseltamivir** at standard and **high dosages**. Int J Antimicrob Agents. 2010 Feb 26.
Earn DJ, He D, Loeb MB, Fonseca K, Lee BE, Dushoff J. Effects of **school closure** on incidence of pandemic influenza in Alberta, Canada. Ann Intern Med. 2011;156:173-81.
Ebell MH, Afonso AM, Gonzales R, et al. Development and validation of a **clinical decision rule** for the diagnosis of influenza. J Am Board Fam Med. 2012 Jan-Feb;25(1):55-62.
Ehrlich HJ, Müller M, Oh HM, et al.; Baxter H5N1 Pandemic Influenza Vaccine Clinical Study Team. A clinical trial of a whole-virus H5N1 vaccine derived from cell culture. N Engl J Med. 2008 Jun 12;358(24):2573-84.
Elkayam O, et al. The Effect of **Infliximab** and Timing of Vaccination on the Humoral Response to Influenza Vaccination in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis. Semin Arthritis Rheum. 2009 Feb 24. [Epub ahead of print] Influenza virus vaccine generated good humoral response in RA & AS patients treated with infliximab.
Elkin PL, Froehling DA, Wahner-Roedler DL, et al. Comparison of **natural language processing biosurveillance** methods for identifying influenza from encounter notes. Ann Intern Med. 2012 Jan 3;156(1 Pt 1):11-8.
EMA Jul 21// - European regulators have recommended restricting the use of GlaxoSmithKline's pandemic flu vaccine **Pandemrix because of a potential risk of narcolepsy** in children or adolescents. The European Medicines Agency said on Thursday that Pandemrix should only be used in people under 20 years in the absence of seasonal trivalent influenza vaccines, following its link to very rare cases of narcolepsy in young people.
Engler RJ, Nelson MR, Klote MM, et al. Walter Reed Health Care System Influenza Vaccine Consortium. **Half- vs full-dose** trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses. Arch Intern Med. 2008 Dec 8;168(22):2405-14. Antibody responses to intramuscular half-dose TIV in healthy, previously immunized adults were not substantially inferior to the full-dose vaccine, particularly for ages 18 to 49 years. Significantly higher geometric mean titer responses in women were identified for all ages, regardless of dose or influenza strain. Half-dose vaccination may be an effective strategy for healthy adults younger than 50 years in the setting of an influenza vaccine shortage.
Erlewyn-Lajeunesse M, et al. Recommendations for the administration of influenza vaccine in children **allergic to egg**. BMJ. 2009 Sep 15;339:b3680. doi: 10.1136/bmj.b3680.
Eurich DT, Marrie TJ, Johnstone J, Majumdar SR. Mortality reduction with influenza vaccine in patients with pneumonia outside "flu" season: pleiotropic benefits or residual confounding? Am J Respir Crit Care Med. 2008 Sep 1;178(5):527-33. Epub 2008 Jun 12. The 51% reduction in mortality with vaccination initially observed in patients with pneumonia who did not have influenza was most likely a result of confounding. Previous observational studies may have overestimated mortality benefits of influenza

TOP

vaccination.
Farley M, Ryan P, Lynfield R, et al. Emerging Infections Program Network. Children with **asthma hospitalized** with seasonal or pandemic influenza, 2003-2009. Pediatrics. 2011 Jul;128(1):e27-32.
FDA Acts to Protect Public from **Fraudulent Avian Flu Therapies** Dec/05 http://www.fda.gov/bbs/topics/NEWS/2005/NEW01274.html
FDA April /08 GlaxoSmithKline informed healthcare professionals of changes to the WARNINGS AND PRECAUTIONS sections of prescribing information for **Relenza** regarding information from postmarketing reports (mostly from Japan) of **delirium and abnormal behavior** leading to injury in patients with influenza who are receiving neuraminidase inhibitors, including Relenza. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of Relenza to these events has not been established. Influenza can be associated with a variety of neurologic and behavioral symptoms which can include seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.
FDA June/10 notified consumers and healthcare professionals about a potentially harmful product represented as "**Generic Tamiflu" sold over the Internet**. FDA tests revealed that the fraudulent product does not contain Tamiflu's active ingredient, oseltamivir, but cloxacillin, an ingredient in the same class of antibiotics as penicillin.
Food and Drug Administration Oct/11 (FDA) isadvising health care professionals **not to use injector devices** to administer influenza vaccines.
Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, Bresee JS, Cox NJ, Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (**ACIP**), 2009. MMWR Recomm Rep 2009 Jul 31;58(RR-8):1-52.
Friedman BC, Goldman RD. **Influenza vaccination for children with asthma**. Can Fam Physician. 2010 Nov;56(11):1137-9.
Esposito S, Pugni L, Daleno C, et al. **Influenza A/H1N1 MF59-Adjuvanted Vaccine in Preterm and Term Children** Aged 6 to 23 Months. Pediatrics 2011 0: peds.2010-1920.
Gagnon R, Primeau MN, Des Roches A, Lemire C, Kagan R, Carr S, Ouakki M, Benoît M, De Serres G; PHAC-CIHR Influenza Research Network. Safe vaccination of patients with **egg allergy with an adjuvanted pandemic H1N1 vaccine**. J Allergy Clin Immunol. 2010 Aug;126(2):317-23.
Garcia-Garcia L, Valdespino-Gómez JL, Lazcano-Ponce E, et al. **Partial protection** of seasonal trivalent inactivated vaccine against novel **pandemic** influenza A/H1N1 2009: case-control study in Mexico City. BMJ. 2009 Oct 6;339:b3928. doi: 10.1136/bmj.b3928.
Gelinck LB, van der Bijl AE, Beyer WE, et al. The effect of **anti-tumor necrosis factor** alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis. 2007 Oct 26; [Epub ahead of print] The antibody response to influenza vaccination in patients treated with anti-TNF is only modestly impaired. The proportion of patients that achieves a protective titer is not significantly diminished by the use of TNF blocking therapies.
Gelinck LB, van den Bemt BJ, Marijt WA, et al. **Intradermal** influenza vaccination in immunocompromized patients is immunogenic and feasible. Vaccine. 2009 Apr 21;27(18):2469-74. Epub 2009 Feb 24.
Gilca R, Deceuninck G, De Serres G, et al. Effectiveness of **Pandemic H1N1 Vaccine** Against Influenza-Related **Hospitalization** in Children. Pediatrics. 2011Nov;128(5):e1084-91.
Glezen WP. Clinical practice. **Prevention and treatment of seasonal influenza**. N Engl J Med. 2008 Dec 11;359(24):2579-85.
Goossen GM, Kremer LC, van de Wetering MD. Influenza vaccination in **children** being treated with **chemotherapy** for cancer. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006484. Paediatric oncology patients receiving chemotherapy are able to generate an immune response to the influenza vaccine, but it remains unclear whether this immune response protects them from influenza infection or its complications.
Greer LG, Sheffield JS, Rogers VL, Roberts SW, McIntire DD, Wendel GD Jr. **Maternal and neonatal outcomes** after antepartum treatment of influenza with antiviral medications. Obstet Gynecol. 2010 Apr;115(4):711-6.
Hambidge SJ, et al. Vaccine Safety Datalink Team. Safety of trivalent inactivated influenza **vaccine** in **children 6 to 23 months** old. JAMA. 2006 Oct 25;296(16):1990-7.
Hambidge SJ et al. the Vaccine Safety Datalink Team. Trivalent Inactivated Influenza Vaccine Is **Not Associated With Sickle Cell Crises** in Children. Pediatrics. 2011 Dec 12.
Han F, Lin L, Warby SC, Faraco J, Li J, et al. **Narcolepsy onset** is seasonal and increased following the 2009 H1N1 pandemic in china. Ann Neurol. 2011 Sep;70(3):410-7.
Harper SA, Bradley JS, Englund JA, File TM, et al. Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in **adults and children**--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. (**IDSA**) Clin Infect Dis 2009 Apr 15;48(8):1003-32. http://www.journals.uchicago.edu/doi/pdf/10.1086/598513
Hatakeyama S, Sugaya N, Ito M, et al. Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. JAMA. 2007 Apr 4;297(13):1435-42. In 1 (1.4%) of the 74 children who had received oseltamivir, we identified a variant with reduced drug sensitivity possessing a Gly402Ser neuraminidase substitution. We also identified variants with reduced sensitivity carrying an Asp198Asn, Ile222Thr, or Ser250Gly mutation in 7 (1.7%) of the 422 viruses from untreated patients. In this population, influenza B viruses with reduced sensitivity to neuraminidase inhibitors do not arise as frequently as resistant influenza A viruses. However, they appear to be transmitted within communities and families, requiring continued close monitoring.
Hayden FG. Antiviral resistance in influenza viruses--implications for management and pandemic response. N Engl J Med. 2006 Feb 23;354(8):785-8.
Hayward AC, Harling R, Wetten S, et la. Effectiveness of an influenza vaccine programme for **care home staff** to prevent death, morbidity, and health service use among residents: cluster randomized controlled trial. BMJ. 2006 Dec 1; [Epub ahead of print]
Health Canada Nov/06 (Tamiflu warning) Informing Canadians of international reports of hallucinations and abnormal behaviour, including self harm, in patients taking the antiviral drug Tamiflu.http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_116_e.html
Heinonen Santtu, Silvennoinen Heli, Lehtinen Pasi, et al. Effectiveness of inactivated **influenza vaccine in children aged 9 months to 3 years**: an observational cohort study, The

TOP

Lancet Infectious Diseases, Volume 11, Issue 1, January 2011
Hernandez Jaime E., Adiga Raghavendra, Armstrong Robert, et al. and on behalf of the eIND Peramivir Investigators. Clinical Experience in Adults and Children Treated with **Intravenous Peramivir** for 2009 Influenza A (H1N1) Under an Emergency IND Program in the United States *Clin Infect Dis.* (2011) 52(6): 695-706 doi:10.1093/cid/cir001
Hessen, Margaret Trexler. **In the Clinic: Influenza**. Ann Intern Med November 3, 2009 151:ITC5-1; doi:10.1059/0003-4819-151-9-200911030-01011.
Hoen AG, Buckeridge DL, Charland KML, et al. Effect of expanded US recommendations for seasonal influenza vaccination: comparison of two **pediatric emergency departments** in the United States and Canada. CMAJ 2011;183:E1021-8.
Holodniy M, Penzak SR, et al. Pharmacokinetics and Tolerability of Oseltamivir (Tamiflu(R)) Combined with **Probenecid**. Antimicrob Agents Chemother. 2008 Jun 16. [Epub ahead of print] Alternate day dosing of oseltamivir plus four times daily probenecid achieved trough oseltamivir carboxylate concentrations adequate for neuraminidase inhibition in vitro; and this combination should be studied further.
Holvast A, van Assen S, et al. Studies of cell-mediated immune responses to influenza vaccination in systemic **lupus** erythematosus. Arthritis Rheum. 2009 Aug;60(8):2438-47.
Holvast A, et al. Safety & efficacy of influenza vaccination in systemic **lupus** erythematosus patients with quiescent disease. Ann Rheum Dis. 2006 Jul;65(7):913-8. Epub 2005 Dec1. In addition to a decreased antibody response, cell-mediated responses to influenza vaccination are diminished in patients with SLE, which may reflect the effects of the concomitant use of immunosuppressive drugs. This may render these patients more susceptible to (complicated) influenza infections.
Hsu J, Santesso N, et al. **Antivirals for Treatment of Influenza**: A Systematic Review and Meta-analysis of Observational Studies. Ann Intern Med. 2012 Apr 3;156(7):512-24.
Hughes RA, et al. No association between immunization and **guillain-barre syndrome** in the United kingdom, 1992 to 2000. Arch Intern Med. 2006 Jun 26;166(12):1301-4.
Hurst FP, Lee JJ, Jindal RM, et al. Outcomes Associated with Influenza Vaccination in the First Year **after Kidney Transplantation**. Clin J Am Soc Nephrol. 2011 Apr 28. April 28
Hurt AC, Hardie K, Wilson NJ et al. **Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza**. N Engl J Med. 2011 Dec 29;365(26):2541-2.
Hurt AC et al. on behalf of the WHO Consultation on Pandemic Influenza A (H1N1) 2009 Virus Resistance to Antivirals. **Antiviral resistance** during the 2009 influenza A H1N1 pandemic: public health, laboratory, and clinical perspectives. Lancet Infect Dis. 2011 Dec 16.
Infectious Diseases and Immunization Committee, Canadian Paediatric Society. **Autistic spectrum disorder**: no causal relationship with vaccines. Paediatrics & Child Health 2007;12(5): 393-5.http://www.cps.ca/english/statements/id/pidnote_jun07.htm (accessed 2007 Dec 4). http://www.cps.ca/english/statements/ID/PIDnote_Jun07.pdf
Influenza vaccine 2005-2006. Med Lett Drugs Ther. 2005 Oct 24;47(1220):85-7
Influenza Vaccination in Children: Missed Second Doses & Use of Antiviral Drugs for Influenza: Canadian Guidelines. Pharmacist's Letter Jan 2007.
Izurieta HS, Haber P, Wise RP, et al. Adverse events reported following live, cold-adapted, **intranasal influenza** vaccine. JAMA. 2005 Dec 7;294(21):2720-5.
Jackson ML, Nelson JC, Weiss NS, et al. Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: a population-based, nested case-control study. Lancet. 2008 Aug 2;372(9636):398-405. The effect of influenza vaccination on the risk of pneumonia in elderly people during influenza seasons might be less than previously estimated.
Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during **pregnancy** in the USA. Lancet. 2009 Jul 28. Pregnant women might be at increased risk for complications from pandemic H1N1 virus infection. These data lend support to the present recommendation to promptly treat pregnant women with H1N1 influenza virus infection with anti-influenza drugs.
Jefferson T, Rivetti D, et al. Efficacy & effectiveness of influenza vaccines in **elderly** people: a systematic review. Lancet. 2005 Oct1;366(9492):1165-74.Epub 2005Sep 22. (InfoPOEMs: Flu shots prevent influenza and influenza-like illness in the elderly. (LOE = 1a-))
Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, et al. Antivirals for influenza in **healthy adults**: systematic review.Lancet. 2006 Jan 28;367(9507):303-13. (InfoPOEMs: Antiviral agents are only slightly effective in preventing confirmed influenza or flu-like illness. When given in the first few days of illness, the M2 ion blockers and neuraminidase inhibitors reduce the duration of illness by **approximately 1 day**. (LOE = 1a)) (Jefferson T, Demet al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev. 2006 Jul 19;3:CD001265.)
Jefferson T, Assessment of the efficacy and effectiveness of influenza vaccines in healthy **children**: systematic review. Lancet. 2005 Feb 26-Mar 4;365(9461):773-80.
Jefferson T, Deeks JJ, Demicheli V, et al. Amantadine and rimantadine for preventing and treating influenza A in adults. Cochrane Database Syst Rev. 2004;(3):CD001169.
Jefferson T, Foxlee R, Del Mar C, et al. **Physical interventions** to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ. 2008 Jan 12;336(7635):77-80.
Jefferson Tom, Mar Chris Del, et al. **Physical interventions** to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2009;339:b3675, doi: 0.1136/bmj.b3675 (Published 22 September 2009)
Jefferson T, et al. Vaccines for preventing influenza in **healthy children**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD004879. Influenza vaccines are efficacious in children older than two but little evidence is available for children under two. There was a marked difference between vaccine efficacy and effectiveness. No safety comparisons could be carried out, emphasizing the need for standardisation of methods and presentation of vaccine safety data in future studies. It was surprising to find only one study of inactivated vaccine in children under two years, given current recommendations to vaccinate healthy children from six months old in the USA and Canada. If immunisation in children is to be recommended as a public health policy, large-scale studies assessing important outcomes and directly comparing vaccine types are urgently required.
Jefferson T, Jones M, Doshi P, Del Mar C. **Possible harms of oseltamivir**—a call for urgent action. Lancet. 2009 Oct 17;374(9698):1312-3.
Jefferson Tom, Jones Mark, Doshi Peter, et al. **Neuraminidase inhibitors** for preventing and treating influenza in healthy **adults**: systematic review and meta-analysis. BMJ 2009;339:b5106, doi: 10.1136/bmj.b5106 (Published 8 December 2009) . Neuraminidase inhibitors have modest effectiveness against the symptoms of influenza in otherwise healthy adults. The drugs are effective postexposure against laboratory confirmed influenza, but this is a small component of influenza-like illness, so for this outcome neuraminidase inhibitors are not effective.
Jefferson T, Di Pietrantonj C, Rivetti A, et al. **Vaccines for preventing influenza** in healthy adults. Cochrane Database Syst Rev. **2010** Jul 7;7:CD001269. Influenza vaccines have a modest effect in reducing influenza symptoms and working days lost. There is no evidence that they affect complications, such as pneumonia, or transmission.
Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965. We found a high risk of publication and reporting biases in the trial programme of oseltamivir. Sub-population analyses of the influenza infected population in the oseltamivir trial programme are not possible because the two arms are non-comparable due to oseltamivir's apparent interference with antibody production. The evidence supports a direct oseltamivir mechanism of action on symptoms but we are unable to draw conclusions about its effect on complications or transmission. We expect full clinical study reports containing study protocol, reporting analysis plan, statistical analysis plan and individual patient data to clarify outstanding issues. These full clinical study reports are at present unavailable to us.

TOP

Joseph KS, Liston RM. H1N1 influenza in **pregnant** women. BMJ. 2011 Jun 14;342:d3237.
Juurlink DN, et al. **Guillain-Barre syndrome** after influenza vaccination in adults: a population-based study. Arch Intern Med. 2006 Nov 13;166(20):2217-21.
Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract **complications** and hospitalizations. Arch Intern Med 2003;163:1667-72.
Kandun IN, et al. Three Indonesian Clusters of **H5N1** Virus Infection in 2005. N Engl J Med. 2006 Nov 23;355(21):2186-2194.
Kawai N, et al. A comparison of the effectiveness of **oseltamivir** for the treatment of influenza A and influenza B: a Japanese multicenter study of the 2003-2004 and 2004-2005 influenza seasons. Clin Infect Dis. 2006 Aug 15;43(4):439-44. Epub 2006 Jun 26.
Kedia S, Stroud B, Parsons J, et al. **Pediatric Neurological Complications of 2009 Pandemic Influenza A (H1N1)**. Arch Neurol. 2011 Apr;68(4):455-62.
Keitel WA, et al. Safety of **high doses** of **influenza vaccine** and effect on antibody responses in **elderly** persons. Arch Intern Med. 2006 May 22;166(10):1121-7.
Kerzner B, Murray AV, Cheng E, et al. Safety and immunogenicity profile of the concomitant administration of ZOSTAVAX and inactivated influenza vaccine in adults aged 50 and older. J Am Geriatr Soc. 2007 Oct;55(10):1499-507. **ZOSTAVAX and influenza vaccine** given concomitantly are generally well tolerated in adults aged 50 and older. Ab responses were similar whether ZOSTAVAX and influenza vaccine were given concomitantly or sequentially.
Kim SH, Hong SB, Yun SC, et al. Korean Society of Critical Care Medicine H1N1 Collaborative. **Corticosteroid** treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 2011;183:1207–1214.
Kohno S et al. Efficacy and safety of intravenous **peramivir** for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother* 2010 Nov; 54:4568.
Kumar Anand; Zarychanski Ryan; Pinto Ruxandra; et al. for the **Canadian** Critical Care Trials Group H1N1 Collaborative.Critically Ill Patients With 2009 Influenza A(**H1N1**) Infection in Canada. JAMA. 2009;0(2009):2009.1496.
Kwong JC, Stukel TA, Lim J, McGeer AJ, et al. The effect of universal influenza immunization on mortality and health care use. PLoS Med. 2008 Oct 28;5(10):e211. Compared to targeted programs in other provinces, introduction of universal vaccination in Ontario in 2000 was associated with relative reductions in influenza-associated mortality and health care use. The results of this large-scale natural experiment suggest that **universal vaccination** may be an effective public health measure for reducing the annual burden of influenza.
Kwong JC, Maaten S, Upshur RE, Patrick DM, Marra F. The effect of **universal** influenza immunization on antibiotic prescriptions: an ecological study. Clin Infect Dis. 2009 Sep 1;49(5):750-6. Universal influenza immunization is associated with reduced influenza-associated antibiotic prescriptions.
Kelso JM, Li JT, Nicklas RA, et al. Joint Task Force on Practice Parameters. **Adverse reactions to vaccines**. Ann Allergy Asthma Immunol. 2009 Oct;103(4 Suppl 2):S1-14.
Khazeni N, Bravata DM, Holty JE, et al. Safety and Efficacy of **Extended-Duration Antiviral Chemoprophylaxis** Against Pandemic and Seasonal Influenza. Ann Intern Med. 2009 Aug 3. [Epub ahead of print]
Kumar D, Michaels MG, Morris MI, et al. American Society of Transplantation H1N1 Collaborative Study Group. Outcomes from pandemic influenza A H1N1 infection in recipients of **solid-organ transplants**: a multicentre cohort study. Lancet Infect Dis. 2010 Aug;10(8):521-6.
Lambert Linda C., Fauci Anthony S., Influenza **Vaccines for the Future**. N Engl J Med 2010; 363:2036-2044.
Lavelle TA, Uyeki TM, Prosser LA. **Cost-Effectiveness of Oseltamivir** Treatment for Children with Uncomplicated Seasonal Influenza. J Pediatr. 2011 Sep 12.
Le QM, Kiso M, Someya K, et al. Avian flu: isolation of drug-resistant H5N1 virus. Nature. 2005 Oct 20;437(7062):1108.
Lee N, Cockram CS, Chan PK, et al. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. Clin Infect Dis 2008;46:1323-4.
Lee, Vernon J., Yap, Jonathan, Cook, Alex R. et al; **Oseltamivir Ring Prophylaxis** for Containment of 2009 H1N1 Influenza Outbreaks, N Engl J Med 2010 362: 2166-2174.
Lehmann HC, Hartung HP, Kieseier BC, Hughes RA. **Guillain-Barré syndrome** after exposure to influenza virus. Lancet Infect Dis. 2010 Sep;10(9):643-51.
Lewis EN, Griffin MR, Szilagyi PG, Zhu Y, et al. Childhood influenza: **number needed to vaccinate** to prevent 1 hospitalization or outpatient visit. Pediatrics. 2007 Sep;120(3):467-72. With 1 outpatient visit being prevented through vaccination of <50 children, influenza vaccination can reduce influenza-attributable medical visits in children significantly, even in years with modest vaccine efficacy.
Lin J, et al. Safety and immunogenicity of an inactivated adjuvanted whole-virion influenza A (**H5N1**) vaccine: a phase I randomised controlled trial. Lancet. 2006 Sep 16;368(9540):991-7.
Loeb M; Russell ML.; Moss L; et al. Effect of **Influenza Vaccination** of Children on Infection Rates in **Hutterite** Communities: A Randomized Trial. JAMA. 2010;303(10):943-950.
Louie JK, Acosta M, Samuel MC, et al. A novel risk factor for a novel virus: **obesity** and 2009 pandemic influenza A (H1N1). Clin Infect Dis. 2011 Feb 1;52:1-12.
Macdonald NE, Riley LE, Steinhoff MC. Influenza Immunization in **Pregnancy**. Obstet Gynecol. 2009 Aug;114(2, Part 1):365-368. PubMed PMID: 19622998.
Madjid M, Miller CC, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed **coronary heart disease death**: results from 8 Years of autopsies in 34 892 subjects. Eur Heart J. 2007 Apr 17; [Epub ahead of print]
Mahmud SM., Becker M, Keynan Y et al. Estimated cumulative incidence of pandemic (H1N1) influenza among **pregnant women** during the first wave of the 2009 pandemic. CMAJ 2010 182: 1522-1524.
Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in **pregnancy**: current evidence and selected national policies. Lancet Infect Dis. 2008 Jan;8(1):44-52.

TOP

Martin ST, Torabi MJ, Gabardi S. Influenza in **Solid Organ Transplant Recipients** (February). Ann Pharmacother. 2012 Jan 10.
Matheson NJ, Harnden AR, Perera R, et al. Neuraminidase inhibitors for preventing and treating influenza in **children**. Cochrane Database Syst Rev 2007;(1):CD002744.
Maxwell SR. Tamiflu and neuropsychiatric disturbance in adolescents. BMJ. 2007 Jun 16;334(7606):1232-3.
Mayor S. Review says oseltamivir and zanamivir should be kept for epidemics of flu. BMJ. 2006 Jan 28;332(7535):196.
McGeer A, Green KA, Plevneshi A, et al. Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis. 2007 Dec 15;45(12):1568-75. There is a significant burden of illness attributable to influenza in this highly vaccinated population. Treatment with antiviral drugs was associated with a significant reduction in mortality.
McGrath LJ, Kshirsagar AV, et al. Influenza vaccine effectiveness in patients on **hemodialysis**: an analysis of a natural experiment. Arch Intern Med. 2012 Apr 9;172(7):548-54.
Mirdamadi K, Einarson A. **H1N1** and influenza viruses: Why **pregnant** women might be hesitant to be vaccinated. Can Fam Physician. 2011 Sep;57(9):1003-4.
Monto AS, et al. Detection of Influenza Viruses **Resistant to Neuraminidase Inhibitors** in Global Surveillance during the First 3 Years of Their Use. Antimicrob Agents Chemother. 2006 Jul;50(7):2395-402.
Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med. 2005 Sep 29;353(13):1363-73.
Moscona A. Global transmission of **oseltamivir-resistant** influenza. N Engl J Med. 2009 Mar 5;360(10):953-6. Epub 2009 Mar 2.
Murphy K, et al. Antibody response **after varicella vaccination** in children treated with **budesonide** inhalation suspension or non-steroidal conventional asthma therapy. Int J Clin Pract. 2006 Dec;60(12):1548-57. VZV antibody responses and tolerability to the live varicella vaccine in paediatric asthma patients treated with BIS vs. NSCAT were comparable, demonstrating that young children with asthma receiving nebulised BIS can be immunised effectively with Varivax.

NACI: National Advisory Committee on Immunization. Statement on seasonal trivalent inactivated influenza vaccine (TIV) for **2010-2011**. CCDR 2010;36(ACS-6):1-49. www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php (accessed August 30, 2010).

NACI: Statement on Seasonal Influenza vaccine for **2011-2012**. CCDR Sept 2011 (ACS-5) Vol 37. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php

NACI 2011: Recommendations on the use of **intradermal trivalent inactivated influenza vaccine** (TIV-ID). http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-4/index-eng.php

Neto HB, Farhat CK, Tregnaghi MW, et al.; for the D153-P504 LAIV Study Group. Efficacy and Safety of **1 and 2 Doses of Live Attenuated** Influenza Vaccine in Vaccine-Naive Children. Pediatr Infect Dis J. 2009 May;28(5):365-371.
Neuzil KM, et al. Immunogenicity and reactogenicity of **1 versus 2 doses** of trivalent inactivated influenza vaccine in vaccine-naive 5-8-year-old children. J Infect Dis. 2006 Oct 15;194(8):1032-9. Epub 2006 Sep 11.
Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the **community-dwelling elderly**. N Engl J Med. 2007 Oct 4;357(14):1373-81. During 10 seasons, influenza vaccination was associated with significant reductions in the risk of hospitalization for pneumonia or influenza and in the risk of death among community-dwelling elderly persons. Vaccine delivery to this high-priority group should be improved.
Nicholson KG, Abrams KR, Batham S, et al. Immunogenicity and safety of a two-dose schedule of **whole-virion and AS03(A)-adjuvanted** 2009 influenza A (H1N1) vaccines: a randomised, multicentre, age-stratified, head-to-head trial. Lancet Infect Dis. 2011 Feb;11(2):91-101.
Noah MA, Peek GJ, Finney SJ, et al. Referral to an **extracorporeal membrane oxygenation center** and mortality among patients with severe 2009 influenza A(H1N1) [published online October 5, 2011]. JAMA. doi:10.1001/jama.2011.1471.
Nolan T, Bernstein DI, Block SL, et al. for the LAIV Study Group. Safety and Immunogenicity of **Concurrent Administration** of Live Attenuated Influenza Vaccine With Measles-Mumps-Rubella and Varicella Vaccines to Infants 12 to 15 Months of Age.Pediatrics. 2008 Mar;121(3):508-516. Concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella vaccine and varicella vaccine provided equivalent immunogenicity, compared with separate administration, and was well tolerated.
Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of **influenza vaccines**: a systematic review and meta-analysis. Lancet Infect Dis 2011; online Oct 26.
Oner AF, et al. Avian Influenza A (**H5N1**) Infection in Eastern Turkey in 2006. N Engl J Med. 2006 Nov 23;355(21):2179-85.
Pasternak B, Svanström H, Mølgaard-Nielsen D, et al. Vaccination against **pandemic A/H1N1 2009 influenza in pregnancy** and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.
Paton Nicholas I, Lee Lawrence, Xu Ying, et al. **Chloroquine** for influenza prevention: a randomised, double-blind, placebo controlled trial, Lancet Infectious Diseases, 5 May 2011.
Pharmacist's Letter. **Canadian** Influenza update 2006-07. Sept 2006
Phrommintikul A, Kuanprasert S, et al. **Influenza vaccination reduces cardiovascular events** in patients with acute coronary syndrome. Eur Heart J. 2011 Jul;32(14):1730-5.
Piedra PA et al. Effects of **oseltamivir on influenza-related complications in children** with chronic medical conditions. *Pediatrics* 2009 Jul; 124:170.
Pierce M, Kurinczuk JJ, Spark P, et al. UKOSS. **Perinatal outcomes** after maternal 2009/H1N1 infection: national cohort study. BMJ. 2011 Jun 14;342:d3214.
Poehling KA, et al. Accuracy and impact of a point-of-care **rapid influenza test** in young children with respiratory illnesses. Arch Pediatr Adolesc Med. 2006 Jul;160(7):713-8. (InfoPOEMs: Rapid influenza testing is very accurate, but the results don't seem to influence care in a meaningful way other than to decrease testing in those children seen in the emergency department. (LOE = 1b))
Poehling KA, et al.; New Vaccine Surveillance Network. The underrecognized burden of influenza in **young children**. N Engl J Med. 2006 Jul 6;355(1):31-40.

TOP

Poehling KA, Szilagyi PG, Staat MA, et al. New Vaccine Surveillance Network. Impact of **maternal immunization** on influenza hospitalizations in infants. Am J Obstet Gynecol. 2011 Jun;204(6 Suppl 1):S141-8.

Presanis AM, Pebody RG, Paterson BJ, et al. **Changes in severity of 2009 pandemic A/H1N1** influenza in England: a Bayesian evidence synthesis. BMJ. 2011 Sep 8;343:d5408.

Price, CS., Thompson, WW., et al. Prenatal and Infant Exposure to **Thimerosal** From Vaccines and Immunoglobulins and Risk of **Autism**. Pediatrics 2010 0: peds.2010-0309.

Public Health Agency of **Canada Statement on Influenza Vaccination for the 2007-2008 Season** http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-07/index_e.html

Public Health Agency of **Canada Statement on Influenza Vaccination for the 2008-2009 Season** http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/acs-3/index-eng.php

Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic **paracetamol/acetaminophen** administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet. 2009 Oct 17;374(9698):1339-50.

Randolph AG et al. **Critically ill children** during the 2009–2010 influenza pandemic in the United States. Pediatrics 2011 Dec; 128:e1

Ribeiro AC, Guedes LK, Moraes JC, et al. **Reduced seroprotection after pandemic H1N1 influenza** adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis. 2011 Dec;70(12):2144-7.

Rivetti D, Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2006 Jul 19;3:CD004876.

Rubinstein E, Predy G, Sauvé L, et al. The responses of **Aboriginal Canadians to adjuvanted pandemic (H1N1)** 2009 influenza vaccine. CMAJ. 2011 Aug 8.

Sachedina N, Donaldson LJ. **Paediatric mortality** related to pandemic influenza A **H1N1** infection in England: an observational population-based study. Lancet. 2010 Oct 26.

Scharpé J, Evenepoel P, Maes B, et al. Influenza Vaccination Is Efficacious and Safe in **Renal Transplant** Recipients. Am J Transplant. 2007 Dec 19; [Epub ahead of print]

Schechter R, Grether JK. Continuing increases in **autism** reported to California's developmental services system: mercury in retrograde. Arch Gen Psychiatry. 2008 Jan;65(1):19-24.

Shuler CM, et al. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004. Pediatrics. 2007 Mar;119(3):e587-95. Full vaccination provided measurable protection against laboratory-confirmed influenza among children who were aged 6 to 59 months during a season with suboptimal vaccine match.

Shun-Shin Matthew, Thompson Matthew, Heneghan Carl, et al. **Neuraminidase inhibitors** for treatment and prophylaxis of influenza in **children**: systematic review and meta-analysis of randomised controlled trials**.** BMJ 2009;339:b3172, doi: 10.1136/bmj.b3172 (Published 10 August 2009)

Simonsen L, Taylor RJ, Viboud C, et al. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007 Oct;7(10):658-66. We conclude that frailty selection bias and use of non-specific endpoints such as all-cause mortality have led cohort studies to greatly exaggerate vaccine benefits. The remaining evidence base is currently insufficient to indicate the magnitude of the mortality benefit, if any, that elderly people derive from the vaccination programme.

Siriwardena AN, Gwini SM, Coupland C. Influenza vaccination, pneumococcal vaccination and risk of **AMI**: Matched case-control study. CMAJ 2010; DOI:10.1503/cmaj.091891.

Skowronski, DM., Hottes, TS., Janjua, NZ., et al. Prevalence of **seroprotection against** the pandemic (H1N1) virus after the 2009 pandemic. CMAJ 2010 0: cmaj.100910.

Skowronski Danuta M, Janjua Naveed Z, De Serres Gaston, et al. Effectiveness of **AS03 adjuvanted pandemic H1N1** vaccine: case-control evaluation based on sentinel surveillance system **in Canada**, autumn 2009. BMJ 2011;342:doi:10.1136/bmj.c7297 (Published 3 February 2011)

Skowronski DM, Hottes TS, Chong M, et al. Randomized controlled trial of dose response to influenza vaccine in **children aged 6 to 23 months**. Pediatrics. 2011 Aug;128(2):e276-89.

Smith S, Demicheli V, Di Pietrantonj C, et al. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004879**.**

Smith SC Jr, et al. AHA/ACC guidelines for **secondary prevention** for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. **2006** May 16;113(19):2363-72. http://circ.ahajournals.org/cgi/reprint/113/19/2363

Smith JR, Sacks S. Incidence of **neuropsychiatric adverse events** in influenza patients treated with oseltamivir or no antiviral treatment. Int J Clin Pract. 2009 Apr;63(4):596-605.

Steinhoff MC, Omer SB, Roy E, et al. Neonatal outcomes after **influenza immunization during pregnancy**: a randomized controlled trial. CMAJ. 2012 Apr 3;184(6):645-53.

Stockwell MS, Kharbanda EO, Martinez RA, et al. Effect of a **text messaging** intervention on influenza vaccination in an urban, lowincome pediatric and adolescent population: a randomized controlled trial. JAMA. 2012;307(16):1702-1708.

Tanaka, Toshihiro, Nakajima, Ken, et al. Safety of **neuraminidase inhibitors** against novel influenza A **(H1N1) in pregnant** and breastfeeding women. CMAJ 2009 0: cmaj.090866

Tessmer A, Welte T, Schmidt-Ott R et al. for CAPNETZ study group. **Influenza vaccination** is associated with reduced severity of community acquired pneumonia. Eur Respir J. 2010 Dec 9.

Thomas RE, RussellM, Lorenzetti D. **Interventions to increase influenza vaccination** rates of those 60 years and older in the community. Cochrane Database of Systematic Reviews 2010, Issue 9. Art.No.: CD005188. DOI: 10.1002/14651858.CD005188.pub2.

Thorne-Humphrey LM, Goralski KB, et al. **Oseltamivir pharmacokinetics in morbid obesity** (OPTIMO trial). J Antimicrob Chemother. 2011;66:2083-91.

Thompson WW, Price C, Goodson B, et al.; Vaccine Safety Datalink Team. Early **thimerosal exposure** and neuropsychological outcomes at 7 to 10 years. N Engl J Med. 2007 Sep 27;357(13):1281-92. Our study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the age of 7 to 10 years.

Treanor JJ, et al. Safety and immunogenicity of an inactivated subvirion influenza A **(H5N1) vaccine**. N Engl J Med. 2006 Mar 30;354(13):1343-51.

Treanor JJ, et al. Safety & immunogenicity of baculovirus-expressed (non-egg) hemagglutinin influenza vaccine: a randomized controlled trial. JAMA. 2007 Apr11;297(14):1577-82.

van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with **rituximab**. Arthritis

TOP

Rheum. 2009 Dec 28;62(1):75-81. [Epub ahead of print]
Vanhems Philippe; Voirin Nicolas; Roche Sylvain; et al. **Risk of Influenza-Like Illness in an Acute Health Care Setting** During Community Influenza Epidemics in 2004-2005, 2005-2006, and 2006-2007: A Prospective Study. Arch Intern Med. 2011;171(2):151-157.
Vesikari T et al. Oil-in-water emulsion **adjuvant** with influenza vaccine in young children. N Engl J Med 2011 Oct 13; 365:1406. (has MF59 contains squalene)
Viasus D, Paño-Pardo JR, Pachón J, et al. for the Novel Influenza A(H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI). **Timing of Oseltamivir** Administration and Outcomes in Hospitalized Adults With Pandemic 2009 Influenza A(H1N1) Virus Infection. Chest. 2011 Oct;140(4):1025-1032.
Vij NK, Stryker CC, Esper FP, et al. Influenza A/H1N1/09-10 **Infections in a NICU** During the 2009-2010 H1N1 **Pandemic**. Pediatrics. 2011 Nov;128(5):e1297-301.
Waddington CS, Walker WT, Oeser C, et al. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. BMJ. 2010 May 27;340:c2649. doi: 10.1136/bmj.c2649.
Wang Z, Tobler S, Roayaei J, Eick A. Live attenuated or **inactivated influenza** vaccines and medical encounters for respiratory illnesses among US military personnel. JAMA. 2009 Mar 4;301(9):945-53. Epub 2009 Mar 2. Vaccination with TIV was associated with fewer medical encounters related to pneumonia and influenza compared with LAIV or no immunization. In this annually immunized population, this effect was less apparent in those vaccinated with LAIV.
Wang C, Cao B, Liu QQ, et al. **Oseltamivir Compared With the Chinese Traditional Therapy Maxingshigan-Yinqiaosan** in the Treatment of H1N1 Influenza: A Randomized Trial. Ann Intern Med. 2011 Aug 16;155(4):217-225.
Webster, Duncan, Li, Yan, Bastien, Nathalie, et al. **Oseltamivir-resistant pandemic H1N1 influenza**. CMAJ 2011 0: cmaj.100313
Williams Derek J.; Hall Matthew; Brogan Thomas V.; et al. **Influenza Coinfection and Outcomes in Children With Complicated Pneumonia**. Arch Pediatr Adolesc Med. 2011;0(2011):archpediatrics.2010.295.
WHO Jan 18/07 - Two people who died of bird flu in Egypt last month had a strain of the H5N1 virus that has shown moderate resistance to the frontline antiviral Tamiflu, the World Health Organization (WHO) said on Thursday. http://www.who.int/csr/disease/avian_influenza/en/index.html
WHO May 2007, New data published by the World Health Organization (WHO) has confirmed a low frequency of resistance to the flu drug Tamiflu between 2003 and 2006, Roche announced. The information, published by WHO's Neuraminidase Inhibitor Susceptibility Network, shows that resistance to Tamiflu (oseltamivir) of approximately 0.3 percent was seen during the past three influenza seasons, during which the drug was used extensively in Japan. This level of resistance is extremely low compared with the 65 percent rate seen in Japan with another antiviral, amantadine.
Wong K, Campitelli MA, Stukel TA, Kwong JC. Estimating influenza vaccine **effectiveness** in **community-dwelling elderly** patients using the instrumental variable analysis method [published online February 27, 2012]. *Arch Intern Med*. 2012.
Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z, Hayden FG, et al. **Update on avian influenza A (H5N1)** virus infection in humans. N Engl J Med. 2008 Jan 17;358(3):261-73.
Writing Committee of the WHO Consultation on Clinical Aspects of **Pandemic (H1N1) 2009 Influenza**, Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection. N Engl J Med 2010 362: 1708-1719.
Wu J et al. **Safety and effectiveness of a 2009 H1N1 vaccine** in Beijing. *N Engl J Med* 2010 Dec 16; 363:2416.
Xiao-Feng Liang, Li Li, Da-Wei Liu, et al. Safety of Influenza A (**H1N1**) Vaccine in **Postmarketing Surveillance** in China. February 2, 2011 (10.1056/NEJMoa1008553)
Yu Hongjie, Liao Qiaohong, Yuan Yuan, et al. Effectiveness of **oseltamivir** on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. BMJ 341:doi:10.1136/bmj.c4779 (Published 28 Sept 2010).
Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, et al.. Effectiveness of **Maternal Influenza Immunization** in Mothers and Infants. N Engl J Med. 2008 Sep 17. [Epub ahead of print] Inactivated influenza vaccine reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants. Maternal influenza immunization is a strategy with substantial benefits for both mothers and infants.

WEBSITES & Updates:

Update: Influenza Activity --- United States, September 28--November 29, 2008

During September 28--November 29, 2008, influenza activity remained low in the United States. Of the few influenza viruses characterized thus far this season, **most are antigenically** related to the strains included in the 2008--09 influenza **vaccine**. Oseltamivir-resistant influenza A (H1N1) viruses have been detected, but currently available data are insufficient to predict their prevalence for the 2008--09 season. This report summarizes U.S. influenza activity* since the last update (1) and reviews new influenza vaccine recommendations for the current season. During September 28--November 29, 2008, approximately 150 World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System collaborating laboratories in the United States tested 24,657 respiratory specimens for influenza viruses; 365 (1.5%) were positive (Figure 1). Of these, 282

TOP

(77.3%) were influenza A viruses, and 83 (22.7%) were influenza B viruses. One hundred twenty-eight (45.4%) of the 282 influenza A viruses were subtyped; 112 (87.5%) of these were influenza A (H1) viruses, and 16 (12.5%) were influenza A (H3) viruses. Influenza-positive tests have been reported from 26 states in eight of the nine surveillance regions since September 28.
Enhanced surveillance for oseltamivir-resistant viruses is ongoing at CDC. Alternatives for antiviral treatment in the context of widely circulating **oseltamivir-resistant** viruses have been suggested. These treatment options, which might include preferential use of zanamivir or therapy with a combination of antivirals for certain patients, have been outlined in the ACIP 2008 influenza recommendations.†† Currently, the neuraminidase inhibitors oseltamivir and zanamivir remain the recommended medications for treatment and chemoprophylaxis of influenza. Clinicians should **remain alert for changes in recommendations** that might occur as the 2008--09 influenza season progresses. Recommendations regarding the use of antiviral medications might be revised if surveillance data indicate a substantial and widespread increase in the prevalence of oseltamivir-resistant influenza viruses in the United States. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5749a3.htm?s_cid=mm5749a3_e

CDC Flu Update:

http://www.cdc.gov/flu/

http://www.cdc.gov/flu/about/season/index.htm

Public Health Agency of Canada- FluWatch:

http://www.phac-aspc.gc.ca/fluwatch/

Swine Flue Outbreak – 2009 (Mexico & worldwide extension)

http://www.who.int/mediacentre/news/statements/2009/h1n1_20090427/en/index.html
http://www.cdc.gov/swineflu/

TOP

Primaquine 26.3mg tab (= 15mg base) ✗▼ PL

Terminal prophylaxis: effective against P. *vivax* & P. *ovale*. Used for pts that have had long exposure to malaria endemic areas (>8wks)[36]. Not required for travel to Haiti or the Dominican Republic as of July06 [2].

- **Chloroquine/doxycycline/mefloquine prophylaxis**: primaquine taken in conjunction with the last 2 wks of post-exposure prophylaxis, but may be taken immediately after.
- **Atovaquone/proguanil prophylaxis:** primaquine is taken during atovaquone/ proguanil post-exposure prophylaxis & then for an additional 7-14 days after.

Pediatric Dosing age >9yrs for prevention; any age for tx

Prophylaxis: 0.5 mg(base)/kg/day
Terminal Prophylaxis: 0.5 mg/kg/day x14d

Adult Dosing

Prophylaxis: 52.6 mg (30 mg base) OD $9
Terminal Proph.: 30 mg base/d x 14d $9

For prophylaxis: begin 1-2d prior to entering MRZ, continue during stay, & 1 wk after leaving

Primaquine eradicates latent parasites in the liver.

Comments

Second-line for chloroquine resistant areas

- 85- 95% effective against P. *falciparum* & P. *vivax*
- **Only therapy to prevent relapse from P. vivax & P.ovale** due to dormant hypnozoites in liver (relapse may occur within 5 years of exposure)

CI: **G6PD deficiency**/favism, pregnancy,rh. arthritis,lupus
SE: Well tolerated. GI upset; Take with food.
Missed Dose: Take next dose ASAP. However, if it is almost time for your next dose, skip the missed dose & go back to your regular dosing schedule. Do not double doses. **Take with food; not grapefruit juice**

Drug Treatment of Malaria: Tx will vary depending on species of malaria. For severe: (IV quinine or artensunate) + (Atovaquone/proguanil or doxycycline or clindamycin)

Other Investigational Drugs: **IV artesunat**e: investigational in the USA for treatement of severe malaria. {May be accessed in Canada through the Canadian Malarial Network. It is an alternative to quinine with less side effects, although limited long term experience with potential side effects from recurrent use.}

{Recent historical resistance trends: {choroquine sensitive areas: travel to **Caribbean** including Haiti and rural areas of Dominican Republic; travelers visiting resort areas not generally at risk; travel to Central America except Panama, Mexico, Argentina; parts of China / Middle east; geographic risk and resistance trends change over time.}

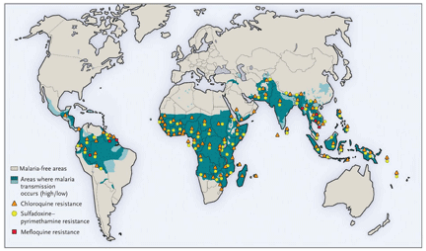
Approximate malaria risk (1 month stay without chemoprophylaxis): (source: CCDR 2000 Malaria Recommendations, p.3)

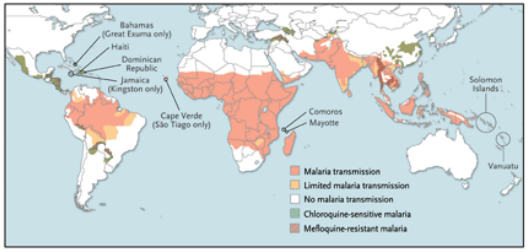
-	Oceania (Papua New Guinea, Irian Jaya, Solomon Islands, and Vanuatu)	1:30 or higher
-	Sub-Saharan Africa	1:50
-	Indian Subcontinent	1:250
-	Southeast Asia	1:1000
-	South America	1:2,500
-	Central America	1:10,000

- Risk also ↑'d with >6month stay, in part due to underuse of protection measures.
- Stand-By Emergency Treatment (self-admin) may be recommended in select cases.

References – Malaria Prophylaxis – www.RxFiles.ca

[1] WHO. Guidelines for the **treatment of malaria, 2nd edition. 2010**. www.who.int/malaria/publications/atoz/9789241547925/en/index.html
World Health Organization. (2006). **WHO Guidelines** for the treatment of Malaria. Geneva, Switzerland:. Website: http://www.who.int/malaria/ {**Other websites**: www.iamat.org & www.istm.org }





Thumbnails: Areas of Malaria Transmission and Antimalarial Drug Resistance. Data on malaria transmission are for 2007 and are from the World Health Organization. Data on drug resistance are for 2004 and are from the Roll Back Malaria partnership.**NEJM** June 5,2008. 2nd Map Thumbnail: NEJM Aug 7, 2008. **CDC Map**: http://cdc-malaria.ncsa.uiuc.edu/

[2] **Health Canada** – Malaria Website: http://www.phac-aspc.gc.ca/tmp-pmv/info/pal_mal_e.html#globaldist {Health Canada 2004. Supplement Canadian Recommendations … Prevention & Treatment of Malaria Among International Travelers. CCDR 2004;30SI:I-62}
Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers – 2009
http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09pdf/35s1-eng.pdf

[3] Baird JK. Effectiveness of antimalarial drugs. New England Journal of Medicine. 352(15):1565-77, 2005 Apr 14.

[4] Malaria in the Dominican Republic: Public Health Agency (n.d.). Retrieved June 15, 2006, from Public Health Agency of Canada Web site: http://www.phac-aspc.gc.ca/tmp-pmv/2006/mal_dr0131_e.html

[5] Gray J (Ed.). (2003). Therapeutic Choices. Ottawa:Canadian Pharmacists Association.

[6] Koda-Kimble MA, et al (Ed.). (2005) Applied Therapeutics: the clinical use of drugs 8th edition. Philadelphia : Lippincott Williams & Wilkins

[7] Recent health advisory: malaria in the Dominican Republic. Parmacist's Letter/Prescriber's Letter 2005;21(1):210122

[8] Hughes C, Tucker R, Bannister B, et al. Malaria prophylaxis for long-term travellers. Commun Dis Public Health. 2003 Sep;6(3):200-8.

[9] **Centers for Disease Control and Prevention (CDC).** Health Information for the International Traveler 2005-2006. Atlanta: US Department of Health and Human Services, Public Health Service, 2005. {"If the switch occurs 4 weeks or more before leaving the risk area, A/P should be taken for the remainder of the stay in the risk area and for one week thereafter. If the switch occurs less than four weeks before leaving the risk area, A/P should be taken for four weeks after the switch."} http://www.cdc.gov/malaria/

[10] Cockburn R, Newton PN, Agyarko EK et al.. The global threat of counterfeit drugs. PLoS Med. 2005 Apr;2(4):e100. http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020100

[11] Canadian Pharmacists Association. (2005). Compendium of Pharmaceuticals and Specialties. Canada: Webcom Limited

[12] Lacy C, Armstrong L, Goldman M, et al. (2004). Lexi-Comp's Drug Information Handbook 12th Edition. Ohio: Lexi-Comp.

[13] Saskatchewan Health. (2006). The Saskatchewan Formulary 56th Edition. Regina.

[14] USP DI (2006). Drug Information for the Healthcare Professional - 26th Ed. Retrieved June 14, 2006, from http://online.statref.com/document.aspx?fxid=6&docid=4023

[15] Canadian Pharmacists Association (2006). Electronic Compendium of Pharmaceuticals and Specialties. Retrieved 17 June 2006, from http://e-cps.pharmacists.ca.cyber.usask.ca/CPHA/main.htm

[16] Gilbert, D. N., R. C. Moellering, G. M. Eliopoulos, and M. A. Sande (eds). (2004). **The Sanford guide** to antimicrobial therapy, 2004. 34th ed. Antimicrobial Therapy, Inc., Hyde Park, VT.

[17] Health Canada. Canadian Immunization Guide 2002. Retrieved 01 August 2006,
from http://www.phac-aspc.gc.ca/publicat/cig-gci/pdf/cdn_immuniz_guide-2002-6.pdf

[18] *Taylor W, Robert J, White, Nicholas J.* Drug Safety. 27(1):25-61, 2004.

[19] van Riemsdijk MM. Sturkenboom MC. Pepplinkhuizen L. Stricker BH. Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in the Netherlands. Journal of Clinical Psychiatry. 66(2):199-204, 2005 Feb.

[20] van Riemsdijk MM. Sturkenboom MC. Ditters JM. Tulen JH. Ligthelm RJ. Overbosch D. Stricker BH. Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine. British Journal of Clinical Pharmacology. 57(4):506-12, 2004 Apr.

[21] Croft AM. Clayton TC. World MJ. Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. Transactions of the Royal Society of Tropical Medicine & Hygiene. 91(2):199-203, 1997 Mar-Apr.

[22] Pennie RA. Koren G. Crevoisier C. Steady state pharmacokinetics of mefloquine in long-term travellers. Transactions of the Royal Society of Tropical Medicine & Hygiene. 87(4):459-62, 1993 Jul-Aug.

[23] Overbosch D. Schilthuis H. Bienzle U. Behrens RH. Kain KC. Clarke PD. Toovey S. Knobloch J. Nothdurft HD. Shaw D. Roskell NS. Chulay JD. Malarone International Study Team. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clinical Infectious Diseases. 33(7):1015-21, 2001 Oct 1.

[24] Lobel HO. Miani M. Eng T. Bernard KW. Hightower AW. Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. Lancet. 341(8849):848-51, 1993 Apr 3.

[25] Knobloch J. Long-term malaria prophylaxis for travelers. Journal of Travel Medicine. 11(6):374-8, 2004 Nov-Dec.

[26] Steffen R. Heusser R. Machler R. Bruppacher R. Naef U. Chen D. Hofmann AM. Somaini B. Malaria chemoprophylaxis among European tourists in tropical Africa: use, adverse reactions, and efficacy. Bulletin of the World Health Organization. 68(3):313-22, 1990.

[27] Croft, AMJ, Garner P. **Mefloquine** for preventing malaria in non-immune adult travelers. The **Cochrane Database of Systematic Reviews** 2000, Issue $. Art No.: CD000138. DOI 10.1002/14651858.CD000138.

[28] Saskatoon District Health. International Travel Manual. (M-10) (pp12-24).

[29] Rosser WW, Pennie RA, Pilla NJ and the Anti-infective Review Panel. **Anti-infective Guidelines** for Community-acquired Infections. (Canadian)Toronto: **MUMS** Guideline Clearinghouse;2005. Updated **2012**.

[30] Treatment Guidelines from the Medical Letter: **Advice for Travelers**. May 2006; Vol4 (Issue 45). Updated **May 2012**

[31] Walsh DS. Eamsila C. Sasiprapha T. et al. Efficacy of monthly tafenoquine for prophylaxis of Plasmodium vivax and multidrug-resistant P. falciparum malaria. [Clinical Trial. Journal Article. Randomized Controlled Trial] Journal of Infectious Diseases. 190(8):1456-63, 2004 Oct

[32] Namale L, Burkiwa H. Tafenoquine for preventing malaria. (protocol) The Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004911.

[33] Graves P, Gelband H. **Vaccines** for preventing Malaria (SPf66). The **Cochrane Database of Systematic Reviews** 2006, Issue 2. Art. No.: CD005966.

[34] Current malaria risk by country: http://www.cdc.gov/malaria/

[35]

Hydroxychloroquine PLAQUENIL,g 200mg tab

{Not used very often! Licensed for malaria in USA**}**

Second-line: chloroquine sensitive malaria

PL

- Only in chloroquine-sensitive P. *falciparum* malaria prevention

{Opthalmological exam periodically if used weekly low dose long term; risk very low in first 5yrs; if >5yrs (BMJ,CDC), or high risk (ACP)}.

Pediatric: 5 mg base/kg weekly (200 mg tab = 155 mg base) (Do not exceed adult dose)

- Adult: 400 mg **weekly**
- Begin **2 wks prior** to entering MRZ, continue during stay & **8 wks after** leaving MRZ

19

- **Caution**: pts with hepatic failure, **G6PD** deficiency, pre-existing auditory damage; psoriasis, prophyria {Pregnancy: considered safe} {May have lower retinal risk than chloroquine.}
- SE: N/V/D(↓ by giving with food or milk), pruritus, fatigue, seizures, headache & dizziness. Uncommon: alopecia, hair depigmentation, skin eruptions & seizures.
- DI: antacids, cimetidine, digoxin (increase dig level)
- Vaccine Interaction[17]: Assume same as chloroquine

[36] Juckett G. Malaria prevention in travelers. Am Fam Physician. 1999 May 1;59(9):2523-30, 2535-6. Review. Erratum in: Am Fam Physician 2000 Jan 1;61(1):50, 52.

Additional References:

AAO Task Force in ACP: Do you need to screen for hydroxychlorquine/Chloroquine retinopathy. 2008. Online at: http://www.acponline.org/clinical_information/guidelines/additional_sources/statement.htm

Abba K, Deeks JJ, Olliaro P, et al. **Rapid diagnostic tests** for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD008122. DOI: 10.1002/14651858.CD008122.pub2. The sensitivity and specificity of all RDTs is such that they can replace or extend the access of diagnostic services for uncomplicated *P. falciparum* malaria. HRP-2 antibody types may be more sensitive but are less specific than pLDH antibody-based tests, but the differences are small. The HRP-2 antigen persists even after effective treatment and so is not useful for detecting treatment failures.

Agnandji ST, Lell B, Soulanoudjingar SS, et al.RTS,S Clinical Trials Partnership. First results of phase 3 trial of **RTS,S/AS01 malaria vaccine** in African children. N Engl J Med. 2011 Nov 17;365(20):1863-75.

Ansah EK, Narh-Bana S, Epokor M, et al. **Rapid testing** for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana. BMJ. 2010 Mar 5;340:c930. doi: 10.1136/bmj.c930.

Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/

Artesunate IV for severe malaria by Special Access Program in Canada.

Asante KP, Abdulla S, Agnandji S, et al. Safety and efficacy of the **RTS,S/AS01(E) candidate malaria vaccine** given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis. 2011 Jul 20.

Batchelor T, Gherardin T. Prevention of malaria in travellers. Aust Fam Physician. 2007;36(5):316-320.

Bazemore A, Huntington M. The **Pretravel Consultation**. Am Fam Physician. 2009;80 (6):583-590.

Briggs G, Freeman, Roger, Yaffe, Sumner, ed. Drugs in Pregnancy and Lactation. 9th ed: TechBooks

Biai S, Rodrigues A, Gomes M, Ribeiro I, Sodemann M, Alves F, Aaby P. Reduced in-hospital mortality after improved management of children under 5 years admitted to hospital with malaria: randomised trial. BMJ. 2007 Oct 22; [Epub ahead of print]

Birbeck Gretchen L, Molyneux Malcolm E, Kaplan Peter W, et al. Blantyre Malaria Project Epilepsy Study (BMPES) of neurological outcomes (**epilepsy**) in retinopathy-positive paediatric **cerebral malaria** survivors: a prospective cohort study, The Lancet Neurology, Volume 9, Issue 12, December 2010

Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers – **2009** http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09pdf/35s1-eng.pdf

CDC: Malaria CDC 2008 **Travel Yellow book 2008** information http://wwwn.cdc.gov/travel/ybToc.aspx ; Peds dosing: http://wwwn.cdc.gov/travel/contentMalariaKidsHC.aspx

Checkley AM, Smith A, Smith V, et al. **Risk factors for mortality from imported** falciparum malaria in the United Kingdom over 20 years: an observational study. BMJ. 2012 Mar 27

Chen LH, Wilson ME, Schulagenhauf P. **Prevention** of malaria in long-term travelers. JAMA 2006;296(18):2234-44.

Chen LH, Wilson ME, Schlagenhauf P. Controversies and misconceptions in malaria **chemoprophylaxis** for travelers. JAMA. 2007 May 23;297(20):2251-63. Despite widespread reports on the adverse effects of mefloquine, controlled studies found that serious neuropsychiatric adverse events occur at rates comparable with or lower than other chemoprophylaxis drugs. Moreover, mefloquine does not appear to impair performance while driving, flying, or diving. Vivax malaria causes significant illness in travelers, but current first-line chemoprophylaxis agents do not prevent relapses of vivax malaria. Although not licensed in most countries as primary prophylaxis, primaquine effectively prevents relapses of vivax malaria.

Chico RM, Mayaud P, Ariti C, et al. Prevalence of **Malaria and Sexually Transmitted and Reproductive Tract Infections in Pregnancy** in Sub-Saharan Africa: A Systematic Review Malaria and STIs/RTIs in Pregnancy in Africa. JAMA. 2012 May 16;307(19):2079-86.

Clinical Knowledge Summaries (CKS) – Malaria. Accessed at: www.cks.nhs.uk

Committee to Advise on Tropical medicine and Travel. **Statement on older travellers**. CCDR 2011;37(ASC2):1-24. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-2/index-eng.php

Committee to Advise on Tropical Medicine and Travel (**CATMAT**). **Fever in the Returning International Traveller** Initial Assessment Guidelines. July 2011 http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-3/pdf/returningtravellerfever-fievrevoyageurderetour-eng.pdf

Corbel V, Akogbeto M, et al. Combination of malaria **vector control interventions in pyrethroid resistance** area in Benin: cluster randomised controlled trial. Lancet Infect Dis; online June 7, 2012.

Dhalla F, Gulati P, Sreerangaiah D, Abraham SM. A man with **thrombocytopenia**. BMJ. 2012 Feb 16;344:e826.

Dicko A, Doumbo O. Efficacy of **RTS,S malaria vaccine** given with EPI vaccines. Lancet Infect Dis. 2011 Jul 20.

Dondorp AM, Fanello CI, Hendriksen IC, et al. **Artesunate** versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010 Nov 7.

Dondorp Arjen M., Fairhurst Rick M., Slutsker Laurence. The Threat of **Artemisinin-Resistant Malaria**. N Engl J Med 365;12 nejm.org september 22, 2011

Enayati A, Hemingway J, Garner P. **Electronic mosquito repellents** for preventing mosquito bites and malaria infection. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005434. Field entomological studies confirm that EMRs have no effect on preventing mosquito bites. Therefore there is no justification for marketing them to prevent malaria infection.

FDA June /09 approved safety labeling revisions for chloroquine phosphate tablets (Aralen, sanofi-aventis US) to warn of the potential for serious adverse events in **nursing infants**. According to the FDA, a decision should be made whether to discontinue therapy or stop nursing, taking into account the potential clinical benefit of the drug to the mother. In a study of 11 lactating mothers, the maximum daily dose of the drug received by the breast-feeding infant was about 0.7% of the maternal start dose (600 mg base) in malaria chemotherapy. Separate chemoprophylaxis for the infant is required.

Flateau Clara, Le Loup Guillaume, Pialoux Gilles. Consequences of **HIV infection on malaria** and therapeutic implications: a systematic review. Lancet Infect Dis 2011; 11: 541–56.

Freedman DO. **Malaria prevention in short-term travelers**. N Engl J Med. 2008 Aug 7;359(6):603-12.

Galappaththy G, Omari A, Tharyan P. Primaquine for preventing relapses in people with Plasmodium vivax malaria. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004389.

Griffith KS, Lewis LS, Mali S, Parise ME. **Treatment of malaria** in the United States: a systematic review. JAMA. 2007 May 23;297(20):2264-77.

Hay SI, Guerra CA, Gething PW, Patil AP, et al. A **world malaria map**: Plasmodium falciparum endemicity in 2007. PLoS Med. 2009 Mar 24;6(3):e1000048.

Hidalgo Kathleen, Lyles Adraine, Dean Stacey R. A Potential Interaction between **Warfarin and Atovaquone**. Ahead of Print on 1 January 2011, DOI 10.1345/aph.1P491. Ann Pharmacother ;45:e3.

Hill DR, et al. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(12):1499-1539.

Hill N, Lenglet A, Arnéz AM, et al. Plant based **insect repellent and insecticide treated bed nets** to protect against malaria in areas of early evening biting vectors: double blind randomised placebo controlled clinical trial in the Bolivian Amazon. BMJ. 2007 Nov 17;335(7628):1023. Epub 2007 Oct 16. Insect repellents can provide protection against malaria. In areas where vectors feed in the early evening, effectiveness of treated nets can be significantly increased by using repellent between dusk and bedtime. This has important implications in malaria vector control programmes outside Africa and shows that the combined use of treated nets and insect repellents, as advocated for most tourists travelling to high risk areas, is fully justified.

Irvine Marie-Hélène, Einarson Adrienne, Bozzo Pina. Prophylactic use of **antimalarials during pregnancy**. Can Fam Physician November 2011 57: 1279-1281

Johnson BA, Kalra MG. **Prevention of Malaria in Travelers**. Am Fam Physician. 2012 May 15;85(10):973-977.

Kabyemela ER, Fried M, Kurtis JD, Duffy PE et al. Decreased susceptibility to Plasmodium falciparum infection in pregnant women with **iron deficiency**. J Infect Dis. 2008 Jul 15;198(2):163-6.

TOP

Lalloo DG, Hill DR. **Preventing malaria in travellers**. BMJ. 2008 Jun 14;336(7657):1362-6.

Laufer MK, et al. Return of chloroquine antimalarial efficacy in Malawi. N Engl J Med. 2006 Nov 9;355(19):1959-66.

Lobel HO, et al. Use of malaria prevention measures by North American and European travelers to **East Africa**. J Travel Med. 2001;8(4):167-172.

Lobel HO, Kozarsky PE. Update on prevention of malaria for travelers. JAMA. 1997;278(21):1767-1771.

Marchant T, Schellenberg D, et al. Assessment of a national voucher scheme to deliver **insecticide-treated mosquito nets** to pregnant women. CMAJ 2010 182: 152-156.

Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF; American Academy of Ophthalmology. Revised recommendations on screening for **chloroquine** and **hydroxychloroquine retinopathy**. Ophthalmology. 2011 Feb;118(2):415-22.

McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of **falciparum and vivax malaria** and the safety of **antimalarial treatment in early pregnancy**: a population based study. Lancet Infect Dis 2011; published online Dec 13. DOI:10.1016/S1473-3099(11)70339-5.

Medical Letter on Drugs and Therapeutics: **Drugs for Parasitic Infections** 1st Ed. 2007.

Medical Letter. Treatment Guidelines: **Advice for Travelers**. Nov 2009.

Meremikwu M, et al. **Chemoprophylaxis and intermittent treatment** for preventing malaria in children. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD003756. Prophylaxis and intermittent treatment with antimalarial drugs reduce clinical malaria and severe anaemia in preschool children.

Mirza DM, Hashim MJ, Sheikh A. **Malaria**. BMJ. 2011 Mar 15;342:d1149. doi:10.1136/bmj.d1149.

Nadjm B, Amos B, Mtove G, et al. WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense **Plasmodium falciparum** transmission: prospective study. BMJ. 2010 Mar 30;340:c1350.

Nevin RL, Pietrusiak PP, Caci JB. Prevalence of **contraindications to mefloquine** use among USA military personnel deployed to Afghanistan. Malar J. 2008 Feb 11;7:30.

Nayyar GM, Breman JG, Newton PN, Herrington J. **Poor-quality antimalarial drugs** in southeast Asia and sub-Saharan Africa. Lancet Infect Dis. 2012 Jun;12(6):488-96.

Obaro S, Greenwood B. **Malaria and bacteraemia** in African children. Lancet. 2011 Sep 6.

Olotu A, Lusingu J, Leach A, et al.Efficacy of **RTS,S/AS01E malaria vaccine** and exploratory analysis on anti-circumsporozoite antibody titres and protection in children aged 5-17 months in Kenya and Tanzania: a randomised controlled trial. Lancet Infect Dis. 2011 Feb;11(2):102-9.

Oniyangi O, Omari AA. Malaria chemoprophylaxis in sickle cell disease. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD003489. It is beneficial to give routine malaria chemoprophylaxis in sickle cell disease in areas where malaria is endemic.

Pasternak Bjorn; Hviid Anders. **Atovaquone-Proguanil Use in Early Pregnancy** and the Risk of Birth Defects. *Arch Intern Med*. 2011;171(3):259-260.

Pharmacist's Letter. **Insect Repellants**. July 2010.

Phiri K et al. **Intermittent preventive therapy for malaria** with monthly artemether-lumefantrine for the post-discharge management of severe anaemia in children aged 4-59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial. Lancet Infect Dis. 2011 Dec 13.

Public Health Agency of Canada. Canada Communicable Disease Report. Committee to Advise on Tropical Medicine and Travel (CATMAT) statement. Statement on **pregnancy and travel**. Mar 2010 http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-2/index-eng.php

Pyae Pho A, Nkhoma S, Stepniewska K, et al. Emergence of **artemisinin-resistant** malaria on the western border of Thailand: a longitudinal study. Lancet 2012; online April 5.

Roestenberg M, Teirlinck AC, McCall MB, et al. Long-term protection against malaria after **experimental sporozoite inoculation**: an open-label follow-up study. Lancet. 2011 Apr 21.

Rosenthal Philip J.. Lessons from **Sickle Cell Disease** in the Treatment and Control of Malaria. N Engl J Med 2011; 364:2549-2551.

Royal College of Obstetricians and Gynaecologists (RCOG). The **prevention of malaria in pregnancy**. London (UK): 2010 Apr.

Royal College of Obstetricians and Gynaecologists (RCOG). The **diagnosis and treatment of malaria in pregnancy**. London (UK) 2010 Apr.

RTS,S Clinical Trials Partnership. First results of phase 3 trial of **RTS,S/AS01 malaria vaccine** in African children. N Engl J Med 2011. DOI: 10.1056/NEJMoa1102287

Rueangweerayut R, Phyo AP, Uthaisin C, et al. **Pyronaridine-artesunate versus mefloquine plus artesunate** for malaria. N Engl J Med. 2012 Apr 5;366(14):1298-309.

Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis 2010;69(1):20-28.

Sandison TG, Homsy J, Arinaitwe E, et al. Protective efficacy of **co-trimoxazole prophylaxis against malaria in HIV exposed** children in rural Uganda: a randomised clinical trial. BMJ. 2011 Mar 31;342:d1617. doi:10.1136/bmj.d1617.

Schwartz BS, Larocque RC, Ryan ET. **Travel medicine**. Ann Intern Med. 2012 Jun 5;156(11):ITC61.

Scott JA, Berkley JA, Mwangi I, et al. Relation between **falciparum malaria and bacteraemia** in Kenyan children: a population-based, case-control study and a longitudinal study. Lancet. 2011 Sep 6.

Shah NK, Dhillon GP, Dash AP, Arora U, Meshnick SR, Valecha N. Antimalarial drug **resistance of Plasmodium falciparum in India**: changes over time and space. Lancet Infect Dis. 2011 Jan;11(1):57-64.

Sinclair D, Donegan S, Lalloo DG. **Artesunate versus quinine for treating severe malaria**. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD005967.

Tan IL, Koralnik IJ, Rumbaugh JA, et al. Progressive multifocal leukoencephalopathy in a patient without immunodeficiency. Neurology. 2011 Jul 19;77(3):297-9. (treated with mefloquine)

Taylor Steve M.; Molyneux Malcolm E.; Simel David L.; et al. **Does This Patient Have Malaria**? *JAMA*. 2010;304(18):2048-2056.

ter Kuile FO, van Eijk AM, Filler SJ. Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during **pregnancy**: a systematic review. JAMA. 2007 Jun 20;297(23):2603-16. In areas in which 1 of 4 treatments with sulfadoxine-pyrimethamine fail in children by day 14, the 2-dose IPT with sulfadoxine-pyrimethamine regimen continues to provide substantial benefit to HIV-negative semi-immune pregnant women. However, more frequent dosing is required in HIV-positive women not using cotrimoxazole prophylaxis for opportunistic infections.

Thera MA, Doumbo OK, Coulibaly D, et al. A field trial to assess a blood-stage **malaria vaccine**. N Engl J Med. 2011 Sep 15;365(11):1004-13.

Trape JF, Tall A, Diagne N, et al.Malaria morbidity and pyrethroid resistance **after the introduction of insecticide-treated bednets and artemisinin-based combination** therapies: a longitudinal study. Lancet Infect Dis. 2011 Aug 17.

van Eijk Anna Maria, Hill Jenny, Alegana Victor A, et al. Coverage of **malaria protection in pregnant women** in sub-Saharan Africa: a synthesis and analysis of national survey data, The Lancet Infectious Diseases, In Press, Corrected Proof, Available online 25 January 2011, ISSN 1473-3099, DOI: 10.1016/S1473-3099(10)70295-4.

Zurovac D, Sudoi RK, Akhwale WS, et al. The effect of **mobile phone text-message** reminders on Kenyan health workers' adherence to malaria treatment guidelines: a cluster randomised trial. Lancet. 2011 Aug 27;378(9793):795-803.

TOP

COMMUNITY ACQUIRED PNEUMONIA – Empiric Antibiotic Selection

References:

1. File TM Jr, Tan JS. **International guidelines** for the treatment of community-acquired pneumonia in adults: the role of macrolides. Drugs. **2003**;63(2):181-205.
2. Mandell LA et al. Canadian guidelines for initial management of community acquired pneumonia: an evidence-based update by the **Canadian** Infectious Diseases Society and the Canadian Thoracic Society. Clin Infec Dis **2000**; 31: 383-421.
3. Bartlett JG et al. **The Infectious Diseases Society of America**. Practice guidelines for management of community acquired pneumonia in adults. Clin Infec Dis **2000**; 31: 347-82.
4. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N, File T, Fine MJ, Gross PA, Martinez F, Marrie TJ, Plouffe JF, Ramirez J, Sarosi GA, Torres A, Wilson R, Yu VL. The Official Statement of the **American** Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med. **2001** Jun;163(7):1730-54.
5. Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C; **Infectious Diseases Society of America**. Update of practice guidelines for the management of community - acquired pneumonia in immunocompetent adults. Clin Infect Dis. **2003** Dec 1;37(11):1405-33. (Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG. **Infectious diseases society of America (IDSA) /American Thoracic Society** consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. **2007** Mar 1;44 Suppl 2:S27-72.) http://www.journals.uchicago.edu/CID/journal/issues/v44nS2/41620/41620.web.pdf?erFrom=5418644572597678115Guest
6. Medical Letter: **Treatment Guidelines.** Drugs for Pneumonia. September, **2003**; (13) pp. 83-88. (Medical Letter: Treatment Guidelines. **Choice of Antibacterial Drugs**. May 2007) Medical Letter. Treatment Guidelines. **Drugs for Bacterial Infections**. June 2010.
7. Dunbar LM, Khashab MM, Kahn JB, Zadeikis N, Xiang JX, Tennenberg AM. Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. Curr Med Res Opin. 2004 Apr;20(4):555-63. Erratum in: Curr Med Res Opin. 2004 Jun;20(6):967.
8. Leophonte P, File T, Feldman C. Gemifloxacin once daily for 7 days compared to amoxicillin/clavulanic acid thrice daily for 10 days for the treatment of community-acquired pneumonia of suspected pneumococcal origin. Respir Med. 2004 Aug;98(8):708-20.
9. Rosser W, Pennie R, Pilla N and the Anti-infective Review Panel (**Canadian**). Anti-infective Guidelines for Community-acquired Infections Toronto: MUMS Guideline Clearinghouse; 2005, 2010 & **Revised 2012**.
10. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med. 2004 Mar 22;164(6):637-44. (Kanwar M, Brar N, Khatib R, Fakih MG. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule. Chest. 2007 Jun;131(6):1865-9. Epub 2007 Mar 30. Linking antibiotic administration within 4 h of hospital admission (as a quality indicator) to financial compensation may result in an inaccurate diagnosis of CAP, inappropriate utilization of antibiotics, and thus less than optimal care.)
11. Mills GD, Oehley MR, Arrol B. Effectiveness of {beta} lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. BMJ 2005; 330:456-60. (InfoPOEMs: Strange, but true: Oral beta-lactam antibiotics -- amoxicillin, amoxicillin/clavulanate (Augmentin), or a cephalosporin -- are as effective in the treatment of community-acquired pneumonia as antibiotics active against atypical pathogens, even in patients infected with Mycoplasma pneumoniae or Chlamydia pneumoniae. These old standbys can be used instead of the more expensive drugs for most patients. Legionella infection still requires treatment with an antibiotic effective against atypical pathogens, but in these studies only 1.1% of the patients with nonsevere pneumonia had Legionella. These results are backed up by similar findings from clinical practice (Hedlund J, et al. Scand J Infect Dis 2002; 34:887-92). (LOE = 1a))
12. Carratala J, Fernandez-Sabe N, Ortega L, et al. Outpatient care compared with hospitalization for community-acquired pneumonia. Ann Intern Med 2005; 142:165-72. (Aujesky D, Auble TE, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med. 2005 Apr;118(4):384-92.) (Espana PP, et al. Development and Validation of a Clinical Prediction Rule for Severe Community-acquired Pneumonia. Am J Respir Crit Care Med. 2006 Dec 1;174(11):1249-56. Epub 2006 Sep 14.)(**CURB-65**: use of CURB-65 (Confusion, Urea > 7 mmol/L, Respiratory rate ≥ 30/min, systolic blood pressure ≤ 90 mm Hg, and diastolic blood pressure ≥ 60 mm Hg, and age 65 years or older). When calculating the 30-day mortality rate, if the CURB-65 score is greater or equal to 3, the site of care should be the intensive care unit (ICU). If the score is 2, admission to a hospital is sufficient. Outpatient management is warranted when the CURB-65 score is 0 or 1.)
13. Torres OH, Munoz J, et al. Outcome predictors of pneumonia in elderly patients: importance of functional assessment. J Am Geriatr Soc. 2004 Oct;52(10):1603-9. (The PSI may overpredict mortality in older adults. Relying on PSI, without taking into account a patients functional status, may lead to unnecessary and potentially harmful hospitalizations for pts who might otherwise have been safely treated at home ACP 2005)
14. Fuller JD, Low DE. A review of Streptococcus pneumoniae infection treatment failures associated with fluoroquinolone resistance. Clin Infect Dis. 2005 Jul 1;41(1):118-21. Epub 2005 May 26. There were 20 ciprofloxacin and levofloxacin treatment failures reported. Physicians should be aware, when treating pneumococcal respiratory tract infections in older patients with a fluoroquinolone, that clinical failures might occur, especially for patients with comorbid illnesses and a history of recent fluoroquinolone use.
15. Doern GV, Richter SS, Miller A, Miller N, Rice C, Heilmann K, Beekmann S. Antimicrobial resistance among Streptococcus pneumoniae in the United States: have we begun to turn the corner on resistance to certain antimicrobial classes? Clin Infect Dis. 2005 Jul 15;41(2):139-48. Epub 2005 Jun 7.
16. Abraham E, Laterre PF, Garg R, et al.; Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med. 2005 Sep 29;353(13):1332-41. CONCLUSIONS: The absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25.
17. Shefet D, Robenshtok E, Paul M, Leibovici L. Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. Arch Intern Med. 2005 Sep 26;165(17):1992-2000. CONCLUSION: Empirical antibiotic coverage of atypical pathogens in hospitalized patients with community-acquired pneumonia showed no benefit of survival or clinical efficacy in this synthesis of randomized trials.
18. D'Ignazio J, Camere MA, et al. Novel, Single-Dose Microsphere Formulation of Azithromycin versus 7-Day Levofloxacin Therapy for Treatment of Mild to Moderate Community-Acquired Pneumonia in Adults. Antimicrob Agents Chemother. 2005 Oct;49(10):4035-41. (InfoPOEMs: Although a single dose of azithromycin in an extended-release formulation was statistically similar to 7 days of levofloxacin, resistance was more common to strep pneumoniae with azithromycin and there was a trend toward worse outcomes with azithromycin using the intention-to-treat analysis. The study was also underpowered to detect clinically important differences based on the author's sample size calculations. (

TOP

19. Lexau CA, Lynfield R, Danila R, et al.; Active Bacterial Core Surveillance Team. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA. 2005 Oct 26;294(16):2043-51.
20. Drehobl MA, et al. **Single-dose azithromycin** microspheres vs clarithromycin extended release for treatment of mild-to-moderate CAP in adults. Chest. 2005 Oct;128(4):2230-7.
21. D'Ignazio J, Camere MA, Lewis DE, Jorgensen D, Breen JD. Novel, **single-dose** microsphere formulation of **azithromycin** versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired Pneumonia in adults. Antimicrob Agents Chemother. 2005 Oct;49(10):4035-41.
22. Epstein BJ, Gums JG. Optimal pharmacological therapy for community-acquired pneumonia: the role of **dual antibacterial therapy**. Drugs. 2005;65(14):1949-71.
23. Noreddin AM, Hoban DJ, Zhanel GG. Comparison of **gatifloxacin and levofloxacin** administered at various **dosing regimens** to hospitalised patients with community-acquired pneumonia: pharmacodynamic target attainment study using North American surveillance data for Streptococcus pneumoniae. Int J Antimicrob Agents. 2005 Aug;26(2):120-5.
24. Shorr AF, Kollef MH. **Ventilator-associated pneumonia**: insights from recent clinical trials. Chest. 2005 Nov;128(5 Suppl 2):583S-591S.
25. Schito GC, Felmingham D. Susceptibility of Streptococcus pneumoniae to penicillin, azithromycin and telithromycin (PROTEKT 1999-2003). Int J Antimicrob Agents. 2005 Dec;26(6):479-85. Epub 2005 Nov 9. Penicillin non-susceptibility rates were stable over the study period; overall, 21.8% of isolates were resistant. Azithromycin resistance increased from 31.0% in Year 1 to 36.3% in Year 4. Resistance rates for penicillin and azithromycin varied between countries and were highest in France, Spain, South Africa, USA and the Far East. Multidrug resistance in S. pneumoniae did not change significantly over the 4 years, with an overall rate of 38.6%. Telithromycin retained good activity against S. pneumoniae (0.1% of isolates resistant), including multidrug-resistant isolates.
26. Morganroth J, Dimarco JP, Anzueto A, Niederman MS, Choudhri S; CAPRIE Study Group. A randomized trial comparing the cardiac rhythm safety of **moxifloxacin** vs levofloxacin 500mg in elderly patients hospitalized with community-acquired pneumonia. Chest. 2005 Nov;128(5):3398-406.
27. Fry AM, et al. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. JAMA. 2005 Dec 7;294(21):2712-9.
28. Shefet D, Robenshtok E, Paul M, Leibovici L. Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. Arch Intern Med. 2005 Sep 26;165(17):1992-2000.(InfoPOEMs: Treating community-acquired pneumonia with antibiotics effective against atypical organisms is no better and no worse than treating with a penicillin or cephalosporin alone. (LOE = 1a))
29. Yealy DM, et al. Effect of increasing the intensity of **implementing pneumonia guidelines**: a randomized, controlled trial. Ann Intern Med. 2005 Dec 20;143(12):881-94.
30. Anzueto A, Niederman MS, Pearle J, et al.; Community-Acquired Pneumonia Recovery in the Elderly Study Group. Community-Acquired Pneumonia Recovery in the Elderly (**CAPRIE**): efficacy and safety of **moxifloxacin** therapy versus that of levofloxacin therapy. Clin Infect Dis. 2006 Jan 1;42(1):73-81. Epub 2005 Nov 22.
31. CAP Adults ICSI 2006 Outpatient Guidelines http://www.icsi.org/knowledge/detail.asp?catID=29&itemID=160
32. Loeb M, et al Effect of a clinical **pathway** to reduce hospitalizations in nursing home residents with pneumonia: a randomized controlled trial. JAMA. 2006 Jun 7;295(21):2503-10.
33. el Moussaoui R, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ. 2006 Jun 10;332(7554):1355. (InfoPOEMs: Dogma successfully challenged: In patients who respond well to initial treatment, stopping antibiotic therapy after 3 days is just as effective as continuing treatment for the standard 8 days. (LOE = 1b))
34. Hoare Z, Lim WS. Pneumonia: update on diagnosis and management. BMJ. 2006 May 6;332(7549):1077-9.
35. Christ-Crain M, et al. Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia: A Randomized Trial. Am J Respir Crit Care Med. 2006 Jul 1;174(1): 84-93. Epub 2006 Apr 7.
36. Canani RB, et al. Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with **gastric acidity inhibitors** increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006 May;117(5):e817-20. (InfoPOEMs: In this weak study, treatment of gastroesophageal reflux disease (GERD) with gastric acid suppressants increased the likelihood of pneumonia compared with the rate in healthy children. It's not known whether the treatment, the presence of GERD, or some other factor caused the pneumonia. Watch for confirmation in randomized research. (LOE = 4))
37. Kabra S, Lodha R, Pandey R. Antibiotics for community acquired pneumonia in **children**. Cochrane Database Syst Rev. 2006 Jul 19;3:CD004874.
38 Canadian Bacterial Surveillance Network (**CBSN**) 2005 Canadian Resistance patterns. http://microbiology.mtsinai.on.ca/data/sp/sp_can.shtml
39. Oosterheert JJ, et al. Effectiveness of early switch from IV to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ. 2006 Nov 7; [Epub ahead of print] Early switch from intravenous to oral antibiotics in patients with severe community acquired pneumonia is safe and decreases length of hospital stay by 2 days.
40. Barton N, et al. Guidelines for the prevention and management of community-associated **methicillin-resistant Staphylococcus aureus**: A perspective for Canadian health care practionioners. Can J Infect Dis Med Microbiol Vol 17 Suppl C Sept/Oct 2006. (At Risk: young, athletes, inmates, military, Iv drug users & aboriginal population. CMRSA 7 (USA400) from Minnesota; CMRSA10 (USA300) from California & BC. http://www.pulsus.com/infdis/17_SC/Pdf/mrsa_ed.pdf
Liu Catherine, Bayer Arnold, Cosgrove Sara E., et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children Clin Infect Dis. ciq146 first published online January 4, 2011 doi:10.1093/cid/ciq146
Wunderink RG, Niederman MS, Kollef MH, et al. **Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia**: a randomized, controlled study. Clin Infect Dis. 2012 Mar 1;54(5):621-9. (vs vancomycin)
41. Gilbert M, MacDonald J, Gregson D, et al. Outbreak in Alberta of community-acquired (**USA300**) **methicillin-resistant Staphylococcus aureus** in people with a history of drug use, homelessness or incarceration. CMAJ. 2006 Jul 18;175(2):149-54. Epub 2006 Jun 27.
42. Majumdar SR, et al. **Statins** and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. BMJ. 2006 Oct 23; [Epub ahead of print]
43. Hazir T, et al. Chest **radiography** in children aged 2-59 months diagnosed with non-severe pneumonia as defined by World Health Organization: descriptive multicentre study in Pakistan. BMJ. 2006 Sep 23;333(7569):629. Epub 2006 Aug 21.
44. Burkhardt O, et al. **Once-daily tobramycin** in cystic fibrosis: better for clinical outcome than thrice-daily tobramycin but more resistance development? J Antimicrob Chemother. 2006 Aug 2; [Epub ahead of print]
45. Metersky ML, et al. Antibiotic timing and **diagnostic uncertainty** in Medicare patients with pneumonia: is it reasonable to expect all patients to receive antibiotics within 4 hours? Chest. 2006 Jul;130(1):16-21.

TOP

46. Bergman M, et al. Macrolide and Azithromycin Use Are Linked to Increased **Macrolide Resistance** in Streptococcus pneumoniae. Antimicrob Agents Chemother. 2006 Aug 28; [Epub ahead of print]
47. Chan EY, Ruest A, Meade MO, Cook DJ. **Oral decontamination** for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. BMJ. 2007 Apr 28;334(7599):889. Epub 2007 Mar 26. Oral decontamination of mechanically ventilated adults using antiseptics is associated with a lower risk of ventilator associated pneumonia. Neither antiseptic nor antibiotic oral decontamination reduced mortality or duration of mechanical ventilation or stay in the intensive care unit.
48. Arnold FW, Summersgill JT, Lajoie AS, Peyrani P, Marrie TJ, Rossi P, Blasi F, Fernandez P, File TM Jr, et al. Community-Acquired Pneumonia Organization (CAPO) Investigators. A worldwide perspective of **atypical pathogens** in community-acquired pneumonia. Am J Respir Crit Care Med. 2007 May 15;175(10):1086-93. Epub 2007 Mar 1. The significant global presence of atypical pathogens and the better outcomes associated with antimicrobial regimens with atypical coverage support empiric therapy for all hospitalized patients with CAP with a regimen that covers atypical pathogens.
49. Atkinson M, et al. Comparison of **oral amoxicillin** and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. Thorax. 2007 Dec;62(12):1102-6. Epub 2007 Jun 13. Oral amoxicillin is effective for most children admitted to hospital with pneumonia (all but those with the most severe disease who were excluded from this study).
50. Hazir T, Fox LM, Nisar YB, ET AL. New Outpatient Short-Course Home Oral Therapy for Severe Pneumonia Study Group. (NO-SHOTS) Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. Lancet. 2008 Jan 5;371(9606):49-56. Home treatment with high-dose oral amoxicillin is equivalent to currently recommended hospitalisation and parenteral ampicillin for treatment of severe pneumonia without underlying complications, suggesting that WHO recommendations for treatment of severe pneumonia need to be revised.
51. Asghar R, Banajeh S, Egas J, et al. for the SPEAR (Severe Pneumonia Evaluation Antimicrobial Research) Study Group. Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-59 months in low resource settings: multicentre randomised controlled trial (SPEAR study). BMJ. 2008 Jan 8 Injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for the treatment of community acquired very severe pneumonia in children aged 2-59 months in low resource settings.
52. Knol W, van Marum RJ, Jansen PA, et al. **Antipsychotic Drug Use** and Risk of Pneumonia in Elderly People. J Am Geriatr Soc. 2008 Feb 7; [Epub ahead of print] Use of antipsychotics in elderly people is associated with greater risk of pneumonia. This risk is highest shortly after the initiation of treatment, with the greatest increase in risk found for atypical antipsychotics.
53. Durrington HJ, Summers C. Recent changes in the management of community acquired pneumonia in adults. BMJ. 2008 Jun 21;336(7658):1429-33.
54. Wunderink RG, Mendelson MH, Somero MS, et al. Early Microbiologic Response to **Linezolid Versus Vancomycin** in Ventilator-Associated Pneumonia (**VAP**) Due to Methicillin-Resistant Staphylococcus aureus (MRSA). Chest. 2008 Aug 21. [Epub ahead of print] Early microbiologic cure rates were not statistically significantly higher with linezolid than with vancomycin despite trends in all secondary clinical outcomes favoring linezolid. These results suggest that any beneficial effect of linezolid may be due to factors other than increased bacterial clearance.
55. Sultan N, Nazareno J, Gregor J. Association between proton pump inhibitors and respiratory infections: A systematic review and meta-analysis of clinical trials. Can J Gastroenterol. 2008 Sep;22(9):761-6.
56. Vardakas KZ Md, Siempos II Md, Grammatikos A Md, Athanassa Z Md, Korbila IP Md, Falagas ME Md Dsc. **Respiratory fluoroquinolones** for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. CMAJ. 2008 Dec 2;179(12):1269-1277.
57. Bitner-Glindzicz M, Pembrey M, Duncan A, Heron J, Ring SM, Hall A, Rahman S. Prevalence of mitochondrial 1555A-->G mutation in European children. N Engl J Med. 2009 Feb 5;360(6):640-2. (aminoglycoside ototoxicity)
58. Venditti M, Falcone M, Corrao S, Licata G, Serra P; Study Group of the Italian Society of Internal Medicine. Outcomes of patients hospitalized with community-acquired, health care-associated, and hospital-acquired pneumonia. Ann Intern Med. 2009 Jan 6;150(1):19-26.
59. Sjögren P, Nilsson E, Forsell M, Johansson O, Hoogstraate J. A systematic review of the preventive effect of **oral hygiene** on pneumonia and respiratory tract infection in elderly people in hospitals and nursing homes: effect estimates and methodological quality of randomized controlled trials. J Am Geriatr Soc. 2008 Nov;56(11):2124-30. Epub 2008 Sep 15.
60. Yandiola PP, Capelastegui A, Quintana J, et al. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. Chest. 2009 Jun;135(6):1572-9. Epub 2009 Jan 13. (Original) The **SCAP score** is as accurate or better than other current scoring systems in predicting adverse outcomes in patients hospitalized with CAP while helping classify patients into different categories of increasing risk for potentially closer monitoring.
61. Dublin Sascha, Jackson Michael L, Nelson Jennifer C, et al. **Statin use** and risk of community acquired pneumonia in older people: population based case-control study. BMJ 2009;338:b2137, doi: 10.1136/bmj.b2137 (Published 16 June 2009)
62. Mills K, Graham AC, Winslow BT, Springer KL. Treatment of **nursing home-acquired pneumonia**. Am Fam Physician. 2009 Jun 1;79(11):976-82.
63. Welker JA, Huston M, McCue JD. **Antibiotic timing** and errors in diagnosing pneumonia. Arch Intern Med. 2008 Feb 25;168(4):351-6.
64. Kaplan V, Clermont G, Griffin MF, et al. Pneumonia: still the old man's friend? Arch Intern Med. 2003 Feb 10;163(3):317-23.
65. Musher DM, Rueda AM, et al. The association between pneumococcal pneumonia and acute **cardiac events**. Clin Infect Dis. 2007 Jul 15;45(2):158-65. Epub 2007 Jun 6.
66. Charles PG, Wolfe R, Whitby M, Fine MJ, et al. Australian Community-Acquired Pneumonia Study Collaboration, Grayson ML. **SMART-COP**: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis. 2008 Aug 1;47(3):375-84.
67.Ramirez J, Aliberti S, Mirsaeidi M, et al. Acute **myocardial infarction** in hospitalized patients with community-acquired pneumonia. Clin Infect Dis. 2008 Jul 15;47(2):182-7.
68. Shorr AF, Bodi M, Rodriguez A, et al. CAPUCI Study Investigators. Impact of antibiotic **guideline compliance** on duration of mechanical ventilation in critically ill patients with community-acquired pneumonia. Chest. 2006 Jul;130(1):93-100.
69. Mortensen EM, et al. Effects of **guideline-concordant** antimicrobial therapy on mortality among patients with community-acquired pneumonia. Am J Med. 2004 Nov 15;117(10):726-31.
70. Yealy DM, et al. Effect of increasing the intensity of **implementing** pneumonia guidelines: a randomized, controlled trial. Ann Intern Med. 2005 Dec 20;143(12):881-94.
71. Fishbane S, Niederman MS, Daly C, et al. The impact of standardized **order sets** and intensive clinical case management on outcomes in community-acquired pneumonia. Arch Intern Med. 2007 Aug 13-27;167(15):1664-9.
72. Niederman MS. Making sense of **scoring systems** in community acquired pneumonia. Respirology. 2009 Apr;14(3):327-35.
73. Brito V, Niederman MS. Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as comp

TOP

nosocomial pneumonia. Curr Opin Infect Dis. 2009 Jun;22(3):316-25.
74. Liapikou A, Ferrer M, Polverino E, et al. Severe Community-Acquired Pneumonia: Validation of the Infectious Diseases Society of America/American Thoracic Society Guidelines to Predict an **Intensive Care** Unit Admission. Clin Infect Dis. 2009 Jan 13. [Epub ahead of print]
75. Niederman MS. Biological markers to determine eligibility in trials for community-acquired pneumonia: focus on **procalcitonin**. Clin Infect Dis. 2008 Dec 1;47 Suppl 3:S127-32.
76. Lim WS, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003 May;58(5):377-82.
77. Aujesky D, Fine MJ. The **pneumonia severity index**: a decade after the initial derivation and validation. Clin Infect Dis. 2008 Dec 1;47 Suppl 3:S133-9.
78. Aujesky D, Auble TE, Yealy DM, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med. 2005 Apr;118(4):384-92.
79. Valencia M, et al. Pneumonia severity index class v patients with community-acquired pneumonia: characteristics, outcomes, and value of severity scores. Chest. 2007 Aug;132(2):515-22. Epub 2007 May 15.
80. Metersky ML, Ma A, Bratzler DW, Houck PM. Predicting bacteremia in patients with community-acquired pneumonia. Am J Respir Crit Care Med. 2004 Feb 1;169(3):342-7. Epub 2003 Nov 20.
81. Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A; Toronto Invasive Bacterial Disease Network. Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis. 2005 May 1;40(9):1288-97. Epub 2005 Mar 31.
82. Yu VL, Chiou CC, Feldman C, et al.; International Pneumococcal Study Group. An international prospective study of pneumococcal bacteremia: correlation with in vitro **resistance**, antibiotics administered, and clinical outcome. Clin Infect Dis. 2003 Jul 15;37(2):230-7. Epub 2003 Jul 7.
83. Baddour LM, Yu VL, Klugman KP, Feldman C, et al. International Pneumococcal Study Group. **Combination antibiotic** therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med. 2004 Aug 15;170(4):440-4. Epub 2004 Jun 7.
84. Leroy O, Saux P, Bédos JP, Caulin E. Comparison of levofloxacin and **cefotaxime combined with ofloxacin** for ICU patients with community-acquired pneumonia who do not require vasopressors. Chest. 2005 Jul;128(1):172-83.
85. Lodise TP, Kwa A, Cosler L, Gupta R, Smith RP. Comparison of beta-lactam and macrolide **combination** therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. Antimicrob Agents Chemother. 2007 Nov;51(11):3977-82. Epub 2007 Aug 20.
86. Torres A, Garau J, Arvis P, et al.; MOTIV (MOxifloxacin Treatment IV) Study Group. Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study--a randomized clinical trial. Clin Infect Dis. 2008 May 15;46(10):1499-509.
87. Kovacs JA, Masur H. Evolving health effects of **Pneumocystis**: one hundred years of progress in diagnosis and treatment. JAMA. 2009 Jun 24;301(24):2578-85.
88. Schuetz Philipp; Christ-Crain Mirjam; Thomann Robert; et al.; for the ProHOSP Study Group. Effect of **Procalcitonin**-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial. JAMA. 2009;302(10):1059-1066.
89 Arnold Forest W.; LaJoie A. Scott; Brock Guy N.; et al.; for the Community-Acquired Pneumonia Organization (CAPO) Investigators. Improving Outcomes in Elderly Patients With Community-Acquired Pneumonia by **Adhering** to National **Guidelines**: Community-Acquired Pneumonia Organization International Cohort Study Results. Arch Intern Med. 2009;169(16):1515-1524.
90. McCabe Caitlin; Kirchner Cheryl; Zhang Huiling; et al. **Guideline-Concordant Therapy** and Reduced Mortality and Length of Stay in Adults With Community-Acquired Pneumonia: Playing by the Rules. Arch Intern Med. 2009;169(16):1525-1531.
91. Miano TA, Reichert MG, Houle TT, et al. Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs **ranitidine** in cardiothoracic surgery patients. Chest. 2009 Aug;136(2):440-7.
92. Rello J et al. Severity of pneumococcal pneumonia associated with genomic **bacterial load**. Chest 2009 Sep; 136:832.
93. Niederman M. et al. **Community-Acquired Pneumonia**-In the Clinic. Ann Intern Med Oct 6 2009.
94. Bjerre LM, Verheij TJ, Kochen MM. Antibiotics for community acquired pneumonia in **adult outpatients**. **Cochrane** Database Syst Rev. 2009 Oct 7;(4):CD002109. Currently available evidence from RCTs is insufficient to make evidence-based recommendations for the choice of antibiotic to be used for the treatment of CAP in ambulatory patients.
95. Nazarian DJ, Eddy OL, Lukens TW, Weingart SD, Decker WW. Clinical policy: critical issues in the management of adult patients presenting to the **emergency department** with community-acquired pneumonia. Ann Emerg Med. 2009 Nov;54(5):704-31. http://www.acep.org/WorkArea/DownloadAsset.aspx?id=45809
96. Labelle AJ, Arnold H, Reichley RM, et al. A comparison of culture-positive and culture-negative **healthcare-associated** pneumonia. Chest. 2009 Dec 4.
97. Siempos II, Ntaidou TK, Falagas ME. Impact of the administration of **probiotics** on the incidence of ventilator-associated pneumonia: A meta-analysis of randomized controlled trials. Crit Care Med. 2009 Dec 15.
98. Bouadma L, Luyt CE, Tubach F, et al. Use of **procalcitonin** to reduce patients` exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010 Jan 22.
99. Snijders D, Daniels JM, de Graaff CS, et al. Efficacy of **Corticosteroids** in Community-acquired Pneumonia - A Randomized Double Blinded Clinical Trial. Am J Respir Crit Care Med. 2010 Feb 4.
100. Jung YJ, Koh Y, Hong SB, et al. Effect of vancomycin plus **rifampicin** in the treatment of nosocomial methicillin-resistant Staphylococcus aureus (**MRSA**) pneumonia. Crit Care Med. 2010 Jan;38(1):175-80.
101. Eurich DT, Sadowski CA, Simpson SH, et al. Recurrent community-acquired pneumonia in patients starting **acid-suppressing drugs**. Am J Med. 2010 Jan;123(1):47-53.
102. Lobo LJ, Reed KD, Wunderink RG. Expanded Clinical Presentation of **Community-Acquired MRSA** Pneumonia. Chest. 2010 Feb 19.

TOP

103. Ross, JS., Normand, Sharon-Lise T., Wang, Yun, et al. Hospital **Volume** and 30-Day **Mortality** for Three Common Medical Conditions. N Engl J Med 2010 362: 1110-1118.
104. Esayag Y, Nikitin I, Bar-Ziv J, et al. Diagnostic value of **chest radiographs** in bedridden patients suspected of having pneumonia. Am J Med. 2010 Jan;123(1):88.e1-5.
105. Trifirò Gianluca, Gambassi Giovanni, Sen Elif F., et al. Association of **Community-Acquired Pneumonia** With **Antipsychotic** Drug Use in Elderly Patients: A Nested Case–Control Study.*Ann Intern Med* April 6, 2010.
106. Terragni Pier Paolo; Antonelli Massimo; Fumagalli Roberto; et al. Early vs Late **Tracheotomy** for Prevention of Pneumonia in Mechanically Ventilated Adult ICU Patients: A Randomized Controlled Trial. *JAMA*. 2010;303(15):1483-1489.
107. Gaieski DF et al. Impact of **time to antibiotics** on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010 Apr; 38:1045.
108. Cals JW, Schot MJ, de Jong SA, et al. Point-of-care **C-reactive protein** testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med. 2010 Mar-Apr;8(2):124-33.
109. Kabra SK, Lodha R, Pandey RM. Antibiotics for community-acquired pneumonia in children. Cochrane Database Syst Rev. 2010 Mar 17;3:CD004874.
110. Peleg AY, Hooper DC. **Hospital-acquired** infections due to gram-negative bacteria. N Engl J Med. 2010 May 13;362(19):1804-13.
111. Givens JL.; Jones RN.; Shaffer ML.; et al. Survival and Comfort After Treatment of Pneumonia in **Advanced Dementia**. Arch Intern Med. 2010;170(13):1102-1107.
112. Mulholland S, Gavranich JB, Chang AB. Antibiotics for community-acquired lower respiratory tract infections secondary to **Mycoplasma pneumoniae in children**. Cochrane Database Syst Rev. 2010 Jul 7;7:CD004875. There is insufficient evidence to draw any specific conclusions about the efficacy of antibiotics for this condition in children (although one trial suggests macrolides may be efficacious in some children with LRTI secondary to Mycoplasma). The use of antibiotics has to be balanced with possible adverse events. There is still a need for high quality, double-blinded RCTs to assess the efficacy and safety of antibiotics for LRTI secondary to M. pneumoniae in children.
113. Rotstein C, et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. **Can** J Infect Dis Med Microbiol 2008Jan;19;1:19-53.
114. Kalil AC, Murthy MH, Hermsen ED, et al. Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: systematic review & meta-analysis. Crit Care Med.2010Jul 15.
115. FDA Aug/10 reminded healthcare professionals of an **increased mortality** risk associated with the use of the intravenous antibacterial Tygacil (**tigecycline**) compared to that of other drugs used to treat a variety of serious infections. The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, but was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infections.
116. Sorde Roger; Falco Vicenc; Lowak Michael; et al. Current and Potential Usefulness of **Pneumococcal Urinary Antigen** Detection in Hospitalized Patients With Community-Acquired Pneumonia to Guide Antimicrobial Therapy. Arch Intern Med. 2010;0(2010):archinternmed.2010.347.
117. Dalton Bruce R, Zuege Danny J, Shahpori Reza, et al. Concomitant **Ceftriaxone** and High-Concentration Intravenous **Calcium** Therapy in Adult Critical Care Patients: A Matched Cohort Study. Ahead of Print on 1 July 2010, DOI 10.1345/aph.1M745. Ann Pharmacother ;44:1158-1163.
118. Walkey AJ, O'Donnell MR, Wiener RS. Linezolid versus Glycopeptide Antibiotics for the Treatment of Suspected Methicillin-Resistant Staphylococcus Aureus Nosocomial Pneumonia: A Meta-Analysis of Randomized Controlled Trials. Chest. 2010 Sep 23.
119. Lassi ZS, Haider BA, Bhutta ZA. **Zinc supplementation** for the prevention of pneumonia in children aged 2 months to 59 months. Cochrane Database Syst Rev. 2010 Dec 8;12:CD005978.
120. Tessmer A, Welte T, Schmidt-Ott R et al. for CAPNETZ study group. **Influenza vaccination** is associated with reduced severity of community acquired pneumonia. Eur Respir J. 2010 Dec 9.
121. Cai Y, Wang R, Liang B, Bai N, Liu Y. Effectiveness and safety of **tigecycline** for the treatment of infectious disease: a systematic review and meta-analysis. Antimicrob Agents Chemother. 2010 Dec 20.
122. Hazir Tabish, Nisar Yasir Bin, Abbasi Saleem, et al. Comparison of Oral **Amoxicillin** with Placebo for the Treatment of **World Health Organization–Defined** Nonsevere **Pneumonia** in Children Aged 2–59 Months: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial in Pakistan. Clin Infect Dis. (2011) 52(3): 293-300.
123. Weiss Anna K., Hall Matthew, Lee Grace E., et al. Adjunct **Corticosteroids in Children** Hospitalized With Community-Acquired Pneumonia. Pediatrics, Jan 2011.
124. Kett DH, Cano E, Quartin AA,et al; Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (**IMPACT-HAP**) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: observational, multicentre cohort study. Lancet Infect Dis. 2011 Jan 19.
125. Martín-Loeches I, Sanchez-Corral A, Diaz E, et al; H1N1 SEMICYUC Working Group. Community-Acquired Respiratory **Coinfection in Critically Ill Patients With Pandemic** 2009 Influenza A(H1N1) Virus. Chest. 2011 Mar;139(3):555-62.
126. Yu VL. Guidelines for **hospital-acquired pneumonia and health-care-associated pneumonia**: a vulnerability, a pitfall, & fatal flaw. Lancet Infect Dis. 2011Mar;11(3):248-52.
127. Voiriot G, Dury S, Parrot A, et al. **Nonsteroidal antiinflammatory drugs** may affect the presentation & course of community-acquired pneumonia.Chest.2011Feb;139(2):387-94.
128. Roquilly Antoine, Mahe Pierre Joachim, Seguin Philippe, et al. **Hydrocortisone** Therapy for Patients With Multiple Trauma: The Randomized Controlled HYPOLYTE Study . JAMA. 2011;305(12):1201-1209.doi:10.1001/jama.2011.360 (reduced risk of hospital acquired pneumonia)
129. Edwards P, Arango M, Balica L, Cottingham R, et al. CRASH trial collaborators. Final results of MRC CRASH, a randomized placebo-controlled trial of intravenous **corticosteroid** in adults with head injury-outcomes at 6 months. Lancet. 2005 Jun 4-10;365(9475):1957-9. (higher mortality, but no difference in pneumonia)
130. Ruuskanen O, Lahti E, Jennings LC et al. **Viral pneumonia**. www.thelancet.com Published online March 23, 2011 DOI:10.1016/S0140-6736(10)61459-6.
131. Ruhnke GW, Coca-Perraillon M, Kitch BT, Cutler DM. **Marked reduction in 30-day mortality** among elderly patients with community-acquired pneumonia. Am J Med. 2011 Feb;124(2):171-178.e1.
132. Chen Y, Li K, Pu H, et al. **Corticosteroids for pneumonia**. Cochrane Database Syst Rev. 2011 Mar 16;3:CD007720. In most patients with pneumonia, corticosteroi

TOP

generally beneficial for accelerating the time to resolution of symptoms. However, evidence from the included studies was not strong enough to make any recommendations.
133. Douglas I, Evans S, Smeeth L. Effect of **statin** treatment on short term mortality after pneumonia episode: cohort study. BMJ 2011;342:d1642.
134. Tang Karen L.; Eurich Dean T.; Minhas-Sandhu Jasjeet K.; et al. Incidence, Correlates, and **Chest Radiographic Yield of New Lung Cancer** Diagnosis in 3398 Patients With Pneumonia. Arch Intern Med. 2011;0(2011):archinternmed.2011.155.
135. Sun HY, Fujitani S, Quintiliani R, Yu VL. Pneumonia Due to **Pseudomonas aeruginosa**: Part II: Antimicrobial Resistance, Pharmacodynamic Concepts, and Antibiotic Therapy. Chest. 2011 May;139(5):1172-85.
136. Walkey AJ, O'Donnell MR, Wiener RS. **Linezolid vs Glycopeptide** (vancomycin or teicoplanin) Antibiotics for the Treatment of Suspected Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Meta-analysis of Randomized Controlled Trials. Chest. 2011 May;139(5):1148-55.
137. Nambiar S, Rellosa N, Wassel RT, et al. **Linezolid-Associated Peripheral and Optic Neuropathy** in Children. Pediatrics. 2011 May 9.
138. Watkins RR, Lemonovich TL. Diagnosis and Management of **Community-Acquired Pneumonia in Adults** . Am Fam Physician. 2011;83(11):1299-1306.
139. Meijvis SC, Hardeman H, Remmelts HH, et al. **Dexamethasone** and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet. 2011 May 31.
140. Wilson KC, Schunemann HJ. An Appraisal of the Evidence Underlying **Performance Measures** for Community-acquired Pneumonia. Am J Respir Crit Care Med. 2011 Jun 1;183(11):1454-62.
141. Williams DJ et al. **Influenza coinfection** and outcomes in children with complicated pneumonia. *Arch Pediatr Adolesc Med* 2011 Jun; 165:506.
142. Schuetz P, Chiappa V, Briel M, et al. **Procalcitonin algorithms** for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011 Aug 8;171(15):1322-31.
143. Neuman MI et al. **Prediction of pneumonia in a pediatric emergency department**. Pediatrics 2011 Aug; 128:246.
144. Peters J, Singh H, Brooks EG, et al. **Persistence** of Community-Acquired Respiratory Distress Syndrome Toxin-Producing **Mycoplasma pneumoniae** in Refractory Asthma. Chest. 2011 Aug;140(2):401-7.
145. Sandiumenge A, Lisboa T, Gomez F, et al. Effect of **antibiotic diversity on ventilator associated pneumonia (VAP) caused by ESKAPE** organisms. Chest. 2011 Jun 9.
146. Neuman MI, Monuteaux MC, Scully KJ, Bachur RG. **Prediction of pneumonia in a pediatric emergency department**. Pediatrics. 2011 Aug;128(2):246-53.
147. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in **infants and children older than 3 months of age**: clinical practice guidelines by the pediatric infectious diseases society and the Infectious Diseases Society of America. (IDSA)Clin Infect Dis. 2011 Oct;53(7):e25-76.
148. Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/
149. Bafadhel M, Clark TW, Reid C, et al. **Procalcitonin and C-reactive protein** in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. Chest. 2011 Jun;139(6):1410-8.
150. Naeije G, Lorent S, Vincent JL, Legros B. Continuous **epileptiform discharges** in patients treated with **cefepime** or meropenem. Arch Neurol. 2011 Oct;68(10):1303-7.
151. Labeau SO, Van de Vyver K, Brusselaers N, et al. Prevention of **ventilator-associated pneumonia** with oral antiseptics: a systematic review and meta-analysis. Lancet Infect Dis. 2011 Jul 26. In intubated patients, oral care with antiseptics reduces the risk of ventilator-associated pneumonia (VAP) as compared with oral care without antiseptics. Current evidence best supports the use of chlorhexidine in this population. (LOE = 1a-)
152. Varner TR, Bookstaver PB, Rudisill CN, Albrecht H. Role of **rifampin-based combination therapy** for severe community-acquired Legionella pneumophila pneumonia. Ann Pharmacother. 2011 Jul;45(7-8):967-76.
153. Finlayson O, Kapral M, Hall R, et al. On behalf of the Investigators of the Registry of the Canadian Stroke Network; For the Stroke Outcome Research Canada (SORCan) Working Group. Risk factors, inpatient care, and outcomes of **pneumonia after ischemic stroke**. Neurology. 2011 Oct 4;77(14):1338-1345.
154. Chen D, Restrepo MI, Fine MJ, et al. Observational study of **inhaled corticosteroids on outcomes for COPD patients with pneumonia**. Am J Respir Crit Care Med. 2011 Aug 1;184(3):312-6.
155. **Drugs in Pregnancy & Lactation**, 9th Ed. Briggs GE,et al. Wilkins;Baltimore, MD. 2011.
156. Bailey JL, Yeung SY. **Probiotics** for disease prevention: a focus on **ventilator-associated pneumonia**. Ann Pharmacother. 2011 Nov;45(11):1425-32. (not recommended)
157. Leis JA, Gold WL. Management of community-acquired pneumonia in the **emergency department**. CMAJ. 2012 Jan 23.
158. Haessler S, Schimmel JJ. Managing community-acquired pneumonia **during flu season**. Cleve Clin J Med. 2012 Jan;79(1):67-78.
159. Esposito S et al. **Procalcitonin** measurements for guiding antibiotic treatment in pediatric pneumonia. Respir Med. 2011 Dec;105(12):1939-45.
160. Health Canada Jan/12 Doribax (doripenem for injection) - Higher Mortality Rate and a Lower Clinical Cure Rate Observed During a Comparative Clinical Trial - Janssen Inc. Decreased Clinical Cure Rates and Increased Mortality in an Investigational Ventilator-Associated Pneumonia (VAP) Study. Doribax will be updated to reflect findings of a higher mortality rate and a lower cure rate among patients taking Doribax 1g every 8 hours in a fixed 7-day course vs a fixed 10-day course of imipenem-cilastatin.
161. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, Thomson A; **British Thoracic Society** Standards of Care Committee. British Thoracic Society-BTS- guidelines for the management of community acquired **pneumonia in children**: update 2011. Thorax. 2011 Oct;66 Suppl 2:ii1-23.
162. Newman RE, Hedican EB, Herigon JC, et al. Impact of a guideline on management of **children hospitalized** with community-acquired pneumonia. Pediatrics. 2012 Mar;129(3):e597-604.
163. Basnet S, Shrestha PS, Sharma A, et al. A Randomized Controlled Trial of **Zinc** as Adjuvant Therapy for Severe Pneumonia in Young Children. Pediatrics. 2012 Mar

TOP

164. Lodise TP Jr, Lomaestro B, Drusano GL. **Piperacillin-tazobactam** for Pseudomonas aeruginosa infection: clinical implications of an **extended-infusion** dosing strategy. Clin Infect Dis. 2007 Feb 1;44(3):357-63.
165. Pugh R, Grant C, Cooke RP, et al. **Short-course** versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2011;(10): CD007577. We conclude that for patients with VAP not due to NF-GNB, a short fixed-course (seven or eight days) antibiotic therapy may be more appropriate than a prolonged course (10 to 15 days). Use of an individualised strategy (incorporating clinical features or serum procalcitonin) appears to safely reduce duration of antibiotic therapy for VAP.
166. Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of **tigecycline** for the treatment of infectious diseases: a meta-analysis. Lancet Infect Dis. 2011 Jul 22.
167. Zhang Y, Fang C, Dong BR, et al. **Oxygen therapy for pneumonia** in adults. Cochrane Database Syst Rev. 2012 Mar 14;3:CD006607. Non-invasive ventilation can reduce the risk of death in the ICU, endotracheal intubation, shorten ICU stay and length of intubation.
168. Myers EM, Ward SL, Myers JP. Life-threatening respiratory **pasteurellosis associated with palliative pet care**. Clin Infect Dis. 2012 Mar;54(6):e55-7.
169. Bari A, Sadruddin S, Khan A, et al. Community case management of severe pneumonia with oral **amoxicillin in children aged 2–59 months** in Haripur district, Pakistan: a cluster randomised trial. Lancet 2011; 378: 1796–803.
170. Wunderink RG, Niederman MS, Kollef MH, et al. **Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia**: a randomized, controlled study. Clin Infect Dis. 2012 Mar 1;54(5):621-9. (vs Vancomycin)
171. Manaseki-Holland S, Maroof Z, Bruce J, et al. Effect on the incidence of pneumonia of **vitamin D** supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial. Lancet. 2012 Apr 14;379(9824):1419-27.
172. Ray WA, Murray KT, Hall K, et al. **Azithromycin and the risk of cardiovascular death**. N Engl J Med 2012; 366:1881-90.
173. Schuetz P, Amin DN, Greenwald JL. Role of **procalcitonin** in managing adult patients with respiratory tract infections. Chest. 2012 Apr;141(4):1063-73.

Web Sites:

American Lung Association
www.lungusa.org/site/apps/nlnet/content3.aspx?c=dvLUK9O0E&b=2060321&content_id={71CC3CFD-4B3E-49C8-AA88-D76EAE1FB9F5}&notoc=1
National Institute of Allergy and Infectious Diseases
http://www3.niaid.nih.gov/topics/pneumonia/default.htm (English)
Centers for Disease Control and Prevention
www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm (pneumococcal vaccine)
www.cdc.gov/vaccines/vpd-vac/flu/default.htm (influenza vaccine)
National Foundation for Infectious Disease
www.nfid.org/pdf/factsheets/pneuadult.pdf

TOP

Additional references: Community Acquired Pneumonia Severity Risk Scores

Arnold Forest W.; LaJoie A. Scott; Brock Guy N.; et al.; for the Community-Acquired Pneumonia Organization (CAPO) Investigators. Improving Outcomes in Elderly Patients With Community-Acquired Pneumonia by Adhering to National Guidelines: Community-Acquired Pneumonia Organization International Cohort Study Results. Arch Intern Med. 2009;169(16):1515-1524.

Aujesky D, Fine MJ. The **pneumonia severity index**: a decade after the initial derivation and validation. Clin Infect Dis. 2008 Dec 1;47 Suppl 3:S133-9.

Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP, Graff LG, et al. Prospective comparison of **three validated prediction** rules for prognosis in community-acquired pneumonia. Am J Med. 2005 Apr;118(4):384-92.

Bont J, Hak E, Hoes AW, Macfarlane JT, Verheij TJ. Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the **CRB-65** severity assessment tool. Arch Intern Med. 2008 Jul 14;168(13):1465-8.

Brown SM, Jones BE, Jephson AR, et al. **Validation** of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. Crit Care Med. 2009 Dec;37(12):3010-6.

Chalmers JD, Singanayagam A, Akram AR, et al. **Severity assessment tools** for predicting mortality in hospitalised patients with community-acquired pneumonia. **Systematic review and meta-analysis**. Thorax. 2010 Oct;65(10):878-83.

Cals JW, Schot MJ, de Jong SA, et al. Point-of-care **C-reactive protein** testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med. 2010 Mar-Apr;8(2):124-33.

Charles PG, Wolfe R, Whitby M, Fine MJ, et al. Australian Community-Acquired Pneumonia Study Collaboration, Grayson ML. **SMART-COP**: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis. 2008 Aug 1;47(3):375-84.

Chen JH, Chang SS, Liu JJ, et al. Comparison of clinical characteristics and performance of **pneumonia severity score** and **CURB-65** among younger adults, **elderly and very old** subjects. Thorax. 2010 Nov;65(11):971-7.

Christ-Crain M, et al. **Procalcitonin** Guidance of Antibiotic Therapy in Community-acquired Pneumonia: A Randomized Trial. Am J Respir Crit Care Med. 2006 Jul 1;174(1):84-93. Epub 2006 Apr 7.

Daubin C, Parienti JJ, Fradin S, et al. **Procalcitonin** levels and bacterial aetiology among COPD patients admitted to the ICU with severe pneumonia: a prospective cohort study. BMC Infect Dis. 2009 Sep 21;9:157.

El-Solh AA, Alhajhusain A, Abou Jaoude P, et al. Validity of severity scores in hospitalized patients with **nursing home-acquired pneumonia**. Chest. 2010 Dec;138(6):1371-6. Epub 2010 May 27. All three British Thoracic Society rules had lower performance accuracy in predicting 30-day mortality of hospitalized NHAP than **SOAR**.

Esposito S et al. **Procalcitonin** measurements for guiding antibiotic treatment in pediatric pneumonia. Respir Med. 2011 Dec;105(12):1939-45.

Esayag Y, Nikitin I, Bar-Ziv J, et al. Diagnostic value of **chest radiographs** in bedridden patients suspected of having pneumonia. Am J Med. 2010 Jan;123(1):88.e1-5.

Jones BE, Jones J, Bewick T, et al. **CURB-65** Pneumonia Severity Assessment Adapted for **Electronic** Decision Support. Chest. 2011 Jul;140(1):156-63.

Kett DH, Cano E, Quartin AA,et al; the Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis. 2011 Jan 19.

Krüger S, Ewig S, Giersdorf S, et al.; CAPNETZ study group. **Cardiovascular and Inflammatory Biomarkers** to Predict Short- and Long-term Survival in Community-acquired Pneumonia. Am J Respir Crit Care Med. 2010 Jul 16.

Leis JA, Gold WL. Management of community-acquired pneumonia in the **emergency department**. CMAJ. 2012 Jan 23.

Loke YK, Kwok CS, Niruban A, Myint PK. Value of **severity scales in predicting mortality** from community-acquired pneumonia: systematic review and meta-analysis. Thorax. 2010;65:884-90.

Mathews B, Shah S, Cleveland RH, Lee EY, et al. Clinical predictors of pneumonia among **children with wheezing**. Pediatrics. 2009 Jul;124(1):e29-36.

McCabe Caitlin; Kirchner Cheryl; Zhang Huiling; et al. Guideline-Concordant Therapy and Reduced Mortality and Length of Stay in Adults With Community-Acquired Pneumonia: Playing by the Rules. Arch Intern Med. 2009;169(16):1525-1531.

McNally M, Curtain J, O`Brien KK, et al. Validity of British Thoracic Society guidance (the **CRB-65 rule**) for predicting the severity of pneumonia in general practice: systematic review and meta-analysis. Br J Gen Pract. 2010 Oct;60(579):e423-33.

Niederman MS. Biological markers to determine eligibility in trials for community-acquired pneumonia: focus on **procalcitonin**. Clin Infect Dis. 2008 Dec 1;47 Suppl 3:S127-32.

Niederman MS. Making sense of **scoring systems** in community acquired pneumonia. Respirology. 2009 Apr;14(3):327-35.

Neuman MI et al. Prediction of pneumonia in a **pediatric emergency department**. *Pediatrics* 2011 Aug; 128:246.

Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, et al. Comparison of **three predictive rules** for assessing severity in elderly patients with CAP. Int J Clin Pract. 2011 Nov;65(11):1165-72. Three prediction rules -- the Pneumonia Severity Index (PSI), CURB-65, and the modified CRB-65 -- perform equally well for predicting 30-day mortality among patients 65 years or older with community-acquired pneumonia (CAP). The simpler CRB-65, which does not require laboratory data, is particularly accurate among patients aged 65 years to 74 years. (LOE = 1b)

Rello J et al. Severity of pneumococcal pneumonia associated with genomic **bacterial load**. Chest 2009 Sep; 136:832.

Schuetz Philipp; Christ-Crain Mirjam; Thomann Robert; et al.; for the ProHOSP Study Group. Effect of **Procalcitonin**-Based Guidelines vs Standard

TOP

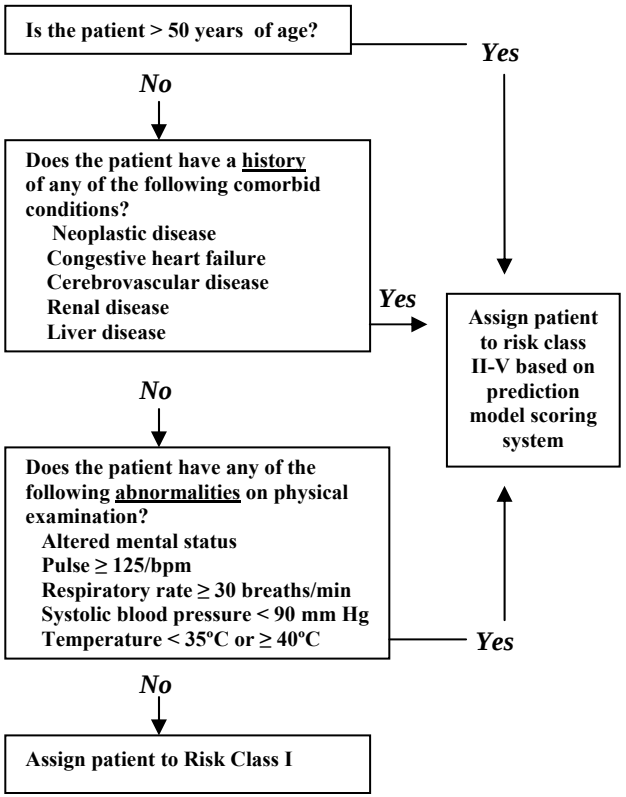
Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial. JAMA. 2009;302(10):1059-1066.
Schuetz P, Amin DN, Greenwald JL. Role of **procalcitonin** in managing adult patients with respiratory tract infections. Chest. 2012 Apr;141(4):1063-73.
Shorr AF, Sun X, Johannes RS, et al. Validation of a Novel **Risk Score** for Severity of Illness in **Acute Exacerbations of COPD**. (**BAP-65**) Chest. 2011 Nov;140(5):1177-83.
Sorde Roger; Falco Vicenc; Lowak Michael; et al. Current and Potential Usefulness of **Pneumococcal Urinary Antigen** Detection in Hospitalized Patients With Community-Acquired Pneumonia to Guide Antimicrobial Therapy. Arch Intern Med. 2010;0(2010):archinternmed.2010.347.
Stolz D, Smyrnios N, Eggimann P, et al. **Procalcitonin** for reduced antibiotic exposure in ventilator-associated pneumonia: randomised study. Eur Respir J. 2009 Dec;34(6):1364-75. Epub 2009 Sep 24.
Valencia M, Badia JR, Cavalcanti M, et al. **Pneumonia severity index class v** patients with community-acquired pneumonia: characteristics, outcomes, and value of severity scores. Chest. 2007 Aug;132(2):515-22. Epub 2007 May 15.
Yandiola PP, Capelastegui A, Quintana J, et al. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. Chest. 2009 Jun;135(6):1572-9. Epub 2009 Jan 13. (Original) The **SCAP score** is as accurate or better than other current scoring systems in predicting adverse outcomes in patients hospitalized with CAP while helping classify patients into different categories of increasing risk for potentially closer monitoring.

TOP

Pneumonia Risk Score Option #1:

Prediction Model for Identification of Patient Risk for Person with COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Pneumonia Severity Index (PSI) Algorithm



This model may be used as a guide in conjunction with clinical judgement in the decision on the most appropriate site of care for patients with CAP.

Adapted from: 1. Fine MJ et al. A prediction rule to identify low risk patients with CAP. N Engl J Med 1997;336:243-50. 2. Mandell LA et al. Canadian guidelines for initial management of community acquired pneumonia. Clin Infec Dis 2000;31:383-421. 3. Bartlett JG et al. Practice guidelines for the management of community acquired pneumonia in adults. Clin Infec Dis 2000; 31: 347-82. 4. Lim WS, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003 May;58(5):377-82. (Kollef KE, et al. The modified APACHE II Score outperforms CURB65 Pneumonia Severity Score as a predictor of 30day mortality in MRSA pneumonia. Chest. 2007 Oct 20). PSI: http://pda.ahrq.gov/clinic/psi/psicalc.asp
CURB-65: http://www.mdcalc.com/curb-65-severity-score-community-acquired-pneumonia

Pneumonia-Specific Severity of Illness Scoring System

Patient's Characteristics	Points Assigned	Your Pt
DEMOGRAPHIC FACTOR		
Age, yr		
Male	(age)	
Female	(age-10)	
Nursing home resident	+10	
COMORBID ILLNESS		
Neoplastic disease	+30	
Liver disease	+20	
Congestive heart failure	+10	
Cerebrovascular disease	+10	
Renal disease	+10	
PHYSICAL EXAMINATION FINDING		
Altered mental status	+20	
Respiratory rate>30/min	+20	
Systolic BP<90 mm Hg	+20	
Temperature<35ºC or>40ºC	+15	
Pulse>125/min	+10	
LABORATORY FINDING		
pH<7.35	+30	
BUN>10.7 mmol/L	+20	
Sodium<130 mmol/L	+20	
Glucose>13.9 mmol/L	+10	
Hematocrit<30%	+10	
PO_2<60mm Hg^2 or O_2 sat <90%	+10	
Pleural effusion	+10	
Total Score		

Stratification of Risk Score

Score ≤90: send home; score ≥91: admit to hospital
(possible short-course admission of those with 71-90 points)

Risk	Risk Class	Based on Algorithm	Mortality
Low	I	0 total points	~0.1%
	II	≤70 total points	~0.6%
	III	71-90 total points	~0.9-2.8%
Moderate	IV	91-130 total points	~9%
High	V	>130 total points	~28%

Above may underestimate risk in young otherwise healthy pts. May overestimate dx severity in elderly. Does not consider for example COPD, HIV or social factors.

SMART-COP

-an ICU intensive respiratory or vasopressor support (IRVS) **prediction score when CAP is confirmed on X-ray.**

	Point
-low **S**ystolic BP <90 mmHg	2
-**M**ultilobar chest Xray involvement	1
-low **A**lbumin level <3.5g/dl *	1
-high **R**espiratory rate (age adjusted)	1
-If age ≤ 50yr then ≥ 25 breaths/min	
-If age > 50yr then ≥ 30 breaths/min	
-**T**achycardia ≥ 125 beats/min	1
-**C**onfusion (new onset)	1
-poor **O**xygenation (age adjusted)	2

Age	≤ 50yr	> 50yr
PaO_2 *	< 70 mmHg	<60 mmHg
Or $O_{2\ satruation}$	≤ 93%	≤ 90 %
Or (if on O_2) PaO_2 / FiO_2 *	< 333	<250

-low arterial **p**H < 7.35 * 2

Total Score=

Interpretation: (This is not a predictor of mortality)

0-2 Points	Low risk of needing IRVS
3-4 Points	Moderate risk (1 in 8) of needing IRVS
5-6 Points	High risk (1 in 3) of needing IRVS
≥7 Points	Very high risk (2 in 3) of needing IRVS

* For primary care doctors, results for albumin, arterial pH, & PaO_2 can be overlooked & the following interpretation can be used:

0 Points	Very low risk of needing IRVS
1 Point	Low risk (1 in 20) of needing IRVS
2 Points	Moderate risk (1 in 10) of needing IRVS
3 Points	High risk (1 in 6) of needing IRVS
≥4 Points	High risk (1 in 3) of needing IRVS

(Adapted from Charles et al. Used with permission.)

Option #2:

CURB-65

1 point for Any of:

	Point
-**C**onfusion *	1
-**U**rea >7mmol/l	1
-**R**espiratory rate ≥30/min	1
-**B**lood pressure (SBP <90 or DBP≤60	1
-Age ≥65years	1
Total=	

CURB-65 Score:	0-1	2	3 or more
	Group 1	Group 2	Group 3
Mortality @30days:	Low <2%	Intermediate ~9%	High >19%
Treatment options:	Outpatient if support	Inpatient or hospital supervised outpatient	Inpatient; or ICU esp. if CURB-65 score= 4 or 5

* defined as a Mental Test Score of 8 or less, or new disorientation in person, place or time.
This scoring does **not** take into account comorbidities or extent of the pneumonia. (The CRB-65 is another version which does not incorporate the Urea into the score).

TOP

DRUGS FOR URINARY TRACT INFECTIONS (UTI)

Prepared by: Loren Regier © *www.RxFiles.ca* **Feb/10**

1. Highlights

- **Acute uncomplicated cystitis in otherwise healthy ♀**
  - Short course - **3 day** therapy – suitable for cotrimoxazole ($10), trimethoprim & fluoroquinolones (~$20)
  - Nitrofurantoin (e.g. Macrobid) – a minimum of 5-**7 days** treatment is recommended.
- **Fluoroquinolones** have excellent activity against most urinary pathogens; however concern that overuse is leading to increasing antimicrobial resistance. *Preserve them for those who really need them!*
- **Asymptomatic bacteriuria** in the institutionalized elderly is common. However, antimicrobial treatment offers no benefit and increases the prevalence of resistant bacteria. *Don't culture asymptomatic residents.*

2. Oral Antimicrobials for Urinary Tract Infections

Trimethoprim/Sulfamethoxazole or Cotrimoxazole (SMX/TMP) {Alternately consider monotherapy with Trimethoprim}

Coverage	*E. coli, P. mirabilis,. K. pneumonia, S. aureus*
Adverse effects	diarrhea, rash, hematologic abnormalities (rare); (May use trimethoprim alone in sulpha allergic patients) (other less common effects: blood dyscrasias, diarrhea, pancreatitis, nephrotoxicity, urolithiasis, hepatotoxicity, hypersensitivity reactions, skin rash, toxic epidermal necrolysis & Stevens-Johnson syndrome. In patients with AIDS, cotrimoxazole produces an increased incidence of toxicity including a syndrome of fever, malaise, nausea and headache. Cotrimoxazole is also associated with disulfiram-like reactions.)
Drug interactions	cyclosporine ↑cyclosp levels & ↑nephrotoxicity, digoxin ↑dig levels, methotrexate ↑MTX toxicity, metronidazole disulfiram reaction, phenytoin ↑phenytoin toxicity, sulfonylureas ↑hypoglycemic effect, warfarin ↑warf effect
Comments	resistance is a problem especially in recurrent UTI; average reported resistance in SK is ~15%, however, higher in some institutional situations. Other antibiotics should be used when resistance ≥20%. maintain hydration

Nitrofurantoin {Macrobid 100mg BID: well tolerated and convenient}

Coverage	*E. coli. K. pneumonia, S. aureus, Enterococcus faecalis*; (not *proteus, pseudomonas*)
Adverse effects	rash, GI upset, increased LFTs; (other less common effects: pneumonitis and other pulmonary reactions, eosinophilia, hemolytic anemia, leukopenia, agranulocytosis, methemoglobinemia, peripheral neuropathy, pseudotumor cerebri, pseudomembranous colitis, nausea, vomiting, pancreatitis, parotitis, hepatitis, systemic lupus erythematosus and cutaneous and allergic reactions)
Drug Interactions	Mg^{++} antacids ↓absorption, norfloxacin ↓norfloxacin effect; Food ↑'s absorption
Comments	maintains excellent activity against *E. coli*, *Enterococci*, & *Staph* avoid in renal dysfunction (CrCl <40-60ml/min); limited tissue penetration; not useful in complicated UTI

Ciprofloxacin {Alternately, norfloxacin & levofloxacin; not moxifloxacin as lower concentration in urine}

Coverage	*E. coli, P. mirabilis,. K. pneumonia, P. aeruginosa, +/- S. aureus* (very broad coverage & effective agent)
Adverse effects	headache, GI upset; (Other less common effects: CNS side effects, including seizures; increases in transaminases and in some cases severe and fatal hepatitis have developed. Additionally, hematuria and anaphylactic reactions have been described)
Drug Interactions	antacids ↓absorption; may use a PPI / H2-antagonist; clozapine, glyburide ↑hypoglycemia, iron ↓ cipro absorption, metoprolol ↑metop level, phenytoin ↑↓pheny levels, theophylline ↑theoph toxicity, warfarin ↑warf effect, zinc ↓cipro absorption; 1A2 substrates inhibited by ciprofloxacin & levofloxacin ∴ ↑ effect of olanzapine, haloperidol, imipramine, cyclobenzaprine, fluvoxamine, zolmitriptan…
Comments	other fluoroquinolones also effective; pseudomonal coverage with ciprofloxacin & norfloxacin. lower doses suitable for uncomplicated UTI; higher doses for complicated UTI & pyelonephritis

Amoxicillin/Clavulinic Acid (Amox/Clav)

Coverage	*E. coli, P. mirabilis, K. pneumonia, S. aureus, Enterococcus faecalis*
Adverse effects	rash, GI upset (diarrhea, more with q8h dosing ~25% formulations than with q12h formulations ~10%) (Other less common effects: eosinophilia, leukopenia and thrombocytosis; superinfections resulting in candidal vaginitis and pseudomembranous colitis may occur. Caution in patients with a sensitivity to penicillin.)
Drug Interactions	oral contraceptives ↓contraceptive effect, methotrexate ↓MTX clearance & ↑toxicity; Lab: false +'ve Coomb's test
Comments	good coverage for more resistant organisms including enterococcus.

Fosfomycin - single dose

Comments (D/C 2010) usually less effective than SMX/TMP , esp for *S. saprophiticus*; however *E. Coli* resistance uncommon

Note: other beta-lactams (amoxicillin, 1st gen cephalosporins) are alternatives although generally less effective clinically than SMX/TMP.

3. Urban Outpatient Susceptibility Patterns (SK) – local susceptibility variation should be considered

- C&S results reflect patients with recurrent/more complicated infections as these patients getting are cultured most frequently
- **Frequency & susceptibility** of pathogens found vary depending on inpatient vs outpatient and complicating factors
- **Probable organisms**: **Acute Cystitis** ⇨ *E. coli, S. saprophyticus*; **Complicated UTI** ⇨ *E. coli, Enterococci, Klebsiella, Proteus, P. aeruginosa*
  Pyelonephritis ⇨ *E. coli, Klebsiella, Enterobacter, Proteus mirabillis*; **Prostatitis** ⇨ E. coli, Gm –ve bacilli, Staph, enterococcus

E. coli (most common uropathogen):	≥83-87% S to SMX/TMP;	≥99% S to NTF;	≥94% S to Cipr; ≥82% S to Amox/Clav
Enterococcus:	Resistant to SMX/TMP	≥99% S to NTF;	≥74% S to Cipr; ≥98% S to Amp

References: **1.** Anti-infective Review Panel. Anti-infective Guidelines for Community-acquired infections **2012**, Toronto, ON (Canada). **1.** Sanford Guide to Antimicrobial Therapy 2011. **3.** Bugs and Drugs, www.dobugsneeddrugs.org. **4.** Micromedex 2011 drug database. **5.** Walker S, et al. Why are antibiotics prescribed for asymtomatic bacteriuria in institutionalized elderly people? CMAJ 2000;163:273-7. **6.** Nicolle L. Empirical treatment of acute cystitis in women. Int J Antimicrob Agents 2003;22:1-6. **7.** Lummus W, Thompson I. Prostatitis. Emerg Med Clin N America 2001;19:691-707. **8.** Warren J, et al. Guidelines for antimicrobial therapy of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Clin Infect Dis 1999;29:745-58. **9.** Miller L, Treatment of Uncomplicated Urinary Tract Infections in an Era of Increasing antimicrobial Resistance. Mayo Clin Proc 2004;79:1048-1054. **10.** Sask. resistance data from 2004 Antibiograms – Saskatoon (SHR) & Regina (RQHR). **11**. McConnell JD, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. N Engl J Med. 2003 Dec 18;349(25):2387-2398. **12**. Vogel T, et al. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial. CMAJ. 2004 Feb 17;170(4):469-73.

Additional sources:

13. Nicolle LE, Bradley S, Colgan R, Rice JC, et al.; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005 Mar 1;40(5):643-54. Epub 2005 Feb 4. (Colgan R, et al. Asymptomatic bacteriuria in adults. Am Fam Physician. 2006 Sep 15;74(6):985-90. Women who are pregnant should be screened for asymptomatic bacteriuria in the first trimester and treated, if positive. Treating asymptomatic bacteriuria in patients with diabetes, older persons, patients with or without indwelling catheters, or patients with spinal cord injuries has not been found to improve outcomes.)
US Preventive Services Task Force. **Screening** for asymptomatic bacteriuria in adults: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2008 Jul 1;149(1):43-7. Summary for patients in: Ann Intern Med. 2008 Jul 1;149(1):I37. Screen for asymptomatic bacteriuria with urine culture in **pregnant women** at 12 to 16 weeks' gestation or at the first prenatal visit, if later. (Grade A recommendation.) Do not screen for asymptomatic bacteriuria in men and nonpregnant women. (Grade D recommendation.).
Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of **catheter-associated** urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America (IDSA). Clin Infect Dis. 2010 Mar 1;50(5):625-63.

AAP-American Academy of Pediatrics. Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the **Initial UTI in Febrile Infants and Children 2 to 24 Months.** Pediatrics. 2011 Aug 28.

Alper BS, Curry SH. Urinary tract infection in **children**. Am Fam Physician. 2005 Dec 15;72(12):2483-8.

American College of Obstetricians & Gynecologists. ACOG Bulletin #91: **Treatment of urinary tract infections in nonpregnant women**. Obstet Gynecol.2008 Mar;111(3):785-94.

Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/

Antoniou T, Gomes T, Mamdani MM, et al. **Trimethoprim-sulfamethoxazole induced hyperkalaemia** in elderly patients receiving **spironolactone**: nested case-control study. BMJ. 2011 Sep 12;343:d5228.

Auer S, Wojna A, Hell M. **Oral treatment options** for ambulatory patients with urinary tract infections caused by **extended-spectrum-beta-lactamase-producing Escherichia coli**. Antimicrob Agents Chemother. 2010 Sep;54(9):4006-8. (options: fosfomycin, nitrofurantoin & pivmecillinam)

Bains A, Buna D, Hoag N. A retrospective review assessing the efficacy and safety of **nitrofurantoin in renal impairment**. Can Pharm J 2009;142:248-252.

Barbosa-Cesnik C, Brown MB, Buxton M, et al. **Cranberry juice** fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clin Infect Dis. 2011 Jan;52(1):23-30.

Beerepoot MA, Ter Riet G, Nys S, et al. **Cranberries vs Antibiotics** to Prevent Urinary Tract Infections: A Randomized Double-blind Noninferiority Trial in Premenopausal Women. Arch Intern Med. 2011 Jul 25;171(14):1270-8.

Bocquet N, Sergent Alaoui A, Jais JP, et al. Randomized Trial of **Oral Versus Sequential IV/Oral Antibiotic** for Acute Pyelonephritis in Children. Pediatrics. 2012 Jan 30.

Brady PW, Conway PH, Goudie A. **Length of intravenous antibiotic therapy** and treatment failure in **infants** with urinary tract infections. Pediatrics. 2010 Aug;126(2):196-203.

Brandstr.m P, Esbj.rner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The **Swedish reflux trial in children**. III. Urinary tract infection pattern. J Urol 2010;184:286-91.

Brill JR. Diagnosis and treatment of **urethritis in men**. Am Fam Physician. 2010 Apr 1;81(7):873-8.

Colgan R, Williams M. Diagnosis and treatment of **acute uncomplicated cystitis**. Am Fam Physician. 2011 Oct 1;84(7):771-6.

Colgan R, Williams M, Johnson JR. Diagnosis and treatment of **acute pyelonephritis in women**. Am Fam Physician. 2011 Sep 1;84(5):519-26.

Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections in **children**: risk factors and association with prophylactic antimicrobials. JAMA. 2007 Jul 11;298(2):179-86. Among the children in this study, antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.

Copp HL, Shapiro DJ, et al. National Ambulatory Antibiotic Prescribing Patterns for Pediatric **Urinary Tract Infection**,1998-2007.*Pediatrics*, 2011; DOI: 10.1542/peds.2010-3465

Cormican M, Murphy AW, Vellinga A. Interpreting **asymptomatic bacteriuria**. BMJ. 2011 Aug 4

Coulthard MG, Verber I, Jani JC, et al. Can **prompt treatment** of childhood UTI prevent kidney **scarring**? Pediatr Nephrol. 2009 Jul 9. [Epub ahead of print]

Craig JC, Simpson JM, Williams GJ, et al. **Prevention of Recurrent** Urinary Tract Infection in **Children** with **Vesicoureteric Reflux** and Normal Renal Tracts (**PRIVENT**) Investigators. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med. 2009 Oct 29;361(18):1748-59. Antibiotic prophylaxis reduces the likelihood of subsequent urinary tract infection (UTI; number needed to treat [NNT] = 16 for 1 year). However, subsequent infections are more likely to be caused by resistant organisms, and prophylaxis is not effective if the index infection was caused by a resistant organism. (LOE = 1b)

Crider Krista S.; Cleves Mario A.; Reefhuis Jennita; et al. Antibacterial Medication Use During **Pregnancy** and Risk of Birth Defects: National Birth Defects Prevention Study. Arch Pediatr Adolesc Med. 2009;163(11):978-985. Patients may ask about a widely reported, case-control study suggesting that certain antibacterial drugs, including sulfonamides and nitrofurantoins, are associated with increased risk for birth defects.

Dai B, Liu Y, Jia J, et al. **Long-term antibiotics for the prevention** of recurrent urinary tract infection in **children**: a systematic review and meta-analysis. Arch Dis Child. 2010 Jul;95(7):499-508. Epub 2010 May 10.

Dore-Bergeron, Marie-Joelle, et al. **Urinary** Tract Infections in 1- to 3-Month-Old **Infants**: **Ambulatory** Treatment With Intravenous Antibiotics. Pediatrics 2009 124: 16-22

Fakih MG, Watson SR, Greene MT, et al. **Reducing inappropriate urinary catheter use**: a statewide effort. Arch Intern Med. doi:10.1001/archinternmed.2011.627.

Ferrara P, et al. **Cranberry juice** for the prevention of recurrent urinary tract infections: a randomized controlled trial in **children**. Scand J Urol Nephrol 2009;43:1-5.

Fourcroy JL, et al. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. Antimicrob Agents Chemother. 2005 Oct;49(10):4137-43. (InfoPOEMs: A single dose of an extended-release version of ciprofloxacin (Cipro XR) is as effective as the immediate-release version taken twice daily for 3 days. The tiny reduction in the likelihood of gastrointestinal adverse effects (number needed to treat (NNT) = 60 - 80) is likely to be heavily promoted, and must be balanced against the higher cost of this formulation. As we are given more such options, it is important to remember the key elements in choosing a drug: its safety, tolerability, efficacy, price, and simplicity. Although extended-release ciprofloxacin is simpler, it is no more effective and will almost certainly cost more. (LOE = 1b))

Garin EH, et al. Clinical significance of **primary vesicoureteral reflux** & urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled stud

TOP

2006 Mar;117(3):626-32. (InfoPOEMs: Following treatment of acute pyelonephritis, antibiotic prophylaxis does not prevent further urinary tract infections in children with no documented vesicoureteral reflux (VUR) or in children with mild to moderate VUR. (LOE = 1b-))

Gauthier M, Gouin S, Phan V, et al. Association of **Malodorous Urine** With Urinary Tract Infection in Children Aged 1 to 36 Months. Pediatrics. 2012 Apr 2.

Gould CV, Umscheid CA, Agarwal RK, et al., Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for **prevention of catheter-associated** urinary tract infections 2009. Atlanta (GA): Centers for Disease Control and Prevention (**CDC**); 2009. http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/CAUTI_Guideline2009final.pdf

Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Uncomplicated urinary tract infections in adult**: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar. http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Urological_Infections.pdf

Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Catheter-associated UTIs**: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.

Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Complicated URIs** due to urological disorders: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.

Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Prostatitis and chronic pelvic pain** syndrome: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.

Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Sepsis syndrome in urology (urosepsis):** Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.

Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **Urinary tract infections in children**: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.

Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. **UTIs in renal insufficiency, transplant recipients, diabetes mellitus and immunosuppression**: Guidelines on urological infections. Arnhem, The Netherlands: **European** Association of Urology (EAU); 2009 Mar.

Guay DR. **Cranberry** and urinary tract infections. Drugs. 2009;69(7):775-807. doi: 10.2165/00003495-200969070-00002. The findings of the Cochrane Collaboration support the potential use of cranberry products in the prophylaxis of recurrent UTIs in young and middle-aged women. However, in light of the heterogeneity of clinical study designs and the lack of consensus regarding the dosage regimen and formulation to use, cranberry products cannot be recommended for the prophylaxis of recurrent UTIs at this time.

Guinto VT, De Guia B, Festin MR, et al. Different antibiotic regimens for treating **asymptomatic bacteriuria in pregnancy**. Cochrane Database Syst Rev. 2010 Sep 8;9:CD007855. We cannot draw any definite conclusion on the most effective and safest antibiotic regimen for the initial treatment of asymptomatic bacteriuria in pregnancy.

Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med. 2007 Nov 12;167(20):2207-12. A 5-day course of nitrofurantoin is equivalent clinically and microbiologically to a 3-day course of trimethoprim-sulfamethoxazole and should be considered an effective fluoroquinolone-sparing alternative for the treatment of acute cystitis in women.

Gupta Kalpana, Hooton Thomas M., Naber Kurt G., et al. International Clinical Practice Guidelines for the Treatment of **Acute Uncomplicated Cystitis and Pyelonephritis in Women**: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases (**IDSA/ESCMID**) Clin Infect Dis. (2011) 52(5): e103-e120 doi:10.1093/cid/ciq257

Gupta K, Trautner B. In the Clinic: **Urinary tract infection.** Ann Intern Med. 2012 Mar 6;156(5):ITC31.

Hay Alastair D, Whiting Penny, Butler Christopher C. Uncertainties Page: How best to **diagnose urinary tract infection in preschool children** in primary care? BMJ 2011;343:doi:10.1136/bmj.d6316 (Published 25 October 2011)

Heintz BH, Halilovic J, Christensen CL. **Vancomycin-resistant enterococcal** urinary tract infections. Pharmacotherapy. 2010 Nov;30(11):1136-49.

Heliovaara-Peippo S, Halmesmaki K, Hurskainen R, et al. The effect of **hysterectomy or levonorgestrel-releasing intrauterine** system on lower urinary tract symptoms: a 10-year follow-up study of a randomised trial. BJOG. 2010 Apr;117(5):602-9. Epub 2010 Feb 15.

Hoberman A, Wald ER, Hickey RW, et al. **Oral versus initial intravenous** therapy for urinary tract infections in young **febrile children**. Pediatrics 1999;104:79-86.

Hodson EM, et al. Antibiotics for **acute pyelonephritis in children**. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003772. These results suggest that children with acute pyelonephritis can be treated effectively with oral antibiotics (cefixime, ceftibuten and amoxycillin/clavulanic acid) or with short courses (2 to 4 days) of IV therapy followed by oral therapy. If IV therapy is chosen, single daily dosing with aminoglycosides is safe and effective.

Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of **catheter-associated urinary tract infection** in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America (IDSA). Clin Infect Dis. 2010 Mar 1;50(5):625-63.

Hooton TM, Roberts PL, Stapleton AE. **Cefpodoxime vs ciprofloxacin** for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA. 2012 Feb 8;307(6):583-9.

Huang YY, Chen MJ, Chiu NT, Chou HH, et al. Adjunctive **Oral Methylprednisolone** in Pediatric Acute Pyelonephritis Alleviates **Renal Scarring**. Pediatrics. 2011 Aug 15.

Hunziker M, Mohanan N, D'Asta F, et al. Incidence of Febrile Urinary Tract Infections in Children after **Successful Endoscopic Treatment of Vesicoureteral Reflux**: A Long-Term Follow-Up. J Pediatr. 2012 Jan 25.

Jeffres MN, Shuster JE, Barclay SM. Treatment of **Ciprofloxacin Nonsusceptible Urinary Tract Infections with Ciprofloxacin**. Ahead of Print on 1 June 2011.

Jepson RG, Craig JC. **Cranberries** for preventing urinary tract infections. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001321. There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. It's effectiveness for other groups is less certain. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules).

Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of **Escherichia coli** from community-acquired urinary tract infections in **Europe**: the ECO·SENS study revisited. Int J Antimicrob Agents. 2011 Nov 2. In E. coli, resistance to mecillinam, cefadroxil (representing oral cephalosporins), nitrofurantoin, fosfomycin trometamol, gentamicin and the third-generation cephalosporins cefotaxime and ceftazidime was<2%, with the following exceptions: gentamicin in Portugal (2.8%); fosfomycin in Greece (2.9%); and cephalosporins in Austria (2.7-4.1%). Resistance levels were higher for amoxicillin/clavulanic acid (2.0-8.9%) and ciprofloxacin (0.5-7.6%) and much higher to ampicillin (21.2-34.0%), sulfamethoxazole (21.2- 31.3%), trimethoprim (14.9-19.1%) and trimethoprim/sulfamethoxazole (14.4-18.2%). Resistance to quinolones and trimethoprim increased between the ECO·SENS I (1999-2000) and ECO·SENS II (2007-2008): nalidixic acid 4.3% to 10.2%; ciprofloxacin 1.1% to 3.9%; and trimethoprim 13.3% to 16.7%. In the previous study, no isolates with extended-spectrum β-lactamase were found; however, in the present study 11 isolates were identified as having either CTX-M or AmpC.

Kallen AJ, et al. Current antibiotic therapy for isolated urinary tract infections in women. Arch Intern Med. 2006 Mar 27;166(6):635-9. CONCLUSIONS: Quinolones have surpassed sulfas as the most common class of antibiotic prescribed for isolated outpatient UTI in women. Few significant predictors of quinolone use exist, suggesting that the increase is not confined to a certain subset of patients. This pervasive growth in quinolone use raises concerns about increases in resistance to this important class of antibiotics.

TOP

Kashanian J, Hakimian P, Blute M Jr, et al. **Nitrofurantoin**: the return of an old friend in the wake of growing resistance. BJU Int. 2008 Dec;102(11):1634-7. Epub 2008 Jul 24.
Katchman EA, Milo G, et al. **Three-day** vs longer duration of antibiotic treatment for cystitis in women: systematic review & meta-analysis. Am J Med. 2005 Nov;118(11):1196-207.
Kodner CM, Gupton EKT. **Recurrent Urinary Tract Infections in Women**: Diagnosis and Management. Am Fam Physician. 2010 Sep 15;82(6):638-643.
Knottnerus BJ, Grigoryan L, Geerlings SE, et al. **Comparative effectiveness** of antibiotics for uncomplicated urinary tract infections: Network meta-analysis of randomized trials. Fam Pract. 2012 Apr 19.
Lee M, Bozzo P, Einarson A, Koren G. **Urinary tract infections in pregnancy**. Can Fam Physician. 2008 Jun;54(6):853-4.
Leroy S, Romanello C, Galetto-Lacour A, et al. **Procalcitonin** is a Predictor for High-Grade Vesicoureteral Reflux in Children: Meta-Analysis of Individual Patient Data. J Pediatr. 2011 Oct;159(4):644-651.e4.
Lin E, Bhusal Y, Horwitz D, Shelburne III SA, Trautner BW. **Overtreatment of enterococcal bacteriuria**. Arch Intern Med. 2012;172(1):33-38.
Little P, Moore M V, Turner S, et al. Effectiveness of **five different approaches** in management of urinary tract infection: randomised controlled trial.BMJ 2010;340:c199, doi: 10.1136/bmj.c199 (5 Feb 2010)
Little P, Merriman R, Turner S, et al. Presentation, pattern, and natural course of severe symptoms, and **role of antibiotics and antibiotic resistance** among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. BMJ. 2010 Feb 5;340:b5633. doi: 10.1136/bmj.b5633.
Loeb M, Brazil K, Lohfeld L, et al. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. BMJ. 2005 Sep 24;331(7518):669. Epub 2005 Sep 8.
Lumbiganon P, Villar J, Laopaiboon M, et al. One-day compared with **7-day nitrofurantoin** for asymptomatic bacteriuria in pregnancy: a randomized controlled trial. Obstet Gynecol. 2009 Feb;113(2 Pt 1):339-45. A 1-day regimen of nitrofurantoin is significantly less effective than a 7-day regimen. Women with asymptomatic bacteriuria in pregnancy should receive the standard 7-day regimen.
Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in **elderly women**. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD001535. Short-course treatment (3 to 6 days) could be sufficient for treating uncomplicated UTIs in elderly women, although more studies on specific commonly prescribed antibiotics are needed.
Mantadakis E, Plessa E, Vouloumanou EK, et al. Serum **procalcitonin** for prediction of renal parenchymal involvement in children with urinary tract infections: a meta-analysis of prospective clinical studies. J Pediatr. 2009 Dec;155(6):875-881.e1. Epub 2009 Oct 21.
McIsaac WJ, et al. Validation of a **decision aid** to assist physicians in reducing unnecessary antibiotic drug use for acute cystitis. Arch Intern Med. 2007 Nov 12;167(20):2201-6. A simple 3-item decision aid could significantly reduce unnecessary antibiotic drug prescriptions and urine culture testing in females with symptoms of acute cystitis.
McKinnell JA, Stollenwerk NS, Jung CW, Miller LG. **Nitrofurantoin** compares favorably to recommended agents as empirical treatment of uncomplicated urinary tract infections in a decision and cost analysis. Mayo Clin Proc. 2011 Jun;86(6):480-8.
McMurdo ME, Argo I, et al. **Cranberry or trimethoprim** for the prevention of recurrent urinary tract infections? A RCT in older women. J Antimicrob Chemother. 2008 Nov 28. [Epub ahead of print] n=137. Trimethoprim had a very limited advantage over cranberry extract in the prevention of recurrent UTIs in older women and had more adverse effects. Our findings will allow older women with recurrent UTIs to weigh up with their clinicians the inherent attractions of a cheap, natural product like cranberry extract whose use does not carry the risk of antimicrobial resistance or super-infection with C. difficile or fungi.
Medical Letter: Treatment Guidelines. **Choice of Antibacterial Drugs**. May 2007.
Medical Letter. Treatment Guidelines. **Drugs for Bacterial Infections**. June 2010.
Mehnert-Kay SA. Diagnosis and management of uncomplicated urinary tract infections. Am Fam Physician. 2005 Aug 1;72(3):451-6.
Milo G, Katchman EA, Paul M, et al. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD004682.
Montini G, Toffolo A, et al. Antibiotic treatment for pyelonephritis in children: multicentre randomized controlled non-inferiority trial. BMJ. 2007 Jul 4; [Epub ahead of print] Treatment with oral antibiotics is as effective as parenteral then oral treatment in the management of the first episode of clinical pyelonephritis in children.
Montini G, Rigon L, Zucchetta P, et al. IRIS Group. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics. 2008 Nov;122(5):1064-71. Prophylactic antibiotic therapy for 12 months following a febrile urinary tract infection (UTI) in children between the ages of 2 months and 7 years does not reduce the risk of subsequent UTI, even in children with vesicoureteral reflux grades I through III. This is the second trial to find that prophylaxis is not necessary. (LOE = 1b-)
Montini Giovanni, Tullus Kjell, Hewitt Ian. **Febrile Urinary Tract Infections in Children**. N Engl J Med 2011;365:239-50.
Mori R, Lakhanpaul M, Verrier-Jones K. Diagnosis and management of urinary tract infection in **children: summary of NICE guidance**. BMJ. 2007 Aug 25;335(7616):395-7.
Mouttalib S, Khan S, Castel-Lacanal E, et al. Risk of urinary tract infection after detrusor **botulinum toxin A injections** for refractory neurogenic detrusor overactivity in patients with no antibiotic treatment. BJU Int. 2010 Jun 29.
Naber KG, Llorens L, Kaniga K, et al.. Intravenous **Doripenem** 500 mg Versus Levofloxacin 250 mg With an Option to Switch to Oral Therapy for the Treatment of Complicated Lower Urinary Tract Infection and Pyelonephritis. Antimicrob Agents Chemother. 2009 Jul 6. [Epub ahead of print]
Nagler EV, Williams G, Hodson EM, et al. **Interventions for primary vesicoureteric reflux.** Cochrane Database Syst Rev. 2011 Jun 15;6:CD001532. Compared with no treatment, use of long-term, low-dose antibiotics did not significantly reduce the number of repeat symptomatic and febrile UTIs in children with VUR. Considerable heterogeneity in the analyses and inclusion of only one adequately blinded study, made drawing firm conclusions challenging. Antibiotic prophylaxis significantly reduced the risk of developing new or progressive renal damage, but assuming an 8% baseline risk, 33 children would need long-term antibiotic prophylaxis to prevent one more child developing kidney damage over the course of two to three years.The added benefit of surgical or endoscopic correction of VUR over antibiotic treatment alone remains unclear. Eight children would require combined surgical and antibiotic treatment to prevent one additional child developing febrile UTI by five years, but it would not cause fewer children developing renal damage.
Nicolle LE. Catheter-related urinary tract infection. Drugs Aging. 2005;22(8):627-39.
Niel-Weise B, van den Broek P. Antibiotic policies for short-term catheter bladder drainage in adults. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005428.
Paschke AA, Zaoutis T, Conway PH, et al. Previous **Antimicrobial Exposure** Is Associated With Drug-**Resistant** Urinary Tract Infections in Children. Pediatrics. 2010 Mar 1.
Peleg AY, Hooper DC. **Hospital-acquired** infections due to gram-negative bacteria. N Engl J Med. 2010 May 13;362(19):1804-13.
Perrotta C, et al. **Oestrogens** for preventing recurrent urinary tract infection in postmenopausal women. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005131. Based on only two

TOP

studies comparing vaginal oestrogens to placebo, vaginal oestrogens reduced the number of UTIs in postmenopausal women with RUTI, however this varied according to the type of oestrogen used and the treatment duration.

Pharmacist's Letter: Treatment of Uncomplicated UTI June 2006

Pharmacists's Letter. **Cystoplus** (sodium citrate) for Cystitis. Aug 2011.

Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003237. DOI: 10.1002/14651858.CD003237.pub2. {Cochrane Summary: Severe urinary tract infection (UTI) is a common infection in adults and children, causing acute disease with a variety of symptoms such as fever and flank pain. This may lead to kidney damage, kidney failure or hypertension. Standard therapy involves antibiotics given at least initially by injection. This review identified 15 studies (1743 participants). The results of this review suggest oral therapy is equally effective in treating UTI and preventing long-term damage. This might reduce costs but also inconvenience for the patient.}

Richards D, Toop L, Chambers S, Fletcher L. Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double blind randomised controlled trial. BMJ 2005; 331:143-46. (InfoPOEMs: No infection, no antibiotic, right? Maybe not. In women with dysuria and frequency but a negative urine dipstick result for nitrites and leukocytes, 3 of 4 women will respond to antibiotic treatment as compared with 1 of 4 taking placebo. The negative dipstick result correlated with culture 92% of the time. These results imply that some women have microbial infections that are not identified by dipstick or culture. Or, perhaps, the antibiotic is doing something other than killing bacteria. (LOE = 1b))

Rotjanapan P; Dosa D; Thomas KS. **Potentially Inappropriate Treatment** of Urinary Tract Infections in Two Rhode Island Nursing Homes. Arch Intern Med. 2011;171(5):438-443.

Sanchez GV, et al. In vitro antimicrobial **resistance** of urinary **Escherichia coli** isolates among US outpatients from 2000 to 2010. Antimicrob Agents Chemother. 2012Apr;56(4):2181-3. Antimicrobial susceptibility results (n = 12,253,679) showed the greatest increases in E. coli resistance from 2000 to 2010 for ciprofloxacin (3% to 17.1%) and trimethoprim-sulfamethoxazole (TMP-SMX) (17.9% to 24.2%), whereas nitrofurantoin (0.8% to 1.6%) and ceftriaxone (0.2% to 2.3%) showed minimal change.

Saint S, et al. Condom versus indwelling urinary catheters: a randomized trial. J Am Geriatr Soc. 2006 Jul;54(7):1055-61. (InfoPOEMs: After adjusting for other factors, using condom catheters in men older than 40 is associated with fewer complications (bacteriuria, symptomatic urinary tract infection, death) than using indwelling catheters. Since more than 40% of men in each group had complications, I wonder if any kind of catheter is really necessary in most patients. (LOE = 2b))

Salo J, Ikäheimo R, Tapiainen T, Uhari M. Childhood Urinary Tract Infections as a **Cause of Chronic Kidney Disease**. Pediatrics. 2011 Oct 10.

Sandberg T, Skoog G, Hermansson AB, et al. **Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis**: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet 2012; online June 21. http://dx.doi.org/10.1016/S0140-6736(12)60608-4.

Schooff M, Hill K. Antibiotics for **recurrent** urinary tract infections. Am Fam Physician. 2005 Apr 1;71(7):1301-2.

Singh-Grewal D, et al. Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. Arch Dis Child. 2005 Aug; 90(8) :853-8. (InfoPOEMs: Routine circumcision does not provide enough reduction in risk of urinary tract infection (UTI) to justify the surgical complication risk. For boys at high risk of UTI, however, the reduction in risk may justify the procedure. (LOE = 2a-))

Sha SH, Qiu JH, Schacht J. Aspirin to prevent **gentamicin**-induced hearing loss. N Engl J Med. 2006 Apr 27;354(17):1856-7.

Shaikh N, Morone NE, Lopez J, Chianese J, et al. Does this **child have a urinary tract infection**? JAMA. 2007 Dec 26;298(24):2895-904.

Shaikh N. Acute **urinary tract infection** in **infants and young children**. CMAJ. 2010 May 18;182(8):800-1.

Shaikh N, Ewing AL, Bhatnagar S, et al. Risk of **renal scarring in children** with a first urinary tract infection: a systematic review. Pediatrics. 2010 Dec;126(6):1084-91.

Sharp VJ, Takacs EB, Powell CR. **Prostatitis**: diagnosis and treatment. Am Fam Physician. 2010 Aug 15;82(4):397-406.

Sheffield JS, Cunningham FG. Urinary tract infection in **women**. Obstet Gynecol. 2005 Nov;106(5):1085-92.

SOGC 2009 Menopause and Osteoporosis Update 2009-SOGC Jan 2009. http://www.sogc.org/media/pdf/advisories/Meno-Osteo-Update_JOGC-Jan_09.pdf

SOGC 2010 Guideline: Recurrent Urinary Tract Infection http://www.sogc.org/guidelines/documents/gui250CPG1010E.pdf (Epp A, Larochelle A, Lovatsis D, et al. Recurrent urinary tract infection. J Obstet Gynaecol Can 2010 Nov;32(11):1082-90.)

Tan IL, Polydefkis MJ, Ebenezer GJ, et al. Peripheral nerve toxic effects of **nitrofurantoin**. Arch Neurol. 2012 Feb;69(2):265-8.

Thomas M. et al. Amoxicillin-Clavulanate vs Ciprofloxacin for the Treatment of Uncomplicated Cystitis in Women -a Randomized Trial. JAMA. 2005;293:949-955.

Torpy JM, Schwartz LA, Golub RM. JAMA **patient page. Urinary tract infection**. JAMA. 2012 May 2;307(17):1877.

van Nieuwkoop C, et al. **Intravesical gentamicin** (80mg od) for recurrent urinary tract infection in patients with intermittent bladder catheterisation. IntJAntimicrob Agents.2010Jun 25.

Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during **pregnancy**. Cochrane Database Syst Rev. 2011 Jan 19;1:CD002256. Although antibiotic treatment is effective for the cure of urinary tract infections, there are insufficient data to recommend any specific drug regimen for treatment of symptomatic urinary tract infections during pregnancy. All the antibiotics studied were shown to be very effective in decreasing the incidence of the different outcomes. Complications were very rare.

White B, Diagnosis and Treatment of **Urinary Tract Infections in Children**. Am Fam Physician. 2011 Feb 15;83(4):409-415.

Williams G, Craig JC. **Long-term antibiotics for preventing recurrent urinary tract infection in children.** Cochrane Database Syst Rev. 2011 Mar 16;3:CD001534. Long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children but the benefit is small and must be considered together with the increased risk of microbial resistance.

Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily **Cranberry Juice** for the Prevention of Asymptomatic Bacteriuria in Pregnancy: A Randomized, Controlled Pilot Study. J Urol. 2008 Aug 14. n=188 These data suggest there may be a protective effect of cranberry ingestion against asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Further studies are planned to evaluate this effect.

Zalmanovici Trestioreanu A, Green H, Paul M, et al. Antimicrobial agents for treating **uncomplicated urinary tract infection in women**. Cochrane Database Syst Rev. 2010 Oct 6;10:CD007182. No differences were observed between the classes of antimicrobials included in this review for the symptomatic cure of acute uncomplicated UTI. Fluoroquinolones proved more effective than beta-lactams for the short-term bacteriological outcome, probably with little clinical significance. Individualised treatment should take into consideration the predictable susceptibility of urinary pathogens in local areas, possible adverse events and resistance development, and patient preference.

TOP

Treatment of Low Back Pain [21, 22]

Red Flags (assessment considerations):

- pain when recumbent
- saddle anesthesia
- pseudoclaudication
- age >55y or <20
- recent UTI
- trauma (major
- pain persisting >1mo

Tx Guidelines:

- symptomatic relief can be accomplished with OTC medication and/or spinal manipulation
- during acute phase, bed rest >4 days may further debilitate the patient
- low-stress aerobic activity & exercise OK in first 2 weeks; may delay trunk muscle exercises
- recommend return to work/normal activities as soon as possible
- if problems persist, reassessment required
- address nonphysical factors (psych/socioeconomic)

Meds: acetaminophen 1st line; NSAIDs option if necessary & not contraindicated; strong opioids may be necessary for some but consider addiction risk, use treatment agreement and set appropriate boundaries; consider referral.

Back Pain Treatment Options: REFERENCES

[1] Hasgen KB, Hilde G, Jamtvedt G. Winnem M. Bed rest for acute low back pain and sciatica (Cochrane Review). The Cochrane Library 2001;Issue 3.

[2] Tulder MW van, Malmivaara A, Esmail R, Koes BW. Exercise therapy for low back pain (Cochrane Review). The Cochrane Library 2001;Issue 3.

[3] Staal JB, Hlobil H, Twisk JWR, et al. Graded activity for low back pain in occupational health care. Ann Intern Med 2004; 140:77-84.

[4] Frost H, Lamb SE, Doll HA, et al. Randomised controlled trial of physiotherapy compared with advice for low back pain. BMJ. 2004 Sep 25;329(7468):708.

[5] Hay EM, Mullis R, Lewis M, et al. Comparison of physical treatments versus a brief pain-management programme for back pain in primary care: a randomised clinical trial in physiotherapy practice. Lancet. 2005 Jun 28;365(9476):2024-30. (Kaapa EH, et al. Multidisciplinary group rehabilitation versus individual physiotherapy for chronic nonspecific low back pain: a randomized trial. Spine. 2006 Feb 15;31(4):371-6.)

[6] Childs JD, Fritz JM, et al. A clinical prediction rule to identify patients with low back pain most likely to benefit from spinal manipulation: a validation study. Ann Intern Med 2004; 141:920-28.

[7] Keos BW, Assendelft W, Van der Heijden G, et al. Spinal manipulation for low back pain: an updated systematic review of randomized clinical trials. Spine 1996;21:2860-71.
Walker BF, French SD, Grant W, Green S. **Combined chiropractic interventions** for low-back pain. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD005427.
Rubinstein SM, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2011, Issue 2. Art. No.: CD008112. DOI: 10.1002/14651858.CD008112.pub2. High quality evidence suggests that there is no clinically relevant difference between SMT and other interventions for reducing pain and improving function in patients with chronic low-back pain. Determining cost-effectiveness of care has high priority.

[8] Cherkin D, Sherman K, et al. A Review of the Evidence for the effectiveness, safety & cost of acupuncture, message thereapy and spinal manipulation for back pain. Ann Intern Med 2003;138:898-906.
Furlan AD, Imamura M, Dryden T, Irvin E. Massage for low-back pain. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD001929. Massage might be beneficial for patients with subacute and chronic non-specific low-back pain, especially when combined with exercises and education. The evidence suggests that acupuncture massage is more effective than classic massage, but this need confirmation. More studies are needed to confirm these conclusions, to assess the impact of massage on return-to-work, and to determine cost-effectiveness of massage as an intervention for low-back pain.
Sherman KJ, Cherkin DC, Wellman RD, et al. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain [published online October 24, 2011]. Arch Intern Med. doi:10.1001/archinternmed.2011.524.
Tilbrook HE, Cox H, Hewitt CE, et al. **Yoga** for chronic low back pain: a randomized trial. Ann Intern Med. 2011 Nov 1;155(9):569-78.

[9] Guzman J, Esmail R, Karjalainen, et al. Multidisciplinary rehabilitation for chronic low back pain: systematic review. *BMJ* 2001;322:1511-1516

[10] Karjalainene K, Malmivaara A, et al. Multidisciplinary biopsychosocial rehabilitation for subacute low back pain among working age adults (Cochrane Review). The Cochrane Library 2001;Issue 4.

[11] Van Tulder MW, Jellema P, van Poppel MNM,et al. Lumbar supports for prevention and treatment of low back pain (Cochrane Review). The Cochrane Library 2001;Issue 3.
Roelofs PD, Bierma-Zeinstra SM, van Poppel MN, et al. Lumbar supports to prevent recurrent low back pain among home care workers: a randomized trial. Ann Intern Med. 2007 Nov 0;147(10):685-92. Summary for patients in: Ann Intern Med. 2007 Nov 20;147(10):I54. {InfoPOEMs Jan07: A lumbar support belt used by people doing moderately strenuous activity who identify themselves as having back pain decreases the number of days they have pain. However, the overall number of days lost from work is not affected. (LOE = 1b-)}

[12] Cherkin D, Sherman K, et al. A Review of the Evidence for the effectiveness, safety & cost of acupuncture, message thereapy & spinal manipulation for back pain. Ann Intern Med 2003;138:898-906.

[13] Manheimer E, White A, et al. Meta-analysis: **Acupuncture** for low back pain. Ann Intern Med 2005; 142:651-63. (InfoPOEMs: Acupuncture is an effective treatment for decreasing pain in pts with chronic low back pain. It doesn't seem to be a placebo effect; acupuncture produces a significantly greater effect on pain than sham acupuncture. There is not enough research to allow a conclusion for the treatment of acute low back pain. (LOE = 1a)). Thomas KJ, et al. Randomised controlled trial of a short course of traditional

TOP

acupuncture compared with usual care for persistent non-specific low back pain. BMJ. 2006 Sep 15; [Epub ahead of print] Weak evidence was found of an effect of acupuncture on persistent non-specific low back pain at 12 months, but stronger evidence of a small benefit at 24 months. Referral to a qualified traditional acupuncturist for a short course of treatment seems safe and acceptable to patients with low back pain. (Haake M, Muller HH, Schade-Brittinger C, Basler HD, Schafer H, Maier C, Endres HG, Trampisch HJ, Molsberger A. German Acupuncture Trials (GERAC) for Chronic Low Back Pain: Randomized, Multicenter, Blinded, Parallel-Group Trial With 3 Groups. Arch Intern Med. 2007 Sep 24;167(17):1892-8. Low back pain improved after acupuncture treatment for at least 6 months. Effectiveness of acupuncture, either verum or sham, was almost twice that of conventional therapy.)

Madsen MV, Gøtzsche PC, Hróbjartsson A. **Acupuncture** treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009 Jan 27;338:a3115. doi: 10.1136/bmj.a3115.

Cherkin Daniel C.; et al. A Randomized Trial Comparing Acupuncture, Simulated Acupuncture, & Usual Care for Chronic Low Back Pain Arch Intern Med. 2009;169(9):858-866.

[14] Van Tulder MW, Scholten RJ, Koes BW, Deyo RA. Non-steroidal anti-inflammatory drugs for low back pain (Cochrane Review). The Cochrane Library 2001;Issue 3.

[15] University of York, Royal Society of Medicine. Acute and chronic low back pain in Effective Health Care 2000;6(5):1-8.

[16] Browning R, Jackson JL, O'Mallery PG. Cyclobenzaprine and back pain; a meta-analysis. Arch Intern Med 2001;161:1613-1620.

[17] Staiger TO, Gaster B, Sullivan MD, Deyo RA. Systematic review of antidepressants in the treatment of chronic low back pain. Spine 2003; 28:2540-45.

[18] University of York, Royal Society of Medicine. Acute and chronic low back pain in Effective Health Care 2000;6(5):1-8.

[19] Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med 2000;32:305-316.

[20] Atkinson JH, Slater MA, Williams RA, Zisook S, Patterson TL. A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. Pain 1998;76:287-96.

[21] Di Iroio D, Henley E, Doughty A. A survey of Primary Care Physician Practice Patterns and Adherence to Acute Low Back Problem Guidelines. Arch Fam Med 2000;9:1015-1021

[22] Car J, Sheikh A. Acute low back pain. BMJ 2003:327-541.

Additional references:

Allan L, et al. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine. 2005 Nov 15;30(22):2484-90.

Allan G. **X-ray scans** for nonspecific low back pain: A nonspecific pain? Canadian Family PhysicianMarch 2012 vol. 58 no. 3275.

Assendelft WJJ, Morton SC, Yu EI, et al. **Spinal manipulative** therapy for low-back pain. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD000447.
There is no evidence that spinal manipulative therapy is superior to other standard treatments for patients with acute or chronic low-back pain.

Balague F, Mannion AF, Pellise F, Cedraschi C. **Clinical update: low back pain**. Lancet. 2007 Mar 3;369(9563):726-8.

Bigos SJ, Holland J, Holland C, et al. High-quality controlled trials on preventing episodes of back problems: systematic literature review in working-age adults. Spine J. 2009 Feb;9(2):147-68. Twenty high-quality controlled trials found strong, consistent evidence to guide prevention of BP episodes in working-age adults. Trials found exercise interventions effective and other interventions not effective, including stress management, shoe inserts, back supports, ergonomic/back education, and reduced lifting programs. The varied successful exercise approaches suggest possible benefits beyond their intended physiologic goals.

Bronfort G, Haas M, Evans RL, Bouter LM. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. Spine J. 2004 May-Jun;4(3):335-56.

Brox J, Sorensen R, Friis A, Nygaard O, Indahl A, Keller A. Randomized clinical trial of **lumbar instrumented fusion** and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine 2003;28:1913-21.

Brox JI, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: A prospective randomized controlled study. Pain. 2006 May;122(1-2):145-55. Epub 2006 Mar 20.

Brox JI, Nygaard OP, Holm I, et al. Four-year follow-up of **surgical versus non-surgical** therapy for chronic low back pain. Ann Rheum Dis. 2010 Sep;69(9):1643-8.

Carpenter KM, Stoner SA, Mundt JM, et al. An online **self-help CBT** intervention for chronic lower back pain. Clin J Pain. 2012 Jan;28(1):14-22.

Carragee EJ. Clinical practice. Persistent low back pain. N Engl J Med. 2005 May 5;352(18):1891-8.

Cherkin Daniel C.; et al. A Randomized Trial Comparing **Acupuncture**, Simulated Acupuncture, and Usual Care for Chronic Low Back Pain Arch Intern Med. 2009;169(9):858-866.

Cherkin D, Kovacs FM, Croft P, et al.; International Organizing Committee of the Ninth International Forum for Primary Care Research on Low Back Pain and All the Participants. The **Ninth International Forum** for Primary Care Research on Low Back Pain. Spine (Phila Pa 1976). 2009 Feb 1;34(3):304-7.

Cherkin Daniel C., Sherman Karen J., Kahn Janet, et al. A Comparison of the Effects of 2 Types of **Massage** and Usual Care on Chronic Low Back Pain: A Randomized, Controlled Trial. Ann Intern Med July 5, 2011 155:1-9

Chilibeck PD, Vatanparast H, Cornish SM, Abeysekara S, Charlesworth S. Evidencebased risk assessment and recommendations for **physical activity**: arthritis, osteoporosis, and low back pain. *Appl Physiol Nutr Metab* 2011;36(Suppl 1):S49-S79.

Choi BK, Verbeek JH, Tam WW, Jiang JY. **Exercises** for prevention of recurrences of low-back pain. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006555.

Chou R, Huffman LH; American Pain Society; American College of Physicians. **Medications for acute and chronic low back pain**: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. **2007** Oct 2;147(7):505-14. Medications with good evidence of short-term effectiveness for low back pain are NSAIDs, acetaminophen, skeletal muscle relaxants (for acute low back pain), and tricyclic antidepressants (for chronic low back pain). Evidence is insufficient to identify one medication as offering a clear overall net advantage because of complex tradeoffs between benefits and harms. Individual patients are likely to differ in how they weigh potential benefits, harms, and costs of various medications.

Chou R, Huffman LH; American Pain Society; American College of Physicians. **Nonpharmacologic therapies for acute and chronic low back pain**: review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. **2007** Oct 2;147(7):492-504. Therapies with good evidence of moderate efficacy for chronic or subacute low back pain are cognitive-behavioral therapy, exercise, spinal manipulation, and interdisciplinary rehabilitation. For acute low back pain, the only therapy with good evidence of efficacy is superficial heat.

Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, Owens DK; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American C

of Physicians; American Pain Society Low Back Pain Guidelines Panel. **Diagnosis and treatment of low back pain**: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. **2007** Oct 2;147(7):478-91. 1: Clinicians should conduct a focused history and physical examination to help place patients with low back pain into 1 of 3 broad categories: nonspecific low back pain, back pain potentially associated with radiculopathy or spinal stenosis, or back pain potentially associated with another specific spinal cause. The history should include assessment of psychosocial risk factors, which predict risk for chronic disabling back pain (strong recommendation, moderate-quality evidence). RECOMMENDATION 2: Clinicians should not routinely obtain imaging or other diagnostic tests in patients with nonspecific low back pain (strong recommendation, moderate-quality evidence). RECOMMENDATION 3: Clinicians should perform diagnostic imaging and testing for patients with low back pain when severe or progressive neurologic deficits are present or when serious underlying conditions are suspected on the basis of history and physical examination (strong recommendation, moderate-quality evidence). RECOMMENDATION 4: Clinicians should evaluate patients with persistent low back pain and signs or symptoms of radiculopathy or spinal stenosis with magnetic resonance imaging (preferred) or computed tomography only if they are potential candidates for surgery or epidural steroid injection (for suspected radiculopathy) (strong recommendation, moderate-quality evidence). RECOMMENDATION 5: Clinicians should provide patients with evidence-based information on low back pain with regard to their expected course, advise patients to remain active, and provide information about effective self-care options (strong recommendation, moderate-quality evidence). RECOMMENDATION 6: For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy (strong recommendation, moderate-quality evidence). For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs. RECOMMENDATION 7: For patients who do not improve with self-care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits-for acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation (weak recommendation, moderate-quality evidence).

Chou R, Atlas SJ, Stanos SP, Rosenquist RW. **Nonsurgical interventional therapies for low back pain**: a review of the evidence for an American Pain Society clinical practice guideline. *Spine (Phila Pa 1976)*. 2009;34(10):1078-1093.

Chou R, Fu R, Carrino JA, Deyo RA. **Imaging strategies** for low-back pain: systematic review and meta-analysis. Lancet. 2009 Feb 7;373(9662):463-72. Lumbar imaging for low-back pain without indications of serious underlying conditions does not improve clinical outcomes. Therefore, clinicians should refrain from routine, immediate lumbar imaging in patients with acute or subacute low-back pain and without features suggesting a serious underlying condition.

Chou R, Loeser JD, Owens DK,; American Pain Society (APS) Low Back Pain Guideline Panel. **Interventional therapies, surgery, and interdisciplinary rehabilitation** for low back pain: an evidence-based clinical practice guideline from the American Pain Society. Spine. 2009 May 1;34(10):1066-77. In patients with nonradicular pain: Interdisciplinary rehabilitation emphasizing cognitive-behavioral approaches should be considered for those who don't respond to usual interventions; Provocative discography (injecting material into a disc nucleus in an attempt to reproduce the patient's typical pain) is not recommended; Facet joint corticosteroid injection, prolotherapy (repeated injections of irritant material to stimulate an inflammatory response), and intradiscal corticosteroid injection are not recommended; Persistent disabling symptoms and degenerative spinal changes should prompt discussion and shared decision-making regarding surgery or interdisciplinary rehabilitation (there is insufficient evidence to weigh the use of vertebral disc replacement in these patients. In patients with persistent radiculopathy: Those with herniated discs should be offered discussion about the use of epidural steroid injection; Those with herniated discs and disabling leg pain from spinal stenosis should be offered discussion about surgery; Those with persistent pain after surgery should be offered discussion on the risks and benefits of spinal cord stimulation.

Chou R, Shekelle P. Will this patient develop persistent **disabling low back pain**?. JAMA. 2010 Apr 7;303(13):1295-302.

Chou Roger, Qaseem Amir, Owens Douglas K., et al. and for the Clinical Guidelines Committee of the American College of Physicians. **Diagnostic Imaging for Low Back Pain**: Advice for High-Value Health Care From the American College of Physicians. *Ann Intern Med* February 1, **2011** 154:181-189. Use an initial trial of therapy rather than immediate imaging. However, imaging is warranted when the patient has major risk factors for cancer, or shows severe or progressive neurologic deficits. Risk factors or signs of vertebral infection or the cauda equina syndrome, although rare, also warrant more immediate imaging.

Cohen SP, Argoff CE, Carragee EJ. **Management of low back pain**. BMJ. 2008 Dec 22;337:a2718. doi: 10.1136/bmj.a2718.

Cohen SP, Gupta A, Strassels SA, et al. Effect of **MRI** on treatment results or decision making in patients with lumbosacral radiculopathy referred for **epidural steroid injections**: a multicenter, randomized controlled trial [online Dec 12, 2011]. Arch Intern Med. doi:10.1001 /archinternmed.2011.593. *Arch Intern Med*. 2012;172(2):134-142.

Cohen SP, White RL, Kurihara C, et al. Epidural **steroids**, etanercept, or saline in subacute sciatica: a multicenter, randomized trial. Ann Intern Med. 2012 Apr 17;156(8):551-9.

Costa Luciola da C Menezes, Maher Christopher G, et al. **Prognosis** for patients with chronic low back pain: inception cohort study. BMJ 2009;339:b3829, doi: 10.1136/bmj.b3829.

Costa LD, Maher CG, Hancock MJ, et al. The **prognosis of acute and persistent low-back pain**: a meta-analysis. CMAJ. 2012 May 14.

Clarke J, van Tulder M, Blomberg S, et al. Traction for low-back pain with or without sciatica. Cochrane Database Syst Rev. 2005 Oct 19;4:CD003010. AUTHORS' CONCLUSIONS: The evidence suggests that traction is probably not effective.Neither continuous nor intermittent traction by itself was more effective in improving pain, disability or work absence than placebo, sham or other treatments for patients with a mixed duration of LBP, with or without sciatica. Although trials studying patients with sciatica had methodological limitations and inconsistent results, there was moderate evidence that autotraction was more effective than mechanical traction for global improvement in this population.

Dahm KT, Brurberg KG, Jamtvedt G, Hagen KB. Advice to rest in bed versus advice to stay active for acute low-back pain and sciatica. Cochrane Database Syst Rev. 2010 Jun 16;6:CD007612. Moderate quality evidence shows that patients with acute LBP may experience small benefits in pain relief and functional improvement from advice to stay active compared to advice to rest in bed; patients with sciatica experience little or no difference between the two approaches. Low quality evidence suggests little or no difference between those who received advice to stay active, exercises or physiotherapy. Further research is very likely to have an important impact on the estimate of effect and is likely to change our confidence in it.

Dionne CE, Bourbonnais R, Fremont P, et al. A clinical return-to-work rule for patients with back pain. CMAJ. 2005 Jun 7;172(12):1559-67& ACP Journal Club. (InfoPOEMs: A clinical decision rule can provide guidance regarding a patient's likelihood of successfully returning to work. Patients at high risk for failure may benefit from more intensive follow-up and therapy. Further study is required. (LOE = 1a))

Dubinsky, Richard M., Miyasaki, Janis. Assessment: Efficacy of **transcutaneous electric nerve stimulation** in the treatment of pain in neurologic disorders (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2009 0: WNL.0b013e3181c918fc.

Dubinsky RM, Miyasaki J. **Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.** Neurology. 2010 Jan 12;74(2):173-6. Epub 2009 Dec 30. Transcutaneous electric nerve stimulation (TENS) is not recommended for the treatment of chronic low back pain (Level A).

Engers A, Jellema P, Wensing M, van der Windt D, et al. **Individual patient education** for low back pain. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004057. For patients with acute or subacute LBP, intensive patient education seems to be effective. For patients with chronic LBP, the effectiveness of individual education is still unclear.

Ernst E, Lee MS. **Acupuncture** for rheumatic conditions: an overview of systematic reviews**.** Rheumatology (Oxford). 2010 Oct;49(10):1957-61. Epub 2010 Jun 29. European Evidence Based Guidelines: 2005 http://www.backpaineurope.org/web/files/WG2_Guidelines.pdf

Fairbank J, Frost H, et al. Randomised controlled trial to compare **surgical stabilisation of the lumbar spine** with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. BMJ. 2005 May 23; [Epub ahead of print] (InfoPOEMs: Intensive rehabilitation results in a reduction of disability due to chronic low back pain, although it was slightly less effective than spinal fusion surgery. Rehabilitation is more cost-effective and results in fewer complications than surgery. (LOE = 1b-))

Ferreira ML, Ferreira PH, Latimer J, et al. Comparison of general exercise, motor control exercise and spinal manipulative therapy for chronic low back pain: A randomized trial. Pain. 2007 Sep;131(1-2):31-7. Epub 2007 Jan 23.

TOP

French SD, et al. Superficial **heat or cold** for low back pain. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004750.

Friedman BW, Esses D, Solorzano C, et al. A randomized placebo-controlled trial of single-dose im corticosteroid for radicular low back pain. Spine. 2008 Aug 15;33(18):E624-9. This study was a negative study, though there was a suggestion of benefit of methylprednisolone acetate in a population of young adults with acute radicular low back pain.

Friedman BW et al. **One-week and 3-month outcomes** after an emergency department visit for undifferentiated musculoskeletal low back pain. Ann Emerg Med 2012 Feb; 59:128.

Garra G et al. **Heat or cold packs** for neck and back strain: A randomized controlled trial of efficacy. Acad Emerg Med 2010 May; 17:484.

Genevay S, Finckh A, Zufferey P et al. **Adalimumab** in acute sciatica reduces the long-term need for surgery: a 3-year follow-up of a randomised double-blind placebo-controlled trial. Ann Rheum Dis. 2012 Apr;71(4):560-2.

Gibson J, Waddell G, Gibson JA. Surgery for degenerative lumbar spondylosis. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001352.

Golden Adam G, Ma Qianli, Nair Vinit, et al. Risk for **Fractures with Centrally Acting Muscle Relaxants**: An Analysis of a National Medicare Advantage Claims Database. Ann Pharmacother 44:1369-1375.

Gross A, Forget M, St George K, et al. **Patient education** for neck pain. Cochrane Database Syst Rev. 2012 Mar 14;3:CD005106.

Hagen KB, Jamtvedt G, Hilde G, Winnem MF. The updated Cochrane Review of bed rest for low back pain and sciatica. Spine 2005; 30:542-46. (InfoPOEMs: When they are studied for 3 months, rest in bed for patients with uncomplicated low back pain causes more pain and slows return to function. Similarly, patients with sciatica experience, at best, no benefit with bed rest. (LOE = 1a))

Hall AM, Maher CG, Lam P, et al. **Tai chi exercise** for treatment of pain and disability in people with persistent low back pain: A randomized controlled trial. Arthritis Care Res (Hoboken). 2011 Nov;63(11):1576-83.

Hancock MJ, Maher CG, Latimer J, et al. Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial. Lancet. 2007 Nov 10;370(9599):1638-1643. Patients with acute low back pain receiving recommended first-line care do not recover more quickly with the addition of diclofenac or spinal manipulative therapy.

Hellum C, Johnsen LG, Storheim K, et al. **Surgery with disc prosthesis versus rehabilitation** in patients with low back pain and degenerative disc: two year follow-up of randomised study. BMJ 2011;342:d2786.

Henschke N, Ostelo RWJG, van Tulder MW, et al. **Behavioural treatment** for chronic low-back pain. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD002014. For patients with CLBP, there is moderate quality evidence that in the short-term, operant therapy is more effective than waiting list and behavioural therapy is more effective than usual care for pain relief, but no specific type of behavioural therapy is more effective than another. In the intermediate- to long-term, there is little or no difference between behavioural therapy and group exercises for pain or depressive symptoms. Further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates.

Hill JC, Whitehurst DG, Lewis M, et al. Comparison of **stratified primary care management** for low back pain with current best practice (STarT Back): a randomised controlled trial. Lancet. 2011 Sep 28.

Hoangmai H. Pham; Bruce E. Landon; et al. Rapidity and Modality of **Imaging** for Acute Low Back Pain in Elderly Patients Arch Intern Med. 2009;169(10):972-981.

Hollinghurst S, Sharp D, Ballard K, et al. Randomised controlled trial of **Alexander technique** lessons, exercise, & massage (ATEAM) for chronic and recurrent back pain: conomic evaluation. BMJ. 2008 Dec 11;337:a2656. doi: 10.1136/bmj.a2656. An exercise prescription and six lessons in Alexander technique alone were both more than 85% likely to be cost effective at values above pound20 000 per QALY, but the Alexander technique performed better than exercise on the full range of outcomes. A combination of six lessons in Alexander technique followed by exercise was the most effective & cost effective option.

Hoy DG, Bain C, Williams G, et al. A systematic review of the **global prevalence of low back pain**. Arthritis Rheum. 2012 Jan 9.

Hsieh LL, et al. Treatment of low back pain by **acupressure** and physical therapy: randomized controlled trial. BMJ. 2006 Feb 17; [Epub ahead of print] (InfoPOEMs: Acupressure was significantly more effective than standard physical therapy modalities and exercise at decreasing disability scores and pain in patients with chronic low back pain. (LOE = 1b))

Iles R, Taylor N, Davidson M, et al. **Telephone coaching** can increase activity levels for people with non-chronic low back pain: a randomised trial. J Physiother.2011;57(4):231-8.

Iversen T, Solberg T, Romner B, et al. Effect of caudal **epidural steroid or saline injection** in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. BMJ 2011;343:d5278.

Jüni P, Battaglia M, Nüesch E, Hämmerle G, Eser P, van Beers R, Vils D, Bernhard J, et al. A randomised controlled trial of **spinal manipulative therapy** in acute low back pain. Ann Rheum Dis. 2008 Sep 5. [Epub ahead of print] **SMT is unlikely to result in relevant early pain reduction** in patients with acute low back pain.

Khadilkar A, et al. **Transcutaneous electrical nerve stimulation** for the treatment of chronic low back pain: a systematic review. Spine. 2005 Dec 1;30(23):2657-66. (InfoPOEMs: These authors only found 2 randomized trials of transcutaneous electrical nerve stimulation (TENS) for managing chronic low back pain. The divergent quality and findings suggest that we cannot draw any reliable conclusions about its efficacy. (LOE = 1a-))

Khadilkar A, Odebiyi DO, Brosseau L, et al. **Transcutaneous electrical nerve stimulation (TENS**) versus placebo for chronic low-back pain. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD003008. At this time, the evidence from the small number of placebo-controlled trials does not support the use of TENS in the routine management of chronic LBP.

Kinkade S. **Evaluation and treatment of acute low back pain**. Am Fam Physician. 2007;75:1181-1188.

Koes BW. Evidence-based management of acute low back pain. Lancet. 2007 Nov 10;370(9599):1595-6.

Korhonen T, Karppinen J, Paimela L, et al. The treatment of disc herniation-induced sciatica with infliximab: one-year follow-up results of FIRST II, a randomized controlled trial. Spine. 2006 Nov 15;31(24):2759-66. Although the long-term results of this randomized trial do not support the use of infliximab compared with placebo for lumbar radicular pain in patients with disc herniation-induced sciatica, further study in a subgroup of patients with L4-L5 or L3-L4 herniations, especially in the presence of Modic changes, appears to be warranted.

Kroenke Kurt; Bair Matthew J.; Damush Teresa M.; et al. **Optimized Antidepressant** Therapy and Pain Self-management in Primary Care Patients With Depression and Musculoskeletal Pain: A Randomized Controlled Trial. JAMA. 2009;301(20):2099-2110. Optimized antidepressant therapy followed by a pain selfmanagement program resulted in substantial improvement in depression as well as moderate reductions in pain severity and disability.

TOP

Kuijpers T, van Middelkoop M, et al. A systematic review on the effectiveness of **pharmacological interventions** for chronic non-specific low-back pain. Eur Spine J. 2010 Jul 31

Lamb SE, Hansen Z, Lall R, et al. on behalf of the Back Skills Training Trial investigators. Group **cognitive behavioural treatment** for low-back pain in primary care: a randomized controlled trial and cost-effectiveness analysis. Lancet. 2010 Feb 25.

Lambeek Ludeke C, van Mechelen Willem, Knol Dirk L, et al. Randomised controlled trial of **integrated care** to reduce disability from chronic low back pain in working and private life. BMJ 2010;340:c1035, doi: 10.1136/bmj.c1035 (Published 16 March 2010)

Lambeek Ludeke C, Bosmans Judith E, Van Royen Barend J, et al. Effect of integrated care for sick listed patients with chronic low back pain: **economic evaluation** alongside a randomised controlled trial. BMJ 341:doi:10.1136/bmj.c6414 (Published 30 Nov 2010)

Langevin P, Peloso PMJ, Lowcock J, et al. **Botulinum toxin for subacute/chronic neck pain**. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD008626. DOI: 10.1002/14651858.CD008626.pub2. Current evidence fails to confirm either a clinically important or a statistically significant benefit of BoNT-A injection for chronic neck pain associated with or without associated cervicogenic headache. Likewise, there was no benefit seen for disability and quality of life at four week and six months.

Larson AM, et al, and the Acute Liver Failure Study Group. Acetaminophen-Induced Acute Liver Failure: Results of a US Muticenter, Prospective Study. Hepatology; Dec 2005. (Of 662 consecutive acute liver failure pts over 6yrs: 42% from acetaminophen liver injury; 48% were unintentional overdoses; only 65% of pts survived)

Last AR, Hulbert K. **Chronic low back pain**: evaluation and management. Am Fam Physician. 2009 Jun 15;79(12):1067-74.

Lavy C, James A, Wilson-MacDonald J, Fairbank J. **Cauda equina syndrome**. BMJ. 2009 Mar 31;338:b936. doi: 10.1136/bmj.b936.

Little P, et al. RCT trial of Alexander technique lessons, exercise, and massage (**ATEAM**) for chronic and recurrent back pain. BMJ. 2008 Aug 19;337:a884. doi: 10.1136/bmj.a884. One to one lessons in the Alexander technique from registered teachers have long term benefits for patients with chronic back pain. Six lessons followed by exercise prescription were nearly as effective as 24 lessons.

Livshits G, Popham M, Malkin I, et al.. **Lumbar disc degeneration and genetic factors** are the main risk factors for low back pain in women: the UK Twin Spine Study. Ann Rheum Dis. 2011 Oct;70(10):1740-5.

Machado LA, Kamper SJ, Herbert RD, et al. **Analgesic effects** of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. Rheumatology (Oxford). 2009 May;48(5):520-7. Epub 2008 Dec 24. The overall analgesic effects of most therapeutic interventions in patients with nonspecific low back pain, regardless of duration, are small. The data are limited by small study size and poor study quality. (LOE = 1a-)

Madsen MV, Gøtzsche PC, Hróbjartsson A. **Acupuncture** treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009 Jan 27;338:a3115. doi: 10.1136/bmj.a3115.

Martimo K, Verbeek J, et al. **Manual material handling advice and assistive devices** for preventing and treating back pain in workers. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005958. There is limited to moderate evidence that MMH advice and training with or without assistive devices do not prevent back pain, back pain-related disability or reduce sick leave when compared to no intervention or alternative interventions. There is no evidence available for the effectiveness of MMH advice and training or MMH assistive devices for treating back pain.

McCullough BJ, Johnson GR, Martin BI, Jarvik JG. **Lumbar MR imaging** and reporting epidemiology: do epidemiologic data in reports affect clinical management? Radiology. 2012 Mar;262(3):941-6.

Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: **Botulinum** neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 May 6;70(19):1707-14. Botulinum neurotoxin (BoNT) should be offered as a treatment option for the treatment of axillary hyperhidrosis and detrusor overactivity (Level A), should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia after spinal cord injury (Level B), and may be considered for gustatory sweating and low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B). There is presently no consistent or strong evidence to permit drawing conclusions on the efficacy of BoNT in chronic daily headache (mainly transformed migraine) (Level U). While clinicians' practice may suggest stronger recommendations in some of these indications, evidence-based conclusions are limited by the availability of data.

Ney JP, Difazio et al. Treatment of chronic low back pain with successive injections of **botulinum toxin** a over 6 months: a prospective trial of 60 patients. Clin J Pain. 2006 May;22(4):363-9.

Nice May 2009 Low back guideline summary http://www.nice.org.uk/nicemedia/pdf/CG88QuickRefGuide.pdf (Savigny P, Watson P, Underwood M; Guideline Development Group. Early management of persistent non-specific low back pain: summary of NICE guidance. BMJ. 2009 Jun 4;338:b1805. doi: 10.1136/bmj.b1805. These guidelines from the United Kingdom's National Institute for Health and Clinical Excellence (NICE) give a nod to exercise, manual therapy, analgesics, acupuncture, and combined physical and psychological therapy for patients with low back pain. They advise against many traditional treatments, including lumbar support, traction, and steroid and other injections, citing either a lack of benefit or a lack of evidence. (LOE = 1a))

Pengel LH, Refshauge KM, Maher CG, et al. **Physiotherapist**-directed exercise, advice, or both for subacute low back pain: a randomized trial. Ann Intern Med. 2007 Jun 5;146(11):787-96. In participants with subacute low back pain, physiotherapist-directed exercise and advice were each slightly more effective than placebo at 6 weeks. The effect was greatest when the interventions were combined. At 12 months, the only effect that persisted was a small effect on participant-reported function.

Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, et al. Drugs for relief of pain in patients with **sciatica**: systematic review and meta-analysis. BMJ 2012;344:e497.

Rodríguez-Oviedo P, Ruano-Ravina A, Pérez-Ríos M, et al. School **children's backpacks**, back pain and back pathologies. Arch Dis Child. 2012 Mar 10.

Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: an updated cochrane review. Spine. 2008 Jul 15;33(16):1766-74. The evidence from the 65 trials included in this review suggests that NSAIDs are effective for short-term symptomatic relief in patients with acute and chronic low back pain without sciatica. However, effect sizes are small. Furthermore, there does not seem to be a specific type of NSAID, which is clearly more effective than others. The selective COX-2 inhibitors showed fewer side effects compared with traditional NSAIDs in the randomized controlled trials included in this review. However, recent studies have shown that COX-2 inhibitors are associated with increased cardiovascular risks in specific patient populations.

Rubinstein SM, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. **Spinal manipulative therapy** for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2011, Issue 2. Art. No.: CD008112. DOI: 10.1002/14651858.CD008112.pub2. High quality evidence suggests that there is no clinically relevant difference between SMT and other interventions

TOP

for reducing pain and improving function in patients with chronic low-back pain. Determining cost-effectiveness of care has high priority.
Santilli V, Beghi E, Finucci S. Chiropractic manipulation in the treatment of acute back pain and sciatica with disc protrusion: a randomized double-blind clinical trial of active and simulated spinal manipulations. Spine J. 2006 Mar-Apr;6(2):131-7. Epub 2006 Feb 3.
Sherman KJ, et al. Comparing **yoga**, exercise, and a self-care book for chronic low back pain: a randomized, controlled trial. Ann Intern Med. 2005 Dec 20;143(12):849-56. (InfoPOEMs: A yoga program specifically aimed at patients with chronic low back pain is more effective than either exercise treatment or self-care in decreasing functional disability in patients with chronic low back pain. The style of yoga is called viniyoga and was adapted for use in patients with low back pain. (LOE = 1b))
Sherman KJ, Cherkin DC, Wellman RD, et al. A randomized trial comparing **yoga, stretching, and a self-care book** for chronic low back pain [online October 24, 2011]. Arch Intern Med. doi:10.1001/archinternmed.2011.524.
Su W, Yegappan C, Carlisle EJF, et al. Reduced level of consciousness from **baclofen** in people with low kidney function. BMJ 2009;339:b4559, doi: 10.1136/bmj.b4559 (31Dec09)
Suri P, Rainville J, Kalichman L, et al. Does this older adult with lower extremity pain have the clinical syndrome of **lumbar spinal stenosis**? JAMA. 2010 Dec 15;304(23):2628-36.
Tilbrook HE, Cox H, Hewitt CE, et al. **Yoga** for chronic low back pain: a randomized trial. Ann Intern Med. 2011 Nov 1;155(9):569-78.
Urquhart D, et al. **Antidepressants** for non-specific **low back pain**. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001703. There is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic low-back pain.
van Wijk RM, Geurts JW, Wynne HJ, et al. Radiofrequency denervation of lumbar facet joints in the treatment of chronic low back pain: a randomized, double-blind, sham lesion-controlled trial. Clin J Pain. 2005 Jul-Aug;21(4):335-44.
Verbeek JH, Martimo KP, Karppinen J, et al. **Manual material handling advice and assistive devices for preventing and treating back pain in workers.** Cochrane Database Syst Rev. 2011 Jun 15;6:CD005958. There is moderate quality evidence that MMH advice and training with or without assistive devices does not prevent back pain or back pain-related disability when compared to no intervention or alternative interventions. There is no evidence available from RCTs for the effectiveness of MMH advice and training or MMH assistive devices for treating back pain.
Walker BF, French SD, Grant W, Green S. **Combined chiropractic interventions** for low-back pain. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD005427. Combined chiropractic interventions slightly improved pain and disability in the short-term and pain in the medium-term for acute and subacute LBP. However, there is currently no evidence that supports or refutes that these interventions provide a clinically meaningful difference for pain or disability in people with LBP when compared to other interventions. Future research is very likely to change the estimate of effect and our confidence in the results.
Waseem Z, Boulias C, Gordon A, et al. **Botulinum toxin injections** (Botox) for low-back pain and sciatica. Cochrane Database Syst Rev. 2011 Jan 19;1:CD008257. We identified three studies that investigated the merits of BoNT for LBP, but only one had a low risk of bias and evaluated patients with non-specific LBP (N = 31).
Weinstein JN, et al. Surgical vs Nonoperative Treatment for Lumbar Disk Herniation: The Spine Patient Outcomes Research Trial (SPORT) Observational Cohort. JAMA. 2006 Nov 22;296(20):2451-2459.
Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, et al. SPORT Investigators. Surgical versus nonsurgical therapy for **lumbar spinal stenosis**. N Engl J Med. 2008 Feb 21;358(8):794-810.
Wilkens Philip; Scheel Inger B.; Grundnes Oliver; et al. Effect of **Glucosamine** on Pain-Related Disability in Patients With Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis: A Randomized Controlled Trial. JAMA. 2010;304(1):45-52.
Williams CM, Maher CG, Hancock MJ, et al. Low back pain and best practice care: A **survey of general practice** physicians. Arch Intern Med. 2010 Feb 8;170(3):271-7.
Woodman JP, Moore NR. Evidence for the effectiveness of **Alexander Technique** lessons in medical and health-related conditions: a systematic review. Int J Clin Pract. 2012 Jan;66(1):98-112.
UK BEAM Trial Team. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ. 2004 Dec 11;329(7479):1377. Epub 2004 Nov 19.

Web Sites:
American Academy of Family Physicians (information available in English and Spanish) http://familydoctor.org/online/famdoces/home/common/pain/treatment/117.html
MedlinePlus http://www.nlm.nih.gov/medlineplus/backpain.html
National Institutes of Neurological Disorders and Stroke http://www.ninds.nih.gov/disorders/backpain/backpain.htm
The Arthritis Foundation http://ww2.arthritis.org/conditions/DiseaseCenter/back_pain.asp

TOP

Extras:

- **Renal Failure –** Considerations: that need to alter approach to drug selection will depend on degree of renal dysfx (e.g. GFR ≥20ml/min, 10-20ml/min, <10ml/min), pain severity & drug dose required, use of dialysis.
  A) Less problematic options may include: acetaminophen, tramadol, topicals (capsaicin, nitro spray?); hydromorphone, fentanyl, methadone. {Always include non-drug techniques.}
- **Cisplatinin** related neuropathy: prevention with Vitamin E 400mg/day starting before, and going for 3 months after cisplatinin treatment.
  [Pace A, Giannarelli D, Galiè E, Savarese A, Carpano S, Della Giulia M, et al. Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. Neurology. 2010 Mar 2;74(9):762-6.]
- **Links FYI**: Patient Info - Pain Management: http://www.medschoolforyou.com/Subjects.aspx
  Cognitive Behavioural Therapy for Insomnia: http://www.cbtforinsomnia.com/
  Pain Training – Online: http://www.algo-md.com/en/index.php (fee for course)
  Pain Approaches: Distinctives in the Acute vs Palliative vs CNCP use of Opioids: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Approaches-Acute-Palliative-CNCP.pdf
  Methadone dosing in pain management: http://pain-topics.org/pdf/OralMethadoneDosing.pdf

REFERENCES - Pain-Chronic Non-malignant Chart (CNMP): www.RxFiles.ca

[1] Micromedex 2010 – Drug Evaluations.
[2] Pringsheim T, Howse D. In-patient treatment of chronic daily headache using dihydroergotamine: a long-term follow-up study. Can J Neurol Sci. 1998 May;25(2):146-50.
[3] Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology. 1986 Jul;36(7):995-7.
Dodick D, Freitag F. Evidence-based understanding of medication-overuse headache: clinical implications. Headache. 2006 Nov;46 Suppl 4:S202-11.
Grande RB et al. Severity of Dependence Scale detects people with medication overuse: The Akershus study of chronic headache. J Neurol Neurosurg Psychiatry 2009 Jul; 80:784.
[4] Wiffen P, McQuay H, Moore R. Carbamazepine for acute and chronic pain. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005451.
Gronseth G, Cruccu G, Alksne J, et al. Practice Parameter: The diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology. 2008 Aug 20. [Epub ahead of print] In patients with trigeminal neuralgia (TN), routine head imaging identifies structural causes in up to 15% of patients and may be considered useful (Level C). Trigeminal sensory deficits, bilateral involvement of the trigeminal nerve, and abnormal trigeminal reflexes are associated with an increased risk of symptomatic TN (STN) and should be considered useful in distinguishing STN from classic trigeminal neuralgia (Level B). There is insufficient evidence to support or refute the usefulness of MRI to identify neurovascular compression of the trigeminal nerve (Level U). Carbamazepine (Level A) or oxcarbazepine (Level B) should be offered for pain control while baclofen and lamotrigine (Level C) may be considered useful. For patients with TN refractory to medical therapy, Gasserian ganglion percutaneous techniques, gamma knife, and microvascular decompression may be considered (Level C). The role of surgery vs pharmacotherapy in the management of TN in patients with MS remains uncertain. Based upon this review of the existing evidence, patients with trigeminal neuralgia should undergo trigeminal reflex testing and be given carbamazepine. Based on weaker evidence, patients with trigeminal neuralgia that is refractory to medical therapy are likely to benefit from surgery. (LOE = 2a-)
Siniscalchi Antonio, Gallelli Luca, Avenoso Tiziana, et al. Effects of Carbamazepine/Oxycodone Coadministration in the Treatment of Trigeminal Neuralgia. Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1Q013. Ann Pharmacother ;45:e33.
Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst Rev. 2011 Sep 7;9:CD007312.
[5] Turk U, Ilhan S, Alp R, Sur H. Botulinum Toxin and Intractable Trigeminal Neuralgia. Clin Neuropharmacol. 2005 July/August;28(4):161-162.
[6] This record should be cited as: He L, Wu B, Zhou M. Non-antiepileptic drugs for trigeminal neuralgia. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004029. DOI: 10.1002/14651858.CD004029.pub2.
[7] Boulton AJ, Vinik AI, Arezzo JC, et al; American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005 Apr;28(4):956-62. (see also Diabetes peripheral neuropathic pain treatment. Pharmacist's Letter Aug 2006.)
[8] Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. The Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD005454. DOI: 10.1002/14651858.CD005454. (Wong MC, Chung JW, Wong TK. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. BMJ. 2007 Jun 11; [Epub ahead of print] Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants. Evidence of the long term effects of oral antidepressants and anticonvulsants is still lacking. Further studies are needed on opioids, N-methyl-D-aspartate antagonists, and ion channel blockers. (InfoPOEMs: Capsaicin and tricyclic antidepressants produce the best response in patients with short-term painful diabetic neuropathy. If these are ineffective, valproate or carbamazepine (Tegretol) should be the next choice, since they are more effective than the new anticonvulsants pregabalin (Lyrica) and gabapentin (Neurontin). Duloxetine (Cymbalta, Yentreve) and opioids also have some evidence of benefit, but not to the same degree as the other choices. (LOE = 1a)))
Moore RA, Straube S, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007076.
Seward B. Rutkove. A 52-Year-Old Woman With Disabling Peripheral Neuropathy: Review of Diabetic Polyneuropathy. JAMA. 2009;302(13):1451-1458.
Bansal D, Bhansali A, Hota D, Chakrabarti A, Dutta P. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. Diabet Med. 2009 Oct;26(10):1019-26.
Dubinsky, Richard M., Miyasaki, Janis. Assessment: Efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2009 0: WNL.0b013e3181c918fc.
Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy : Report of the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*; Prepublished online April 11, 2011; DOI 10.1212/WNL.0b013e3182166ebe. http://www.neurology.org/content/early/2011/04/08/WNL.0b013e3182166ebe.full.pdf+html
Kaur H, Hota D, Bhansali A, et al. A Comparative Evaluation of Amitriptyline and Duloxetine in Painful Diabetic Neuropathy: A randomized, double-blind, cross-over clinical trial. Diabetes Care. 2011 Apr;34(4):818-22.
Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010 Sep;17(9):1113-e88.
Callaghan B, McCammon R, Kerber K, Xu X, Langa KM, Feldman E. Tests and expenditures in the initial evaluation of peripheral neuropathy. Arch Intern Med. 2012;172(2):127-132.
Callaghan BCC, Cheng HT, Stables CL et al. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 2012; 11: 521–34.
[9] Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain. 2004 Aug;110(3):697-706. Erratum in: Pain. 2005 Jan;113(1-2):248.
[10] Kochar DK, Rawat N, Agrawal RP, Vyas A, Beniwal R, Kochar SK, Garg P. Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. QJM. 2004 Jan;97(1):33-8.
[11] Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. Neurology. 2001 Aug 14;57(3):505-9.
[12] Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med. 2005 Sep-Oct;6(5):346-56.
(Arnold LM, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005 Dec;119(1-3):5-15. Epub 2005 Nov 17. (InfoPOEMs: Duloxetine (Cymbalta, Xeristar, Yentreve) is effective in some women with fibromyalgia, whether or not they are depressed. The average decrease in pain score as compared with placebo is small -- 1.31 to 1.44 of a possible 10 -- and many women will discontinue treatment (35% - 39% in this study). However, a significant proportion of women will experience a 50% or greater drop in average pain scores. The number needed to treat is 6 for 3 months. (LOE = 1b-))
[13] Wernicke JF; Pritchett YL; D'Souza DN; Waninger A; Tran P; Iyengar S; Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006; 67(8):1411-20. {InfoPOEMs Jan07: In this study, duloxetine (Cymbalta) 60 mg daily was more effective than placebo in reducing pain from neuropathy in patients with diabetes. Higher doses of duloxetine didn't provide much additional benefit. The biases in this study favor treatment, so it is likely that the real benefit is less than what these investigators observed. Finally, we don't know if duloxetine is any more effective than other treatments used for painful diabetic neuropathy. (LOE = 2b-).}
[14] Watson CP, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003 Sep;105(1-2):71-8.
[15] Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2004 Sep 28;63(6):959-65.
[16] Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med. 2005 Jul;2(7):e164. Epub 2005 Jul 26. http://www.pubmedcentral.gov/articlerender.fcgi?tool=pubmed&pubmedid=16013891
[17] Mounsey A, Matthew L, Slawson D. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. American Family Physician 2005;72:1075-79. (Wareham DW, Breuer J. Herpes zoster. BMJ. 2007 Jun 9;334(7605):1211-5.)
[18] Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2002 Oct 8;59(7):1015-21. (Oxman MN, Levin MJ, Johnson GR, et al.; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005 Jun 2;352(22):2271-84.)
(Chandra K, et al. Gabapentin versus nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial--the GONIP Trial. Int J Clin Pharmacol Ther. 2006 Aug;44(8):358-63. Gabapentin was shown to be equally efficacious but was better tolerated compared to nortriptyline and can be considered a suitable alternative for the treatment of PHN.)
Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006866. Oral acyclovir did not reduce the incidence of PHN significantly. There is insufficient evidence from randomised controlled trials to determine whether other antiviral treatments prevent PHN. Additional well-designed, randomised controlled trials of famciclovir or other new antiviral agents, with a greater number of participants are needed.
Moore RA, Straube S, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007076
Chen N, Li Q, Zhang Y, et al. Vaccination for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2011 Mar 16;3:CD007795.
Fashner J, Bell AL. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. Am Fam Physician. 2011 Jun 15;83(12):1432-1437.
Irving G et al. Efficacy and tolerability of gastric-retentive gabapentin for the treatment of postherpetic neuralgia: results of a double-blind, randomized, placebo-controlled clinical trial. Clin J Pain 2009; 25:185. (gabapentin daily not better than placebo)
Wallace MS et al. Gabapentin extended-release tablets for the treatment of patients with postherpetic neuralgia: a randomized, double-blind, placebo-controlled, multicentre study. Clin Drug Investig 2010; 30:765. (gabapentin not better than placebo)
Edelsberg JS, Lord C, Oster G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs used to treat postherpetic neuralgia. Ann Pharmacother. 2011 Dec;45(12):1483-90.
[19] Leijon G, Boivie J. Central post-stroke pain--a controlled trial of amitriptyline and carbamazepine. Pain. 1989 Jan;36(1):27-36.
[20] Vestergaard K, Andersen G, Gottrup H, Kristensen BT, Jensen TS. Lamotrigine for central poststroke pain: a randomized controlled trial. Neurology. 2001 Jan 23;56(2):184-90.
Kim JS, Bashford G, Murphy TK, et al. Safety and efficacy of pregabalin in patients with central post-stroke pain. Pain. 2011 May;152(5):1018-23. (similar to placebo for pain effect)
[21] Levendoglu F, Ogun CO, Ozerbil O, Ogun TC, Ugurlu H. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. Spine. 2004 Apr 16;29(7):743-51.
[22] Tai Q, Kirshblum S, Chen B, Millis S, et al. Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. J Spinal Cord Med. 2002 Summer;25(2):100-5.
[23] Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. Pain. 2002 Apr;96(3):375-83.
[24] Kvarnstrom A, Karlsten R, Quiding H, Gordh T. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. Acta Anaesthesiol Scand. 2004 Apr;48(4):498-506.
[25] Boviatsis EJ, Kouyialis AT, Korfias S, Sakas DE. Functional outcome of intrathecal baclofen administration for severe spasticity. Clin Neurol Neurosurg. 2005 Jun;107(4):289-95.
[26] Cardenas DD, Warms CA, Turner JA, Marshall H, Brooke MM, Loeser JD. Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. Pain. 2002 Apr;96(3):365-73.
[27] Drewes AM, Andreasen A, Poulsen LH. Valproate for treatment of chronic central pain after spinal cord injury. A double-blind cross-over study. Paraplegia. 1994 Aug;32(8):565-9.
[28] Siddall PJ, et al. Pregabalin (150-600mg/d)in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2006 Nov 28;67(10):1792-800. 12wek n=137
[29] Dini D, Bertelli G, Gozza A, Forno GG. Treatment of the post-mastectomy pain syndrome with topical capsaicin. Pain. 1993 Aug;54(2):223-6.
[30] Watson CP, Evans RJ, Watt VR. The post-mastectomy pain syndrome and the effect of topical capsaicin. Pain. 1989 Aug;38(2):177-86.
[31] Harden RN. Pharmacotherapy of complex regional pain syndrome. Am J Phys Med Rehabil. 2005 Mar;84(3 Suppl):S17-28. (Kalita J, Vajpayee A, Misra UK. Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. QJM. 2006 Feb;99(2):89-95. Epub 2006 Jan 20. (InfoPOEMs: Prednisolone provides short-term relief of pain in patients with complex regional pain syndrome (CRPS). Longer studies are needed to assess the persistence of this benefit and to better define its risks. (LOE = 1b)))
Goebel Andreas, Baranowski Andrew, Maurer Konrad, Et al. Intravenous Immunoglobulin Treatment of the Complex Regional Pain Syndrome: A Randomized Trial. *Ann Intern Med* February 2, 2010 152:152-158.
[32] Ribbers GM, Geurts AC, Stam HJ, Mulder T. Pharmacologic treatment of complex regional pain syndrome I: a conceptual framework. Arch Phys Med Rehabil. 2003 Jan;84(1):141-6.
[33] Manicourt DH, Brasseur JP, Boutsen Y, et al. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. Arthritis Rheum. 2004 Nov;50(11):3690-7.
[34] Quisel A, Gill JM, Witherell P. Complex regional pain syndrome: which treatments show promise? J Fam Pract. 2005 Jul;54(7):599-603.
Sigtermans MJ, van Hilten JJ, Bauer MC, et al.. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009 Jul 13. [Epub ahead of print]
Straube S, Derry S, Moore RA, McQuay HJ. Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD002918. The practice of surgical and chemical sympathectomy for neuropathic pain and CRPS is based on very little high quality evidence. Sympathectomy should be used cautiously in clinical practice, in carefully selected patients, and probably only after failure of other treatment options.
Marinus Johan, Moseley G Lorimer, Birklein Frank, et al. Clinical features and pathophysiology of complex regional pain syndrome (CRPS). The Lancet Neurology 1 July 2011 (Volume 10 Issue 7 Pages 637-648 DOI: 10.1016/S1474-4422(11)70106-5)
[35] van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1. BMC Neurol. 2004 Sep 29;4(1):13.
[36] Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev. 2003;(2):CD004257. (Watkins PB, et al. **Aminotransferase elevations** in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):87-93.))
Sinusas K. Osteoarthritis: diagnosis and treatment. Am Fam Physician. 2012 Jan 1;85(1):49-56.
[37] Bartels EM, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsøe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005523. DOI: 10.1002/14651858.CD005523.pub2

TOP

[38] Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G. Glucosamine therapy for treating osteoarthritis. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD002946. DOI: 10.1002/14651858.CD002946.pub2. (Clegg et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808. InfoPOEMs: 03May2006. **Glucosamine** This update includes 20 studies with 2570 patients. Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function while those studies evaluating the Rotta preparation show that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. WOMAC outcomes of pain, stiffness and function did not show a superiority of glucosamine over placebo for both Rotta and non-Rotta preparations of glucosamine. Glucosamine was as safe as placebo. {When compared to the previous review, this review which analyzes newer studies and more high quality studies, shows there is "platinum" level evidence that pain does not improve as much when taking glucosamine for 2 to 3 months. Depending on the scale used to measure function (physical ability), function may not improve at all or as much.
Glucosamine seems to be safe}
Ringdahl E, Pandit S. Treatment of Knee **Osteoarthritis**. Am Fam Physician. 2011;83(11):1287-1292.
Avouac J, Gossec L, Dougados M. Efficacy and safety of **opioids** for osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2007; 15: 957–65.
Reginster JY, Deroisy R, Rovati LC, et al. Long-term eff ects of **glucosamine** sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001; 357: 251–56.
Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after **glucosamine** sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage 2008; 16: 254–60.
Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of **chondroitins** 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2009; 60: 524–33.

[39] Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD005328.

[40] Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ 2005; 172:1039-43. *InfoPOEMs*-The evidence that intra-articular hyaluronic acid helps patients with knee osteoarthritis is of poor quality. Improvements in pain at rest and pain during exercise is seen in a minority of studies, and those studies were of lower quality than those showing no benefit. There is no evidence of functional improvement. Injections like this have a potentially powerful placebo effect, so any benefit seen in unblinded studies without concealed allocation is likely represent the placebo effect rather than any effect of the drug. (LOE = 1a-)

[41] Dagenais S. Intra-articular hyaluronic acid (viscosupplementation) for knee osteoarthritis. [Issues in emerging health technologies issue 94]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006. Accessed 16Jan07 at:: http://www.cadth.ca/media/pdf/E0010_viscosupplementation_cetap_e.pdf

[42] Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of **hyaluronic** acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 2009; 61: 1704–11.
Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. **Viscosupplementation** for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; 2: CD005321.
Chevalier X, Jerosch J, et al. Single, intra-articular treatment with 6 ml **hylan** G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis 2010; 69: 113–19.

[43] Little CV, Parsons T. Herbal therapy for treating osteoarthritis. Cochrane Database Syst Rev. 2001;(1):CD002947.

[44] Ernst E. Avocado-soybean unsaponifiables (ASU) for osteoarthritis - a systematic review. Clin Rheumatol. 2003 Oct;22(4-5):285-8.

[45] Bandolier. Avocado/soybean unsaponifiables for osteoarthritis, 2005. Accessed 17Aug05 @ http://www.jr2.ox.ac.uk/bandolier/band122/b122-3.html
Bijlsma Johannes W J, Berenbaum Francis, Lafeber Floris P J G. **Osteoarthritis**: an update with relevance for clinical practice. Lancet 2011; 377: 2115–26.
Chappell AS, Ossanna MJ, Liu-Seifert H, et al. **Duloxetine**, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009; 146: 253–60.

[46] Leo R. Chronic Pain and Comorbid Depression. Current Treatment Options in Neurology 2005;7:403-12.

[47] Maizels M. The Patient with Daily Headaches. American Family Physician 2004;70:2299-306, 2313-4.

[48] Dodick DW. Clinical practice. **Chronic daily headache**. N Engl J Med. 2006 Jan 12;354(2):158-65. Erratum in: N Engl J Med. 2006 Feb 23;354(8):884

[49] Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. Reg Anesth Pain Med. 2002 Sep-Oct;27(5):481-6.
Alviar MJ, Hale T, Dungca M. Pharmacologic interventions for treating **phantom limb pain**. Cochrane Database Syst Rev. 2011 Dec 7;12:CD006380. The short- and long-term effectiveness of opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and anaesthetics for clinically relevant outcomes that include pain, function, mood, sleep, quality of life, satisfaction and adverse effects remains unclear. Morphine, gabapentin and ketamine demonstrate trends towards short-term analgesic efficacy. Memantine and amitriptyline were ineffective for PLP.

[50] Robinson LR, Czerniecki JM, Ehde DM, et al. Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study. Arch Phys Med Rehabil. 2004 Jan;85(1):1-6.

[51] Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol Suppl. 2005 Aug;75:6-21.

[52] Fibromyalgia Treatment Guideline. University of Texas, School of Nursing, Family Nurse Practitioner Program. Fibromyalgia treatment guideline. Austin (TX): University of Texas, School of Nursing; 2005 May. 13 http://www.guideline.gov/summary/summary.aspx?view_id=1&doc_id=7352#s23

[53] American Pain Society. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. 2005
Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003786. There is 'gold' level evidence (www.cochranemsk.org) that supervised aerobic exercise training has beneficial effects on physical capacity and FMS symptoms. Strength training may also have benefits on some FMS symptoms.

[54] Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Arch Intern Med. 2005 Nov 28;165(21):2527-35. (Martin DP, Sletten CD, Williams BA, Berger IH. Improvement in fibromyalgia symptoms with acupuncture: results of a randomized controlled trial. Mayo Clin Proc. 2006 Jun;81(6):749-57. (InfoPOEMs: A 6-session acupuncture treatment significantly improves fibromyalgia symptoms in women, at least in the short term. Overall fibromyalgia scores were significantly improved 1 month after treatment ended, but not 7 months after treatment ended. (LOE = 1b)))
Baker R, Shaw EJ. Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy): summary of NICE **guidance**. BMJ. 2007 Sep 1;335(7617):446-8.
(Rooks DS, Gautam S, Romeling M, Cross ML, Stratigakis D, Evans B, Goldenberg DL, Iversen MD, Katz JN. Group **exercise**, education, and combination self-management in women with fibromyalgia: a randomized trial. Arch Intern Med. 2007 Nov 12;167(20):2192-200.)
Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis. 2008 Apr;67(4):536-41. Epub 2007 Jul 20.Antidepressants, pramipexole (Mirapex and Sifrol), pregabalin (Lyrica), tramadol (Ultram), tropisetron (Navoban), and heated pool treatments have been shown to have short-term effectiveness in the treatment of fibromyalgia pain. (LOE = 1a-)
Häuser W, Bernardy K, Uçeyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a **meta-analysis**. JAMA. 2009 Jan 14;301(2):198-209. Antidepressant medications are associated with improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in patients with FMS.
Moore RA, Straube S, et al. **Pregabalin** for **acute and chronic pain** in adults. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007076
Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain. 2010 Jun;11(6):505-21.
De Silva V, El-Metwally A, Ernst E, et al. Evidence for the efficacy of **complementary and alternative medicines** in the management of fibromyalgia: a systematic review. Rheumatology (Oxford). 2010 Jun;49(6):1063-8.
Arnold LM et al. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: Results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010 Sep; 62:2745.
Glombiewski JA, Sawyer AT, Gutermann J, et al. Psychological treatments for fibromyalgia: a meta-analysis. Pain. 2010 Nov;151(2):280-95.
White PD, Goldsmith KA, Johnson AL, et al. PACE trial management group. Comparison of adaptive pacing therapy, **cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome** (PACE): a randomized trial. Lancet. 2011 Mar 5;377(9768):823-36.
Moore RA, Wiffen PJ, Derry S, et al. **Gabapentin for chronic neuropathic pain and fibromyalgia** in adults. Cochrane Database Syst Rev. 2011 Mar 16;3:CD007938. Gabapentin provides pain relief of a high level in about a third of people who take if for painful neuropathic pain. Adverse events are frequent, but mostly tolerable. More conservative estimates of efficacy resulted from using better definitions of efficacy outcome at higher, clinically important, levels, combined with a considerable increase in the numbers of studies and participants available for analysis.
Hauser W, Petzke F, Uceyler N, et al. Comparative efficacy and acceptability of **amitriptyline, duloxetine and milnacipran** in fibromyalgia syndrome: a systematic review with meta-analysis. Rheumatology (Oxford). 2011 Mar;50(3):532-43.
van Koulil S, van Lankveld W, Kraaimaat FW, et al. Tailored **cognitive-behavioral therapy** and exercise training for high-risk patients with fibromyalgia. Arthritis Care Res (Hoboken). 2010 Oct;62(10):1377-85.
Reid S, Chalder T, Cleare A, Hotopf M, Wessely S. Chronic fatigue syndrome. Clin Evid (Online). 2011 May 26;2011. pii: 1101.
Häuser W, Wolfe F, Tölle T, Uçeyler N, Sommer C. The role of **antidepressants in the management of fibromyalgia** syndrome: a systematic review and meta-analysis. CNS Drugs. 2012 Apr 1;26(4):297-307.
Spaeth M, Bennett RM, Benson BA, et al. **Sodium oxybate** therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. Ann Rheum Dis. 2012 Jun;71(6):935-42.

[55] O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med. 2000 Sep;15(9):659-66.

[56] Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. Arthritis Rheum. 2004 Feb 15;51(1):9-13.

[57] Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum. 1996 Nov;39(11):1852-9.

[58] Crofford LJ, Rowbotham MC, Mease PJ,et al; Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005 Apr;52(4):1264-73. (Arnold LM, Goldenberg DL, et al. Gabapentin in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum. 2007 Mar 28;56(4):1336-1344 [Epub ahead of print] (12week n=150) Gabapentin (1,200-2,400 mg/day) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia.) Pharmacist's Letter. Lyrica for Fibromyalgia. Aug 2007.

[59] Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain. 1999 Dec;83(3):389-400.

[60] Larson AM, et al, and the Acute Liver Failure Study Group. Acetaminophen-Induced Acute Liver Failure: Results of a US Muticenter, Prospective Study. Hepatology; Dec 2005. (Of 662 consecutive acute liver failure pts over 6yrs: 42% from acetaminophen liver injury; 48% were unintentional overdoses; only 65% of pts survived)

[61] Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery. N Engl J Med. 2005 Feb 15; [Epub ahead of print]

[62] Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial. *N Engl J Med 2005; 352:1092-102.* (InfoPOEMs: For every 62 patients who take rofecoxib instead of placebo for 3 years, 1 additional patient will experience a serious cardiovascular event. Remember, there is no greater symptomatic relief with COX-2 inhibitors than with older drugs; acetaminophen is a very safe alternative. The decrease in risk of serious gastrointestinal complications is marginal with COX-2 inhibitors and the cost is high. (LOE = 1b))

[63] Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention. N Engl J Med 2005; 352:1071-80. (InfoPOEMs: One additional cardiovascular event or cardiovascular death occurs for every 126 patients treated for 1 year with celecoxib. There appears to be a dose response relationship. It is difficult to justify continued use of this and other coxibs, except in the most exceptional circumstances. (LOE = 1b))

[64] Lynch M. A review of the use of methadone for the treatment of noncancer pain. Pain Res Manage 2005;10(3):133-44.

[65] Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD006146. DOI: 10.1002/14651858.CD006146.

[66] RM Dühmke, DD Cornblath, JRF Hollingshead. Tramadol for neuropathic pain. *The Cochrane Database of Systematic Reviews* 2005 Issue 3; Copyright © 2005 The Cochrane Collaboration.

[67] Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol. 2005 Jun;96(6):399-409.

[68] Bandolier. Antidepressants in neuropathic pain. Accessed online 10Aug05 @ http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Chronrev/antidc/CP072.html

[69] Barkin RL, Barkin S. The Role of Venlafaxine and Duloxetine in the Treatment of Depression with Decremental Changes in Somatic Symptoms of Pain, Chronic Pain, and the Pharmacokinetics and Clinical Considerations of Duloxetine Pharmacotherapy. Am J Ther. 2005 September/October;12(5):431-438.

[70] (*Duplicate*) Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol. 2005 Jun;96(6):399-409.

[71] Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001133.

[72] Medical Letter: Gabapentin (Neurontin for Chronic Pain). The Medical Letter 2004;46:29-31. (Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain - a systematic review of randomized controlled trials. Pain. 2006 Jul 15; [Epub ahead of print])

[73] Wiffen P, McQuay H, Edwards J, Moore R. Gabapentin for acute and chronic pain. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005452.

[74] Therepeutics Initiative. Therapeutic Letter: Gabapentin for pain: New evidence from hidden data. July-Dec 2009. Accessed online 25 Mar, 2010 at: http://ti.ubc.ca/letter75.

[75] (*Duplicate*) Wiffen P, McQuay H, Moore R. Carbamazepine for acute and chronic pain. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005451.

[76] Hadj Tahar A. Pregabalin for peripheral neuropathic pain [Issues in emerging health technologies issue 67]. Ottawa CCOHTA; 2005. Accessed online 16Aug05 http://www.ccohta.ca/entry_e.html.

[77] Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. Drugs. 2005;65(1):111-8; discussion 119-20.

[78] Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. Drugs. 2004;64(24):2813-20; discussion 2821.

[79] (*Duplicate*) Hadj Tahar A. Pregabalin for peripheral neuropathic pain [Issues in emerging health technologies issue 67]. Ottawa CCOHTA; 2005. Accessed online 16Aug05 http://www.ccohta.ca/entry_e.html.

[80] Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2003 Apr 22;60(8):1274-83.

[81] Richy F, Bruyere O, Ethgen O et al: Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. Arch Intern Med 2003; 163(13):1514-1522.

[82] McAlindon TE, LaValley MP, Gulin JP et al: Glucosamine and chondroitin for treatment of osteoarthritis; a systematic quality assessment and meta-analysis. JAMA 2000; 238(11):1469-1475.

[83] Towheed TE, Maxwell L, Anastassiades TP et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD002946. Review.

[84] Jüni P, Reichenbach S, Trelle S, et al. Swiss Viscosupplementation Trial Group. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. Arthritis Rheum. 2007 Nov;56(11):3610-9. We found no evidence for a difference in efficacy between hylan and HAs. In view of its higher costs and potential for more local adverse events, we see no rationale for the continued use of hylan in patients with knee OA. {Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: A systematic review and meta-analysis. Arthritis Rheum. 2007 Nov 29;57(8):1410-1418 [Epub ahead of print] Given the likely lack of a superior effectiveness of hylan over hyaluronic acids and the increased risk of local adverse events associated with hylan, we discourage the use of intraarticular hylan in patients with knee osteoarthritis in clinical research or practice.
Richette P, Ravaud P, Conrozier T, et al. Effect of hyaluronic acid in symptomatic hip osteoarthritis: A multicenter, randomized, placebo-controlled trial. Arthritis Rheum. 2009 Feb 26;60(3):824-830. [Epub ahead of print] N=85. Our findings indicate that a single IA injection of HA is no more effective than placebo in treating the symptoms of hip OA.
Bannuru RR, Natov NS, Obadan IE, et al. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis. Arthritis Rheum.2009 Nov 30;61(12):1704-1711.
Munteanu SE, Zammit GV, Menz HB, et al. Effectiveness of intra-articular hyaluronan (Synvisc, hylan G-F 20) for the treatment of first metatarsophalangeal joint osteoarthritis: a randomized placebo-controlled trial. Ann Rheum Dis. 2011 Oct;70(10):1838-41.
Navarro-Sarabia F, Coronel P, Collantes E, et al. on behalf of the AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis. 2011 Nov;70(11):1957-1962.

[85] Galer BS, Jensen MP, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clin J Pain. 2002;18:297-301.

[86] Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ. 2004 Apr 24;328(7446):991. Epub 2004 Mar 19.
Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neurpathic pain in adults. Cochrane Database Syst Rev. 2009;(4):CD007393.

[87] Bandolier Extra Mar 2005. Topical Analgesics: a review of reviews and a bit of perspective. Accessed online 11Aug05@ http://www.jr2.ox.ac.uk/bandolier/Extraforbando/Topextra3.pdf

[88] Bandolier Extra Mar 2005. Topical Analgesics: a review of reviews and a bit of perspective. Accessed online 11Aug05@ http://www.jr2.ox.ac.uk/bandolier/Extraforbando/Topextra3.pdf

[89] Lynch ME, Clark AJ, Sawynok J. A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. Clin J Pain. 2003 Sep-Oct;19(5):323-8.

[90] Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. Pain. 2009 Nov;146(1-2):18-25.

[91] Epstein JB, Grushka M, Le N. Topical clonidine for orofacial pain: a pilot study. J Orofac Pain. 1997 Fall;11(4):346-52.

[92] Formula mentioned is: **Morphine** 10mg in 8 grams of intrasite gel. Applied to open ulcers once daily (not active through intact skin); may provide analgesia for up to 24 hours.

TOP

Additonal articles:

Abou-Setta AM, Beaupre LA, Rashiq S, et al. Comparative effectiveness of pain management interventions for **hip fracture:** a systematic review. Ann Intern Med. 2011 Aug 16;155(4):234-45.

American Society of Anesthesiologists Task Force on Chronic Pain Management; American Society of Regional Anesthesia & Pain Medicine. Practice guidelines for chronic pain management: updated report by the American Society of Anesthesiologists (ASA) Task Force on **Chronic Pain Management** and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2010 Apr;112(4):810-33.

APS-Opioid Treatment Guidelines Clinical Guidelines for the Use of **Chronic Opioid Therapy in Chronic Noncancer Pain** Feb/09 http://download.journals.elsevierhealth.com/pdfs/journals/1526-5900/PIIS1526590008008316.pdf
(Chou R, Fanciullo GJ, Fine PG, et al. **American Pain Society**-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009 Feb;10(2):113-30.)

Arnold LM, Rosen A, et al. A randomized, double-blind, placebo-controlled trial of **duloxetine** in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005 Dec 15;119(1-3):5-15. Epub 2005 Nov 17. InfoPOEMs: 26Apr2006. **Duloxetine** (Cymbalta, Xeristar, Yentreve) is effective in some women with fibromyalgia, whether or not they are depressed. The average decrease in pain score as compared with placebo is small -- 1.31 to 1.44 of a possible 10 -- and many women will discontinue treatment (35% - 39% in this study). However, a significant proportion of women will experience a 50% or greater drop in average pain scores. The number needed to treat is 6 for 3 months. (LOE = 1b-)

Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, European Federation of Neurological Societies. **EFNS** guidelines on the pharmacological treatment of **neuropathic pain**: 2010 revision. Eur J Neurol 2010 Sep;17(9):1113-e88.

Bandolier: InfoPOEMs: 03May2006. **Avocado/soybean** unsaponifiables reduce pain, NSAID use in knee OA. The limited data to date support the safety and possible efficacy of ASU for osteoarthritis of the knee. More and longer studies are needed before we can recommend this to our patients without hesitation. (LOE = 1b-)

Baron R, Binder A, Wasner G. **Neuropathic pain**: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010 Aug;9(8):807-19.

Bender JL, Radhakrishnan A, Diorio C, et al. Can **pain be managed through the Internet**? A systematic review of randomized controlled trials. Pain. 2011 Aug;152(8):1740-50.

Bennett MI, Bagnall AM, Raine G, et al. Educational **interventions by pharmacists to patients with chronic pain**: systematic review and meta-analysis. Clin J Pain. 2011 Sep;27(7):623-30.

Bernardy K, Fuber N, Kollner V, et al. Efficacy of **cognitive-behavioral therapies in fibromyalgia** syndrome - a systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2010 Oct;37(10):1991-2005. Epub 2010 Aug 3.

Berry JD, Petersen KL. A single dose of **gabapentin** reduces acute pain and allodynia in patients with **herpes zoster**. Neurology. 2005 Aug 9;65(3):444-7.

Boureau F, Legallicier P, Kabir-Ahmadi M. **Tramadol in post-herpetic neuralgia**: a randomized, double-blind, placebo-controlled trial. Pain. 2003 Jul;104(1-2):323-31.

Branco JC, Zachrisson O, Perrot S, et al. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of **milnacipran** in treatment of fibromyalgia. J Rheumatol. 2010 Apr;37(4):851-9.

Bril V, England J, Franklin GM, et al. Evidence-based guideline: **Treatment of painful diabetic neuropathy** : Report of the American Academy of Neurology (**AAN**), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*; Prepublished online April 11, 2011; DOI 10.1212/WNL.0b013e3182166ebe. http://www.neurology.org/content/early/2011/04/08/WNL.0b013e3182166ebe.full.pdf+html

Busch AJ, Barber KAR, Overend TJ, Peloso PMJ, Schachter CL. Exercise for treating **fibromyalgia** syndrome. **Cochrane** Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003786. DOI: 10.1002/14651858.CD003786.pub2

CADTH. Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, and Tricyclic Antidepressants in Management of Neuropathic Pain: A Meta-Analysis and Economic Evaluation. Jan 2009. Accessed online at: http://www.cadth.ca/media/pdf/H0458_Management_of_Neuropathic_Pain_tr_e.pdf

Castel A, Cascon R, Padrol A, et al. Multicomponent cognitive-behavioral group therapy with **hypnosis** for the treatment of **fibromyalgia**: long-term outcome. J Pain. 2012 Mar;13(3):255-65.

Cepeda MS, Camargo F, Zea C, Valencia L. **Tramadol** for **osteoarthritis**. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005522. Review.

{Tramadol or tramadol/paracetamol decreases pain intensity, produces symptom relief, and improves function in patients with OA, but these benefits are small}

Chandra K, et al. **Gabapentin versus nortriptyline** in **post-herpetic neuralgia** patients: a randomized, double-blind clinical trial--the GONIP Trial. Int J Clin Pharmacol Ther. 2006 Aug;44(8):358-63. Gabapentin was shown to be equally efficacious but was better tolerated compared to nortriptyline and can be considered a suitable alternative for the treatment of PHN.

Chappell AS, Ossanna MJ, Liu-Seifert H, et al. **Duloxetine**, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-controlled trial. Pain. 2009 Jul 20. [Epub ahead of print]

Clegg DO, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808. InfoPOEMs: 03May2006. **Glucosamine** HCl and **chondroitin** provides modest if any symptomatic benefit for patients with mild osteoarthritis of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (LOE = 1b)

Carville SF, Arendt-Nielsen S, Bliddal H, et al. **EULAR** evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2008;7:536-541. {InfoPOEMs: Antidepressants, pramipexole (Mirapex and Sifrol), pregabalin (Lyrica), tramadol (Ultram), tropisetron (Navoban), and heated pool treatments have been shown to have short-term effectiveness in the treatment of fibromyalgia pain. (LOE = 1a-)}

Clarke H, Bonin RP, Orser BA, et al. The Prevention of **Chronic Postsurgical Pain** (CPSP) Using Gabapentin and Pregabalin: A Combined Systematic Review and Meta-Analysis. Anesth Analg. 2012 Mar 13.

Daniels Jane; Gray Richard; Hills Robert K.; et al; on behalf of the LUNA Trial Collaboration. Laparoscopic **Uterosacral Nerve Ablation** (not helfpul) for Alleviating Chronic Pelvic Pain: A Randomized Controlled Trial. JAMA. 2009;302(9):955-961.

DeGroot H 3rd, Uzunishvili S, Weir R, et al**. Intra-articular injection of hyaluronic acid is not** superior to saline solution injection for ankle arthritis: a randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am. 2012 Jan 4;94(1):2-8.

Derry CJ, Derry S, Moore RA. **Caffeine** as an analgesic adjuvant for acute pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD009281. DOI: 10.1002/14651858.CD009281.pub2. The addition of caffeine (≥100 mg) to a standard dose of commonly used analgesics provides a small but important increase in the proportion of participants who experience a good level of pain relief.

Drug and Therapeutics Bulletin. Management of **medication overuse headache**. BMJ 2010;340:c1305, doi: 10.1136/bmj.c1305 (Published 28 April 2010)

Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010 Jan 12;74(2):173-6. Epub 2009 Dec 30. Transcutaneous electric nerve stimulation (TENS) is not recommended for the treatment of chronic low back pain (Level A). TENS should be considered in the treatment of painful diabetic neuropathy (Level B). Further research into the mechanism of action of TENS is needed, as well as more rigorous studies for determination of efficacy.

Dworkin RH, et al. Pharmacologic management of **neuropathic pain**: evidence-based recommendations. Pain. 2007 Dec 5;132(3):237-51. Epub 2007 Oct 24.

Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of **medication-overuse headache**. Lancet Neurol. 2010 Apr;9(4):391-401.

Freynhagen R, Bennett MI. Diagnosis and management of **neuropathic pain**. BMJ. 2009 Aug 12;339:b3002. doi: 10.1136/bmj.b3002.

Gilron I, et al. Neuropathic pain: a practical guide for the clinician. CMAJ. 2006 Aug 1;175(3):265-75.

Gilron I, Bailey JM, Tu D, et al. **Nortriptyline and gabapentin**, alone and in combination for **neuropathic** pain: a double-blind, randomised controlled crossover trial. Lancet. 2009 Oct 10;374(9697):1252-61. Epub 2009 Sep 30.

Hawkins, Joy L. **Epidural Analgesia** for Labor and Delivery. N Engl J Med 2010 362: 1503-1510.

Hearn L, Derry S, Moore RA. **Lacosamide** for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2012 Feb 15;2:CD009318. Lacosamide has limited efficacy in the treatment of peripheral diabetic neuropathy. Higher doses did not give consistently better efficacy, but were associated with significantly more adverse event withdrawals.

Hogan ME et al. Systematic review and meta-analysis of the effect of **warming local anesthetics** on injection pain. Ann Emerg Med 2011 Jul; 58:86.

Hollingshead J, Duhmke RM, Cornblath DR. **Tramadol** for neuropathic pain. Cochrane Database Syst Rev. 2006 Jul 19;3:CD003726. The number needed to treat with tramadol compared to placebo to reach at least 50% pain relief was 3.8 (95% confidence interval 2.8 to 6.3) & the number needed to harm was 8.3 (95% confidence interval 5.6 to 17.

InfoPOEMs Sep2007: {Capsaicin and tricyclic antidepressants produce the best response in patients with short-term painful diabetic neuropathy. If these are ineffective, valproate or carbamazepine (Tegretol) should be the next choice, since they are more effective than the new anticonvulsants pregabalin (Lyrica) and gabapentin (Neurontin). Duloxetine (Cymbalta, Yentreve) and opioids also have some evidence of benefit, but not to the same degree as the other choices. (LOE = 1a)} Irvine G. Contemporary assessment and management of **neuropathic** pain. Nuerology 2005;64(Suppl 3): S21-S27.

Huang ST, Good M, Zauszniewski JA. The effectiveness of **music** in relieving pain in cancer patients: a randomized controlled trial**.** Int J Nurs Stud. 2010 Nov;47(11):1354-62.

Jackman RP, Purvis JM, Mallett BS. **Chronic nonmalignant pain in primary care**. Am Fam Physician. 2008 Nov 15;78(10):1155-62.

Jørgensen A, Stengaard-Pedersen K, Simonsen O, et al. Intra-articular **hyaluronan is without clinical effect** in knee osteoarthritis: a multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. Ann Rheum Dis. 2010 Jun;69(6):1097-102.

Kahan Meldon, Mailis-Gagnon Angela, Wilson Lynn, et al. **Canadian guideline** for safe and effective use of opioids for chronic noncancer pain: Clinical summary for family physicians. **Part 1: general population**. Can Fam Physician November 2011 57: 1257-1266.

Kahan Meldon, Wilson Lynn, Mailis-Gagnon Angela, et al. **Canadian guideline** for safe and effective use of opioids for chronic noncancer pain: Clinical summary for family physicians. **Part 2: special populations**. Can Fam Physician November 2011 57: 1269-1276.

Kalita J, Vajpayee A, Misra UK. Comparison of **prednisolone** with piroxicam in **complex regional pain** syndrome following stroke: a randomized controlled trial. QJM. 2006 Feb;99(2):89-95. Epub 2006 Jan 20. InfoPOEMS: 06July2006. Prednisolone effective short-term for complex regional pain syndrome. Clinical Question: Which is more effective for complex regional pain syndrome following stroke: prednisolone or piroxicam? Prednisolone provides short-term relief of pain in patients with complex regional pain syndrome (CRPS). Longer studies are needed to assess the persistence of this benefit and to better define its risks. (LOE = 1b)

Kashikar-Zuck S et al.A randomized clinical trial of **cognitive behavioral therapy** for the treatment of **juvenile fibromyalgia**. Arthritis Rheum. 2011 Nov 22.

Lane Nancy E., Schnitzer Thomas J., Birbara Charles A., et al. **Tanezumab** for the Treatment of Pain from Osteoarthritis of the Knee. September 29, 2010 (10.1056/NEJMoa0901510)

Leveille Suzanne G.; Jones Richard N.; Kiely Dan K.; et al. Chronic Musculoskeletal Pain and the Occurrence of **Falls** in an Older Population. *JAMA*. 2009;302(20):2214-2221.

Langhorst J, Klose P, Musial F, et al. Efficacy of **acupuncture in fibromyalgia** syndrome--a systematic review with a meta-analysis of controlled clinical trials. Rheumatology (Oxford). 2010 Apr;49(4):778-88. Epub 2010 Jan 25. Lynch ME, Watson CP. The pharmacotherapy of chronic pain: A review. Pain Res Manag. 2006 Spring;11(1):11-38.

Luciano JV, Martinez N, Penarrubia-Maria MT, et al. Effectiveness of a **psychoeducational treatment program implemented in general practice for fibromyalgia** patients: a randomized controlled trial. Clin J Pain. 2011 Jun;27(5):383-91.

Madsen MV, Gøtzsche PC, Hróbjartsson A. **Acupuncture** treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009 Jan 27;338:a3115. doi: 10.1136/bmj.a3115.

McBeth J, Prescott G, Scotland G, et al. **Cognitive behavior therapy, exercise,** or both for treating chronic widespread pain [published online November 14, 2011]. Arch Intern Med. doi:10:1001/archinternmed.2011.555.

Medical Letter: Treatment guidelines. **Drugs for Pain**. April 2007; April 2010.

Molsberger AF, Schneider T, Gotthardt H, Drabik A. German Randomized **Acupuncture** Trial for chronic shoulder pain (**GRASP**) - a pragmatic, controlled, patient-blinded, multi-centre trial in an outpatient care environment. Pain. 2010 Oct;151(1):146-54.

Moon DE, Lee DI, Lee SC, et al. Efficacy and tolerability of **pregabalin** using a flexible, optimized dose schedule in Korean patients with peripheral neuropathic pain: a 10-week, randomized, double-blind, placebo-controlled, multicenter study. Clin Ther. 2010 Dec;32(14):2370-85.

Moore RA, Straube S, et al. **Pregabalin** for **acute and chronic pain** in adults. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007076. Pregabalin has proven efficacy in neuropathic pain conditions and fibromyalgia. A minority of patients will have substantial

TOP

benefit with pregabalin, and more will have moderate benefit. Many will have no or trivial benefit, or will discontinue because of adverse events. Individualisation of treatment is needed to maximise pain relief and minimise adverse events. There is no evidence to support the use of pregabalin in acute pain scenarios.
Moore RA, Wiffen PJ, Derry S, et al. **Gabapentin for chronic neuropathic pain and fibromyalgia** in adults. Cochrane Database Syst Rev. 2011 Mar 16;3:CD007938. Gabapentin provides pain relief of a high level in about a third of people who take if for painful neuropathic pain. Adverse events are frequent, but mostly tolerable. More conservative estimates of efficacy resulted from using better definitions of efficacy outcome at higher, clinically important, levels, combined with a considerable increase in the numbers of studies and participants available for analysis.
Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, et al; **Canadian** Pain Society. Pharmacological management of chronic **neuropathic pain** - consensus statement and **guidelines** from the Canadian Pain Society. Pain Res Manag. 2007 Spring;12(1):13-21.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2670721/pdf/prm12013.pdf
Najafi N, Van de Velde A, Poelaert J. Potential risks of **hemolysis** after short-term administration of analgesics in children with **glucose-6-phosphate dehydrogenase deficiency**. J Pediatr. 2011 Dec;159(6):1023-8.
Nayak-Rao S. Achieving effective pain relief in patients with chronic kidney disease: a review of analgesics in renal failure. J Nephrol. 2011; Jan-Feb;24(1):35-40.
NICE: Centre for Clinical Practice. **Neuropathic pain**. The pharmacological management of neuropathic pain in adults in non-specialist settings. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Mar. http://guidance.nice.org.uk/CG96/Guidance
Nijhof SL, Bleijenberg G, Uiterwaal CSPM, Kimpen JLL, van de Putte EM. Effectiveness of internet-based **cognitive behavioural treatment for adolescents with chronic fatigue syndrome** (**FITNET**): a randomised controlled trial. Lancet 2012; online March 1.
Oregon Systematic Review on Drugs for Neuropathic Pain. http://www.ohsu.edu/drugeffectiveness/reports/final.cfm
Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A **vaccine to prevent herpes zoster** and postherpetic neuralgia in older adults.N Engl J Med. 2005 Jun 2;352(22):2271-84.
Pan SL, Yen MF, Chiu YH, et al. **Increased risk of trigeminal neuralgia after hypertension**: a population-based study. Neurology. 2011 Oct 25;77(17):1605-10.
Papaleontiou M, Henderson CR Jr, Turner BJ, et al. Outcomes associated with **opioid use** in the treatment of chronic noncancer pain in **older adults**: a systematic review and meta-analysis. J Am Geriatr Soc. 2010 Jul;58(7):1353-69.
Patorno E; Bohn RL.; Wahl PM.; Avorn Jerry; et al. Anticonvulsant Medications and the **Risk of Suicide**, Attempted Suicide, or Violent Death. JAMA. 2010;303(14):1401-1409.
Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, et al. Drugs for relief of pain in patients with **sciatica**: systematic review and meta-analysis. BMJ 2012;344:e497.
Pontari Michel A.; Krieger John N.; Litwin Mark S.; et al.; for the Chronic Prostatitis Collaborative Research Network-2. **Pregabalin** for the Treatment of Men With Chronic **Prostatitis/Chronic Pelvic Pain** Syndrome: A Randomized Controlled Trial. Arch Intern Med. 2010;170(17):1586-1593. Pregabalin therapy for 6 weeks was not superior to placebo use in the rate of a 6-point decrease (improvement) in the NIH-CPSI total score in men with CP/CPPS.
Ralf Baron, Andreas Binder, Gunnar Wasner, **Neuropathic pain**: diagnosis, pathophysiological mechanisms, and treatment, The Lancet Neurology, Volume 9, Issue 8, August 2010, Pages 807-819
Rossi P, et al. Advice alone vs. structured detoxification programmes for **medication overuse headache**: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. Cephalalgia. 2006 Sep;26(9):1097-105. In patients with migraine plus MOH and low medical needs, effective drug withdrawal may be obtained through the imparting of advice alone.
Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain. 2008 Apr 3; [Epub ahead of print] N=520 Study results demonstrated that duloxetine at doses of 60mg/day and 120mg/day appears to be safe and efficacious in patients with fibromyalgia.
Russell IJ, Perkins AT, Michalek JE; Oxybate SXB-26 Fibromyalgia Syndrome Study Group. **Sodium oxybate** relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. Arthritis Rheum. 2009 Jan;60(1):299-309. {InfoPOEMs: In highly selected patients with fibromyalgia, sodium oxybate (Xyrem) improves symptom scores. Sodium oxybate is a schedule III drug and is only available through the manufacturer with tight eligibility and monitoring requirements. (LOE = 2b)}
Saarto T, et al. Antidepressants for **neuropathic pain**. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005454. TCAs: NNT=3.6CI:1.8-2.5, NNH AMI - major=28 CI:17-69, minor=6 CI:4-11, (not effective for HIV-related neuropathies); Venlafaxine: NNT=3.1CI :2.2.-5.1, NNHmajor=16.2CI:8-436, minor=9, CI:4-13; Gabapentin, Pregabalin, Carbamazepine: NNT≥3
Siddall PJ, et al. Pregabalin (150-600mg/d)in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2006 Nov 28;67(10):1792-800. 12wek n=137
Silva LE ; Valim V ; Pessanha AP ; Oliveira LM ; et al. **Hydrotherapy** versus conventional land-based exercise for the management of patients with **osteoarthritis** of the knee: a randomized clinical trial. Phys Ther. 2008; 88(1):12-21. {Both water-based and land-based exercises reduced knee pain and increased knee function in participants with OA of the knee. Hydrotherapy was superior to land-based exercise in relieving pain before and after walking during the last follow-up. Water-based exercises are a suitable and effective alternative for the management of OA of the knee.}
Simpson DM, Schifitto G, Clifford DB, et al. 1066 HIV Neuropathy Study Group.Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology. 2010 Feb 2;74(5):413-20. In this study, patients with HIV-associated peripheral neuropathy taking pregabalin (Lyrica) had no more pain relief than patients taking placebo. (LOE = 2b)
Standridge JB, Adams SM, Zotos AP. **Urine drug screening**: a valuable office procedure. Am Fam Physician. 2010 Mar 1;81(5):635-40.
Straube S, Derry S, Moore RA, et al. **Pregabalin in fibromyalgia**: meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology (Oxford). 2010 Apr;49(4):706-15. Epub 2010 Jan 7. Pregabalin is effective in treating FM and is relatively safe.
Tan T, Barry P, Reken S, Baker M; On behalf of the Guideline Development Group. Pharmacological management of **neuropathic pain** in non-specialist settings: summary of **NICE** guidance. BMJ. 2010 Mar 24;340:c1079.
Teasell RW, Mehta S, Aubut JA, et al. A systematic review of pharmacologic treatments of pain after spinal cord injury. Arch Phys Med Rehabil. 2010 May;91(5):816-31.
Tepper Stewart J., Tepper Deborah E.. Breaking the cycle of **medication overuse headache**. Cleveland Clinic Journal of Medicine 2010; 77(4):236-242; doi:10.3949/ccjm.77a.09147.
Trescot AM, Boswell MV, Atluri SL, Hansen NC, Deer TR, Abdi S, Jasper JF, Singh V, Jordan AE,et al Opioid guidelines in the management of chronic non-cancer pain. Pain Phys 2006;9(1):1-39.
van Seventer R, et al. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. Curr Med Res Opin. 2006 Feb;22(2):375-84.
Wong MC, Chung JW, Wong TK. Effects of treatments for symptoms of **painful diabetic neuropathy**: systematic review. BMJ. 2007 Jun 11. {CONCLUSION: Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants. Evidence of the long term effects of oral antidepressants and anticonvulsants is still lacking. Further studies are needed on opioids, N-methyl-D-aspartate antagonists, and ion channel blockers.}
Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose **naltrexone**: a pilot study. Pain Med. 2009 May-Jun;10(4):663-72.

van Kuppeveld Frank J M, de Jong Arjan S, Lanke Kjerstin H, et al. Prevalence of **xenotropic murine leukaemia virus**-related virus in patients with chronic fatigue syndrome in the Netherlands: retrospective analysis of samples from an established cohort. BMJ 2010;340:c1018, doi: 10.1136/bmj.c1018
Van Kuppeveld FJM, Van der Meer JWN. **XMRV** and CFS –the sad end of a story. Lancet June 21, 2011.Vedula SS et al. Outcome reporting in **industry-sponsored trials of gabapentin** for off-label use. N Engl J Med 2009 Nov 12; 361:1963.
Wang C, Schmid CH, Rones R, et al. A randomized trial of **Tai Chi for Fibromyalgia**. N Engl J Med. 2010 Aug 19;363(8):743-54.
Wetherell JL, Afari N, Rutledge T, et al. A randomized, controlled trial of **acceptance and commitment therapy** and cognitive-behavioral therapy for chronic pain. Pain. 2011 Sep;152(9):2098-107.
Ziconotide (Prialt) For Chronic Pain. Med Letter Dec 2005;47:103-104. (Lynch SS, et al. Intrathecal ziconotide for refractory chronic pain. Ann Pharmacother. 2006 Jul;40(7):1293-300. Epub 2006 Jul 18.)
Ziegler D, Hidvégi T, Gurieva I, et al.; **Lacosamide** SP743 Study Group. Efficacy and safety of lacosamide in painful diabetic neuropathy. Diabetes Care. 2010 Apr;33(4):839-41.

Pain Links:
Geriatrics: http://www.geriatricsandaging.ca

TOP

Web sites:

CDC http://www.cdc.gov/arthritis/basics/gout.htm

References: Gout Chart – www.RxFiles.ca

1 Choi HK, Mount DB, Reginato AM; American College of Physicians; American Physiological Society. **Pathogenesis of gout**. Ann Intern Med. 2005 Oct 4;143(7):499-516.

2 Teng GG, Nair R, Saag KG. Pathophysiology, Clinical Presentation and **Treatment of Gout**. Drugs 2006; 66(12):1547-63.

Fam AG, Dunne SM, Iazzetta J, Paton TW. Efficacy and safety of **desensitization to allopurinol** following cutaneous reactions. Arthritis Rheum. 2001 Jan;44(1):231-8.

3 Zhang W, Doherty M, Pascual E, Bardin T, et al.; **EULAR** Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. **Part I: Diagnosis**. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. **2006** Oct;65(10):1301-11. Epub 2006 May 17. http://ard.bmj.com/cgi/reprint/65/10/1301

4 Wheeler JG, Juzwishin KD, Eiriksdottir G, et al. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: prospective study and meta-analysis. PLoS Med. 2005 Mar;2(3):e76. Epub 2005 Mar 29.

5 Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008 Oct 23;359(17):1811-21.

6 Strasak A, et al. Serum uric Acid and risk of cardiovascular mortality: a prospective long-term study of 83 683 austrian men. Clin Chem. 2008 Feb;54(2):273-84. Epub 2007 Nov 26.

7 Canadian Rheumatology Association Handbook

8 Hak AE, Curhan G, Grodstein FD, Choi HK. Menopause, postmenopausal hormone use and risk of incident gout. Ann Rheum Dis. 2009 Jul 9.

9 Eggebeen AT. Gout: an update. Am Fam Physician. 2007 Sep 15;76(6):801-8. Review. Summary for patients in: Am Fam Physician. 2007 Sep 15;76(6):811-2.

10 Underwood M. Diagnosis and management of Gout. Clinical Review. BMJ. 2006 June 5;332:1315-9.

11 Gurwitz JH et al. Thiazide diuretics and the initiation of anti-gout therapy. Journal of Clinical Epidemiology; 1997 50:953-57.

12 Gurwitz JH, Kalish SC, Bohn RL et al. Thiazide Diuretics and the Initiation of Anti-Gout Therapy. Journal of Clinical Epidemiology. 1997 Aug;50(8):953-9

13 Zhang W, Doherty M, Bardin T, et al. **EULAR** Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. **Part II: Management**. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. **2006** Oct;65(10):1312-24. Epub 2006 May 17. http://ard.bmj.com/cgi/reprint/65/10/1312

14 Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ. 2008 Feb 9;336(7639):309-12. Epub 2008 Jan 31

15 Choi HK, Atkinson K, Karlson EW, et al. Alcohol intake and risk of incident gout in men: a prospective study. Lancet. 2004 Apr 17;363(9417):1251-2.

16 Underwood M. Sugary drinks, fruit, and increased risk of gout. BMJ. 2008 Feb 9;336(7639):285-6.

Choi Hyon K.; Willett Walter; Curhan Gary. Fructose-Rich Beverages and Risk of Gout in Women. JAMA. 2010;0(2010):jama.2010.1638.

17 Willacy H; Gout; Clinical Knowledge Summary, 5 Jan 2008

18 Janssens HJ, Lucassen PL, et al. Systemic corticosteroids for acute gout. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005521.

19 Alloway JA, Moriarty MJ, Hoogland YT, Nashel DJ. Comparison of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. J Rheumatol. 1993 Jan;20(1):111-3.

20 Janssens HJ, Janssen M, van de Lisdonk EH, et al. Use of oral prednisolone (35mg od x 5 days) or naproxen (500mg bid x 5 days) for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet. 2008 May 31;371(9627):1854-60. Oral prednisolone and naproxen are equally effective in the initial treatment of gout arthritis over 4 days. Oral prednisolone and naproxen are equivalent in treating acute gout. (LOE = 1b)

21 Man CY, Cheung IT, Cameron PA, Rainer TH. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial. Ann Emerg Med. 2007 May;49(5):670-7.

22 Fox R. Management of recurrent gout. BMJ. 2008 Feb 9;336(7639):329.

23 Peterson GM, Sugden JE. Educational program to improve the dosage prescribing of allopurinol. Med J Aust. 1995 Jan 16;162(2):74-7.

24 Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol. 2004 Dec;31(12):2429-32.

Wortmann RL, Macdonald PA, Hunt B, et al. Effect of Prophylaxis on Gout Flares After the Initiation of Urate-Lowering Therapy: Analysis of Data From Three Phase III Trials. Clin Ther. 2010 Dec;32(14):2386-97. (6months better than 8weeks, with either colchicine 0.6mg/d or naproxen 250mg bid)

25 Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.

26 Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, Naldi L, Dunant A, Viboud C, Roujeau JC; EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol. 2008 Jan;58(1):25-32. Epub 2007 Oct 24.

27 Fam AG, Dunne SM, Iazzetta J, Paton TW. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. Arthritis Rheum. 2001 Jan;44(1):231-8.

28 Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005 Dec 8;353(23):2450-61.

Febuxostat for the management of hyperuricaemia in people with gout. NICE Dec 2008 Guidance http://www.nice.org.uk/TA164

Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum. 2008 Nov 15;59(11):1540-8. Significantly (P < or = 0.05) higher percentages of subjects treated with febuxostat 80 mg (48%), 120 mg (65%), and 240 mg (69%) attained the primary end point of last 3 monthly serum urate levels <6.0 mg/dl compared with allopurinol (22%) and placebo (0%). At all doses studied, febuxostat more effectively lowered and maintained serum urate levels <6.0 mg/dl than did allopurinol (300 or 100 mg) or placebo in subjects with hyperuricemia and gout, including those with mild to moderately impaired renal Function.

Gelber AC. Febuxostat versus allopurinol for gout. N Engl J Med. 2006 Apr 6;354(14):1532-3; author reply 1532-3.

29 Hare JM, Mangal B, Brown J, ; OPT-CHF Investigators. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol. 2008 Jun 17;51(24):2301-9. Oxypurinol did not produce clinical improvements in unselected patients with moderate-to-severe heart failure. However, post-hoc analysis suggests that benefits occur in patients with elevated SUA in a manner correlating with the degree of SUA reduction. Serum uric acid may serve as a valuable biomarker to target XO inhibition in heart failure.

30 Würzner G, Gerster JC, Chiolero A, Maillard M, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. J Hypertens. 2001 Oct;19(10):1855-60.

31 Jordan KM, Cameron JS, Snaith M, et al; British Society for Rheumatology and **British** Health Professionals in Rheumatology Standards Guideline for the **Management of Gout**. Rheumatology (Oxford). **2007** Aug;46(8):1372-4. Epub 2007 May 23.
http://rheumatology.oxfordjournals.org/cgi/reprint/kem056av1

32 Lee MH, Graham GG, Williams KM, Day RO. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? Drug Saf. 2008;31(8):643-65.

Peterson GM, Sugden JE. Educational program to improve the dosage prescribing of allopurinol. Med J Aust. 1995 Jan 16;162(2):74-7.

Reinders MK, van Roon EN, et al. Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. Ann Rheum Dis. 2008 Apr 23. [Epub ahead of print] This study demonstrates a poor efficacy and tolerability profile of allopurinol 300 mg/day to attain a biochemical predefined target level of sUr </=0.30 mmol/l after 2-months treatment. In stage 2, benzbromarone 200 mg/day is more effective and better tolerated than probenecid 2000mg/day.

Reinders MK, Haagsma C, et al.. A randomised controlled trial on the efficacy and tolerability with dose-escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in patients with gout. Ann Rheum Dis. 2008 Jul 16. [Epub ahead of print] Increase of allopurinol dosage from 300 mg to 600 mg/day and benzbromarone dosage from 100 mg to 200 mg/day according to target sUr, gives significantly higher success rates (both 78% success in sUr </=0.30 mmol/l). No significant differences in treatment success between benzbromarone and allopurinol groups were found after dosage escalation combination in relieving pain but is associated with fewer adverse effects.

33 Choi HK, Curhan G. Coffee consumption and risk of incident gout in women: the Nurses' Health Study. Am J Clin Nutr. 2010 Oct;92(4):922-7. Epub 2010 Aug 25.

Choi HK, Willett W, Curhan G. Coffee consumption and risk of incident gout in men: a prospective study. Arthritis Rheum. 2007 Jun;56(6):2049-55.

34. Zhang W, Doherty M, Bardin T, et al. European League Against Rheumatism recommendations for **calcium pyrophosphate deposition (CPPD)**. Part I: terminology and diagnosis. Ann Rheum Dis. 2011 Jan 7.

Zhang W, Doherty M, Pascual E, et al. EULAR recommendations for **calcium pyrophosphate deposition (CPPD)**. Part II: **Management**. Ann Rheum Dis. 2011 Jan 20.

Additional References ----------

Burns CM, Wortmann RL. Gout therapeutics: **new drugs** for an old disease. Lancet. 2010 Aug 16.

TOP

Cayley WE Jr. **Gout-10 minute Consultation**. BMJ. 2010 Nov 15;341:c6155. doi: 10.1136/bmj.c6155.

Choi HK, Curhan G. Coffee, tea, and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey. Arthritis Rheum. 2007 Jun 15;57(5):816-21. These findings from a nationally representative sample of US adults suggest that **coffee** consumption is associated with lower serum uric acid level and hyperuricemia frequency, but tea consumption is not. The inverse association with coffee appears to be via components of coffee other than caffeine.

Choi HK, Gao X, Curhan G. **Vitamin C** intake and the risk of gout in men: a prospective study. Arch Intern Med. 2009 Mar 9;169(5):502-7. Higher vitamin C intake is independently associated with a lower risk of gout. Supplemental vitamin C intake may be beneficial in the prevention of gout.

Choi HK, Soriano LC, Zhang Y, Rodriguez LAG. **Calcium channel blockers, losartan**, and the risk of **incident gout** among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.

Coutsouvelis J, Wiseman M, Hui L, et al. Effectiveness of a single fixed dose of **rasburicase 3mg** in the management of tumour lysis syndrome. Br J Clin Pharmacol. 2012 Jun 11.

Dalbeth N, Schauer C, MacDonald P, et al. Methods of **tophus assessment** in clinical trials of chronic gout: a systematic literature review and **pictorial** reference guide. Ann Rheum Dis 2011;70:597-604. Online 7 Jan 2011 doi:10.1136/ard.2010.139899

Dalbeth N, Ames R, Gamble GD, et al. Effects of **skim milk powder enriched with glycomacropeptide and G600 milk fat extract** on frequency of gout flares: a proof-of-concept randomised controlled trial. Ann Rheum Dis. 2012 Jun;71(6):929-34.

Demarco MA, Maynard JW, Baer AN, et al. **Diuretic use**, increased serum urate and the risk of incident gout in a population-based study of hypertensive adults: The atherosclerosis risk in the communities cohort. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33315.
Thiazide and loop diuretics were associated with increased gout risk, an association mediated by a change in serum urate.

De Vera MA, Rahman MM, Bhole V, et al. Independent impact of gout on the risk of acute **myocardial infarction** among elderly women: a population-based study. Ann Rheum Dis 2010; DOI:10.1136/ard.2009.1227701.

Diav-Citrin O, Shechtman S, Schwartz V, et al. **Pregnancy outcome** after in utero exposure to colchicine. Am J Obstet Gynecol. 2010 Jun 24.

El-Zawawy H, Mandell BF. Managing **gout**: How is it different in patients with **chronic kidney disease**? Cleveland Clinic Journal of Medicine 2010; 77(12):919-928; doi:10.3949/ccjm.77a.09080

Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol (200mg bid) on blood pressure of **adolescents with newly diagnosed essential hypertension**: a randomized trial. JAMA. 2008 Aug 27;300(8):924-32. In this short-term, crossover study of adolescents (n=30) with newly diagnosed hypertension, treatment with allopurinol resulted in **reduction of BP (by 6.9/5.1).** The results represent a new potential therapeutic approach, although not a fully developed therapeutic strategy due to potential adverse effects.

Forman JP, Scheven L, de Jong PE, et al. Association between **sodium intake and change in uric acid**, urine albumin excretion and risk of developing hypertension. Circulation 2012.

Frassetto L, Kohlstadt I. Treatment and prevention of **kidney stones**: an update. Am Fam Physician. 2011 Dec 1;84(11):1234-42. Gaffo AL, Saag KG. Management of hyperuricemia and **gout in CKD**. Am J Kidney Dis. 2008 Nov;52(5):994-1009.

Glazebrook KN et al. Identification of intraarticular and periarticular uric acid crystals with **dual-energy CT**: Initial evaluation. Radiology 2011 Nov; 261:516.

Goicoechea M, Vinuesa SG, Verdalles U, et al. Effect of Allopurinol in **Chronic Kidney Disease** Progression and **Cardiovascular Risk**. Clin J Am Soc Nephrol. 2010 Jun 10.

Gooch K, Culleton BF, Manns BJ, et al. **NSAID use** and progression of **chronic kidney disease**. Am J Med. 2007 Mar;120(3):280.e1-7.

Gout patient information (including **purine** content of food) http://www.niams.nih.gov/Health_Info/Gout/

Gratton SB, Scalapino KJ, Fye KH. Case of **anakinra** as a steroid-sparing agent for gout inflammation. Arthritis Rheum. 2009 Sep 15;61(9):1268-70.

Grayson PC, Kim SY, Lavalley M, Choi HK. Hyperuricemia and **incident hypertension**: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2011;63:102-10.

Holeggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, et al. The impact of serum uric acid on **cardiovascular outcomes** in **LIFE** study. Kidney Int 2004;65:1041-9.

Howard Scott C., Jones Deborah P., Pui Ching-Hon. The **Tumor Lysis Syndrome**. N Engl J Med 2011; 364:1844-1854.

Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y. **Recent diuretic use and the risk of recurrent gout attacks**: the online case-crossover gout study. J Rheumatol 2006;33:1341-1345.

Hyon K. Choi; Walter Willett; Gary Curhan. **Fructose-Rich Beverages** and Risk of Gout in Women. JAMA. 2010;0(2010):jama.2010.1638.

Imazio Massimo, Trinchero Rita, Brucato Antonio, et al. **Colchicine** for the Prevention of the **Post-pericardiotomy Syndrome** (**COPPS**): a multicentre, randomized, double-blind, placebo-controlled trial Eur Heart J (2010) 31(22): 2749-2754.

Imazio M, Brucato A, Cemin R, et al. **Colchicine for Recurrent Pericarditis** (**CORP**) A Randomized Trial. Ann Intern Med. 2011 Oct 4;155(7):409-414.

Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces **postoperative atrial fibrillation**. Results of the colchicine for the prevention of **postperiocardiotomy symdrome (COPPS)** atrial fibrillation substudy. Circulation 2011; 124:2290-2295.

Janssens Hein J. E. M.; Fransen Jaap; van de Lisdonk Eloy H.; et al. A **Diagnostic Rule for Acute Gouty Arthritis** in Primary Care Without Joint Fluid Analysis Arch Intern Med. 2010;170(13):1120-1126.

Clinical calculator http://www.umcn.nl/goutcalc

Kaya MG, Uyarel H, Akpek M et al. Prognostic Value of Uric Acid in Patients With ST-Elevated **Myocardial Infarction** Undergoing Primary Coronary Intervention. Am J Cardiol. 2011 Nov 17.

Kekre N, Djordjevic B, Touchie C. Spontaneous **tumour lysis syndrome**. CMAJ. 2012 Apr 10.

Kim HR et al. Detection of gouty arthritis of atlantoaxial joint using **dual-energy CT**. Arthritis Rheum. 2011 Dec 2.

Krishnan E, Svendsen K, et al. MRFIT Research Group. Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med. 2008 May 26;168(10):1104-10. Among middle-aged men, a diagnosis of gout accompanied by an elevated uric acid level imparts significant independent CVD mortality risk.

Krishnan E. Hyperuricemia and **incident heart failure**. Circ Heart Fail. 2009;2:556 –562.

Lotrionte M, Biondi-Zoccai G, Imazio M, et al. International collaborative systematic review of controlled clinical trials on pharmacologic treatments for **acute pericarditis** and its recurrences. Am Heart J. 2010 Oct;160(4):662-70.

Mack Diana R, Cahoon William D, Jr, Lowe Denise K. Colchicine for the **Primary Prevention of the Postpericardiotomy Syndrome**. Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1Q112. Ann Pharmacother ;45:803-806.

McAdams DeMarco MA et al. **Diuretic use**, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: The Atherosclerosis Risk in Communities cohort study. Arthritis Rheum 2012 Jan; 64:121.

Miao Yan, et al. Effect of a Reduction in Uric Acid on Renal Outcomes During **Losartan** Treatment: A Post Hoc Analysis of the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Trial (Renaal). Hypertension. 2011

Miao Y, Ottenbros SA, Laverman GD, et al. Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. (RENAAL) Hypertension. 2011 Jul;58(1):2-7.

Moon KW, Kim J, Kim JH, et al. Risk factors for acute kidney injury by **non-steroidal anti-inflammatory drugs** in patients with hyperuricaemia. Rheumatology (Oxford). 2011 Oct 22.

Ndrepepa G, Braun S, Haase HU et al. Prognostic Value of Uric Acid in Patients With **Acute Coronary Syndromes**. Am J Cardiol. 2012 Feb 9.

Neogi Tuhina, **Gout**. N Engl J Med 2011; 364:443-452.

Neogi T, George J, Rekhraj S, et al. Are either or both hyperuricemia and xanthine oxidase directly **toxic to the vasculature**? A critical appraisal. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33369.

Noman A, Ang DS, Ogston S, et al. Effect of high-dose allopurinol on exercise in patients with **chronic stable angina**: a randomised, placebo controlled crossover trial. Lancet. 2010 Jun 7.

Papanicolas LE, Hakendorf P, Gordon DL. **Concomitant septic arthritis** in crystal monoarthritis. J Rheumatol. 2012 Jan;39(1):157-60.

Pharmacist's Letter. **Febuxostat** (Uloric). Nov, 2010.

Richette P, Bardin T. **Gout. Lancet. 2009** Aug 17. [Epub ahead of print]

Schlesinger N, Mysler E, Lin HY, et al. **Canakinumab** reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis. 2011 Jul;70(7):1264-71.

Shahinfar S, Simpson RL, Carides AD, et al. Safety of **losartan in hypertensive patients with thiazide-induced hyperuricemia**. Kidney Int 1999;56:1879-1885.

Singh JA, Yang S, Strand V, et al. **Validation of pain and patient global scales** in chronic gout: data from two randomised controlled trials. Ann Rheum Dis. 2011 Jul;70(7):1277-81.

Stamp LK, O'Donnell JL, Zhang M, et al. Using **allopurinol above the dose based on creatinine clearance** is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum. 2011 Feb;63(2):412-21.

Stamp LK, Taylor WJ, Jones PB, et al. **Starting dose** is a risk factor for **allopurinol hypersensitivity syndrome**: A proposed safe starting dose of allopurinol. Arthritis Rheum. 2012 Apr 5.

Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of **pegloticase** for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011 Aug 17;306(7):711-20.

Tamariz L, Agarwal S, Soliman EZ, et al. Association of Serum **Uric Acid With Incident Atrial Fibrillation** (from the Atherosclerosis Risk in Communities [ARIC] Study). Am J Cardiol. 2011 Aug 17.

Tausche AK, Panzner I, Aust D; et al. **Disabling gout**. Lancet. 2010 Sep 25;376(9746):1093.

Teng GG, Ang LW, Saag KG, et al. **Mortality due to coronary heart disease and kidney disease** among middle-aged and elderly men and women with gout in the Singapore Chinese Health Study. Ann Rheum Dis. 2012 Jun;71(6):924-8.

Terkeltaub RA, Furst DE, Digiacinto JL, et al. Evidence basis of a novel **colchicine dose reduction algorithm** to predict & prevent colchicine toxicity in the presence of **P-gp/CYP P450 3A4 inhibitors**. Arthritis Rheum. 2011 Apr 7. doi: 10.1002/art.30389.

Thanassoulis George; Brophy James M.; Richard Hugues; et al. Gout, Allopurinol Use, and **Heart Failure** Outcomes. Arch Intern Med. 2010;170(15):1358-1364.

Terkeltaub RA, Furst DE, Bennett K, et al. High-vs **low-dosing of oral colchicine** for early acute gout flare: Twenty-four hour outcome results of the first randomized, placebo-controlled, dose comparison colchicine trial. Arthritis Rheum. 2010 Jan 21.

Wang JY, Chen YL, Hsu CH, et al. Predictive Value of Serum Uric Acid Levels for the **Diagnosis of Metabolic Syndrome** in Adolescents. J Pediatr. 2012 May 9.

Wilson JF. **Gout-In the Clinic.** Ann Intern Med. 2010 Feb 2;152(3):ITC21.

Worcester EM, Coe FL. Clinical practice. **Calcium kidney stones**. N Engl J Med. 2010 Sep 2;363(10):954-63.

Zhang Y, Chen C, Choi H, et al. **Purine-rich foods intake** and recurrent gout attacks. Ann Rheum Dis. 2012 May 30.

Zhu Y, Pandya BJ, Choi HK. Prevalence of **gout and hyperuricemia** in the US general population: The National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011 Oct;63(10):3136-41. doi: 10.1002/art.30520.

Zhu Y, Pandya BJ, Choi HK. **Comorbidities of Gout** and Hyperuricemia in the US General Population: NHANES 2007-2008. Am J Med. 2012 May 23.

TOP

Web Sites:

American College of Rheumatology: Gout www.rheumatology.org/public/factsheets/diseases_and_conditions/gout.asp?aud=pat

Arthritis Foundation: Gout www.arthritis.org/disease-center.php?disease_id=42

National Institute of Arthritis and Musculoskeletal and Skin Diseases: Questions and Answers About Gout www.niams.nih.gov/Health_Info/Gout/default.asp

Gout and Uric Acid Education Society www.gouteducation.org/

Acknowledgements: We would like to thank those who contributed to the development, review for this chart. Dr. W. Olszynski (Rheumatology, Saskatoon), Dr. J. Kappel (Nephrology, SHR, Dr. T. Laubscher (Family Medicine, U of S, Saskatoon), Dr. A. Milne (Rheumatology, Regina), Dr. J. Richardson (SHR Pharmacy), D. Lamb (SHR Pharmacy) and the RxFiles Advisory Committee. *Prepared by* Zack Dumont BSP, Loren Regier BSP BA, Brent Jensen BSP

TOP

NSAIDS, COXIBs & OTHER ANALGESICS: Comparison Chart

[1] Micromedex 2011

[2] Silverstein F, Faich G, Goldstein J, et al. Gastrointestinal toxicity with celecoxib versus non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the **CLASS** study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247-55.

[3] Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. **VIGOR** study group. N Engl J Med 2000;343:1520-8. (Curfman GD, Morrissey S, Drazen JM. Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 2000;343:1520-8. N Engl J Med. 2005 Dec 8; [Epub ahead of print])

[4] Detailed study results for CLASS; FDA Feb 2001 - http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_01_searle.pdf & http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf Access verified, May 6, 2002.

[5] Detailed study results for VIGOR; FDA Feb, 2001 - http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_01_merck.pdf Access verified, May 6, 2002.

[6] Singh G, Ramey D, Triadafilopoulos G. Early experience with selective COX-2 inhibitors: safety profile in over 340,000 patient years of use [Abstract]. Arthritis Rheum 1999;42(Suppl 9):S296.

[7] Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA. 2001;286:954-9.

[8] Singh G, Ramey D. NSAID-induced gastrointestinal complications: the ARAMIS perspective-1997. J Rheumatol 1998;25(suppl 51):8-16.

[9] Wolfe M, Lichtenstein D, Singh G. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. N Engl J. Med 1999; 340:1888-99.

[10] Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46.

[11] Treatment Guidelines: Drugs for Rheumatoid Arthritis. The Medical Letter: January, 2003; (5) pp. 25-32 & **Dec 2005**.

[12] Hawkey C, Kahan A, Steinbruck K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. Br J Rheumatol 1998;37:937-45.

[13] Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerbility of the selective cyclogenase (COX)-2 inhibitor meloxicam, compared with piroxicam: Results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trial in osteoarthritis. Br J Rheumatol 1998;37:946-51.

[14] http://www.oregonrx.org/OrgrxPDF/NSAIDS%20review/NSAID%20Update%20Report/5-12-03%20NSAID%20update.pdf

[15] http://www.oregonrx.org/OrgrxPDF/NSAID%20Review.htm

[16] Hunt RH, Barkun AN, Baron D, et al. Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can J Gastroenterol. 2002 Apr;16(4):231-40.

[17] Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery. N Engl J Med. 2005 Feb 15; [Epub ahead of print]

[18] Bresalier RS, et al. Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial (**APPROVe**). *N Engl J Med 2005; 352:1092-102.* (InfoPOEMs: For every 62 patients who take rofecoxib instead of placebo for 3 years, 1 additional patient will experience a serious cardiovascular event. Remember, there is no greater symptomatic relief with COX-2 inhibitors than with older drugs; acetaminophen is a very safe alternative. The decrease in risk of serious gastrointestinal complications is marginal with COX-2 inhibitors and the cost is high. (LOE = 1b))

[19] Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention. (**APC** trial) N Engl J Med 2005; 352:1071-80. (InfoPOEMs: One additional cardiovascular event or cardiovascular death occurs for every 126 patients treated for 1 year with celecoxib. There appears to be a dose response relationship. It is difficult to justify continued use of this and other coxibs, except in the most exceptional circumstances. (LOE = 1b)) (Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. (APC study) N Engl J Med 2006; 355:873-884. Follow-up colonoscopies were completed at year 1 in 89.5 percent of randomized patients, and at year 3 in 75.7 percent. The estimated cumulative incidence of the detection of one or more adenomas by year 3 was 60.7 percent for patients receiving placebo, as compared with 43.2 percent for those receiving 200 mg of celecoxib twice a day (risk ratio, 0.67; 95 percent confidence interval, 0.59 to 0.77; P<0.001) and 37.5 percent for those receiving 400 mg of celecoxib twice a day (risk ratio, 0.55; 95 percent confidence interval, 0.48 to 0.64; P<0.001). Serious adverse events occurred in 18.8 percent of patients in the placebo group, as compared with 20.4 percent of those in the low-dose celecoxib group (risk ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3; P=0.5) and 23.0 percent of those in the high-dose group (risk ratio, 1.2; 95 percent confidence interval, 1.0 to 1.5; P=0.06). As compared with placebo, celecoxib was associated with an increased risk of cardiovascular events (risk ratio for the low dose, 2.6; 95 percent confidence interval, 1.1 to 6.1; and risk ratio for the high dose, 3.4; 95 percent confidence interval, 1.5 to 7.9).) (Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. (PreSAP trial) N Engl J Med 2006; 355:885-895. Colonoscopies were performed at year 1 on 88.7 percent of the subjects who had undergone randomization and at year 3 on 79.2 percent. Of the 557 subjects in the placebo group and the 840 subjects in the celecoxib 400mg od group who were included in the efficacy analysis, 264 and 270, respectively, were found to have at least one adenoma at year 1, at year 3, or both. The cumulative rate of adenomas detected through year 3 was 33.6 percent in the celecoxib group and 49.3 percent in the placebo group (relative risk, 0.64; 95 percent confidence interval, 0.56 to 0.75; P<0.001). The cumulative rate of advanced adenomas detected through year 3 was 5.3 percent in the celecoxib group and 10.4 percent in the placebo group (relative risk, 0.49; 95 percent confidence interval, 0.33 to 0.73; P<0.001). Adjudicated serious cardiovascular events occurred in 2.5 percent of subjects in the celecoxib group and 1.9 percent of those in the placebo group (relative risk, 1.30; 95 percent confidence interval, 0.65 to 2.62). (Kerr DJ, Dunn JA, Langman MJ, Smith JL, Midgley RS, Stanley A, Stokes JC, Julier P, Iveson C, Duvvuri R, McConkey CC; VICTOR Trial Group. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. N Engl J Med. 2007 Jul 26;357(4):360-9. Rofecoxib therapy was associated with an increased frequency of adverse cardiovascular events among patients with a median study treatment of 7.4 months' duration.)

[20] Farkouh ME, Kirshner H., Harrington RA. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (**TARGET**), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364:675-84. At 1-year follow-up, incidence of the primary endpoint was low, both with lumiracoxib (59 events [0.65%]) and the non-steroidal anti-inflammatory drugs (50 events [0.55%]; hazard ratio 1.14 [95% CI 0.78-1.66], p=0.5074). Incidence of myocardial infarction (clinical and silent) in the overall population in the individual substudies was 0.38% with lumiracoxib (18 events) versus 0.21% with naproxen (ten) and 0.11% with lumiracoxib (five) versus 0.16% with ibuprofen (seven).

[21] Schnitzer TJ., Burmester GR., Mysler E., Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (**TARGET**), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665-74. (18325 patients age 50 years or older with osteoarthritis were randomised to lumiracoxib 400 mg once daily (n=9156), naproxen 500 mg twice daily (4754), or ibuprofen 800 mg three times daily (4415) in two substudies of identical design. Randomisation was stratified for low-dose aspirin use and age. In patients not taking aspirin, the cumulative 1-year incidence of ulcer complications was 1.09% (95% CI 0.82-1.36) with non-steroidal anti-inflammatory drugs (64 events) versus 0.25% (95% CI 0.12-0.39) with lumiracoxib (14 events; hazard ratio 0.21 [95% CI 0.12-0.37], p<0.0001). Reductions in ulcer complications were also significant in the overall population (0.34 [0.22-0.52], p<0.0001) but not in those taking aspirin (0.79 [0.40-1.55], p=0.4876). In the overall population, 0.55% (50/9127) of those on non-steroidal anti-inflammatory drugs and 0.65% (59/9117) of those on lumiracoxib reached the cardiovascular endpoint (1.14 [0.78-1.66], p=0.5074).) (see also Pharmacists Letter Dec/06) Hawkey CJ et al. Effect of risk factors on complicated and uncomplicated ulcers in the TARGET lumiracoxib outcomes study. Gastroenterology 2007 Jul; 133:57-64. Lumiracoxib was associated with a reduced risk of ulcer complications compared with NSAIDs in all significant subgroups except aspirin users.

[22] Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ. 2004 Feb 21;328(7437):434.

[23] **Treatment Guidelines**: Drugs for Rheumatoid Arthritis. **The Medical Letter**: January, **2003**; (5) pp. 25-32 & **Dec 2005**.

Nakhai-Pour HR, Broy P, Sheehy O, Bérard A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of **spontaneous abortion**. CMAJ. 2011 Sep 6.

[24] Mazieres B, Rouanet S, Guillon Y, Scarsi C, Reiner V. Topical ketoprofen patch in the treatment of tendinitis: a randomized, double blind, placebo controlled study. J Rheumatol. 2005 Aug;32(8):1563-70.

Underwood M, Ashby D, Cross P, et al; on behalf of the TOIB study team. Advice to use **topical or oral ibuprofen** for chronic knee pain in older people: randomised controlled trial & patient preference study. BMJ. 2007 Dec 4; [Epub ahead of print] Advice to use oral or topical preparations has an equivalent effect on knee pain over one year, and there are more minor side effects with oral NSAIDs. Topical NSAIDs may be a useful alternative to oral NSAIDs.

Massey T, Derry S, Moore RA, McQuay HJ. **Topical NSAIDs** for acute pain in adults. Cochrane Database Syst Rev. 2010 Jun 16;6:CD007402. Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs, when used to treat acute musculoskeletal conditions.

[25] Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ. 2004 Aug 7;329(7461):324. (Towheed TE. **Pennsaid** therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2006 Mar;33(3):567-73.)

[26] Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. CMAJ. 2004 Aug 17;171(4):333-8.

[27] Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. Arch Intern Med. 2004 Oct 11;164(18):2017-23.

28. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ. 2004 Dec 4;329(7478):1317. Epub 2004 Nov 23. Conclusion NSAIDs can reduce short term pain in osteoarthritis of the knee slightly better than placebo, but the current analysis does not support long term use of NSAIDs for this condition. As serious adverse effects are associated with oral NSAIDs, only limited use can be recommended.

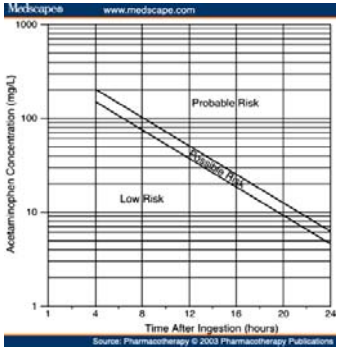
29. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet. 2005 Mar 12;365(9463):965-73.

30. Savage R. Cyclo-oxygenase-2 inhibitors : when should they be used in the elderly? Drugs Aging. 2005;22(3):185-200.

31. Hippisley-Cox J, Coupland C. Risk of MI in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ.2005 Jun 11;

TOP

32. Hudson M, et al. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. BMJ. 2005 Jun 11;330(7504):1370.
33. Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ. 2005 Apr 12;172(8):1039-43. (InfoPOEMs: The evidence that intra-articular hyaluronic acid helps patients with knee osteoarthritis is of poor quality. Improvements in pain at rest and pain during exercise is seen in a minority of studies, and those studies were of lower quality than those showing no benefit. There is no evidence of functional improvement. Injections like this have a potentially powerful placebo effect, so any benefit seen in unblinded studies without concealed allocation is likely represent the placebo effect rather than any effect of the drug. (LOE = 1a-)) Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol. 2006 May;33(5):951-6.
34. Verhamme KM, Dieleman JP, Van Wijk MA, et al. Nonsteroidal anti-inflammatory drugs and increased risk of acute urinary retention. Arch Intern Med. 2005 Jul 11;165(13):1547-51.
35. Sudbo J, Lee JJ, Lippman SM, et al. Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study. Lancet. 2005 Oct 15-21;366(9494):1359-66.
Long-term use of NSAIDs is associated with a reduced incidence of oral cancer (including in active smokers), but also with an increased risk of death due to cardiovascular disease. These findings highlight the need for a careful risk-benefit analysis when the long-term use of NSAIDs. (Jan/06 The Norwegian daily newspaper Dagbladet reports that a number of **statistical improbabilities** were found in the data set of the cancer trial, published in the Lancet in October last year. Lancet editor Dr Richard Horton told the BBC he would be speaking to the coauthors of the study to seek their permission to retract the paper. One example of the improbabilities" is the fact that of the 908 people in the trial, 250 shared the same birthday.)
36. **Acetaminophen Overdose**: Medscape article: http://www.medscape.com/viewarticle/459187_4 ; Merck Manual's Online Medical Manual: http://www.merck.com/mmpe/sec21/ch326/ch326c.html {Rumack-Matthew nomogram for predicting (Caution with units of measure!) } (10ug/ml = 66.2umol/L) {Acetaminophen level: 4hrs post ingestion & repeat in 4hrs; if ≥150mg/kg and 8hr post, may start n-acetylcysteine while awaiting levels; TOXIC levels: 4hr level >993umol/L; 6hr >728umol/L; 8hr >496.5umol/L; 24hr >29.8umol/L } {LFTs: AST usually ↑ first}
Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med. 2008 Jul 17;359(3):285-92.
Ferner Robin E, Dear James W, Bateman D Nicholas. Management of acetaminophen/paracetamol poisoning. BMJ 2011;342:doi:10.1136/bmj.d2218 (Published 20 April 2011)



{There is some evidence for the use of fomepizole as a CYP2E1 inhibitor and for decreased hepatotoxicity in the setting of acetaminophen overdose... To date, the evidence is all animal models but when the patient will otherwise die, the potential benefit outweighs the lack of human evidence.}
Yarema MC, Johnson DW, Berlin RJ, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med. 2009 Oct;54(4):606-14. Epub 2009 Jun 25. It favored the 20-hour protocol for patients presenting early and favored the 72-hour protocol for patients presenting late after acute acetaminophen overdose. Johnson Michael T, McCammon Craig A, Mullins Michael E, et al. Evaluation of a Simplified N-Acetylcysteine Dosing Regimen for the Treatment of Acetaminophen Toxicity. Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1P613. Ann Pharmacother ;45:713-720.
Blackford MG, Felter T, Gothard MD, Reed MD. Assessment of the Clinical Use of Intravenous and Oral N-Acetylcysteine in the Treatment of Acute Acetaminophen Poisoning in Children: A Retrospective Review. Clin Ther. 2011 Sep 2.

ADAPT Research Group. Cognitive Function Over Time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): Results of a Randomized, Controlled Trial of Naproxen and Celecoxib. Arch Neurol. 2008 May 12. [Epub ahead of print] Use of naproxen or celecoxib did not improve cognitive function. There was weak evidence for a detrimental effect of naproxen.
Al-Sukhun J, Koivusalo A, Tornwall J, Lindqvist C. COX-2 inhibitors and early **failure of free vascular flaps**. N Engl J Med. 2006 Aug 3;355(5):528-9.
Amendolia B, Lynn M, Bhat V, et al. Severe pulmonary hypertension with therapeutic L-lysine **Ibuprofen** in 2 preterm neonates. Pediatrics. 2012 May;129(5):e1360-3.
Amin AK, et al. Does **obesity** influence the clinical outcome at five years following total **knee replacement** for osteoarthritis? J Bone Joint Surg Br. 2006 Mar;88(3):335-40. (InfoPOEMs: In this study, obese patients undergoing primary knee arthroplasty had comparable long-term outcomes with nonobese patients. (LOE = 1b-))
Amin SB, Sinkin RA, Glantz JC. Metaanalysis of the effect of antenatal **indomethacin** on **neonatal outcomes**. Am J Obstet Gynecol. 2007 Nov;197(5):486.e1-10. Antenatal indomethacin may be associated with an increased risk of periventricular leukomalacia and necrotizing enterocolitis in premature infants and therefore should be used judiciously for tocolysis.
Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, Nonsteroidal Anti-inflammatory Drug Use, and **Risk for Crohn Disease and Ulcerative Colitis**: A Cohort Study (NHS). Ann Intern Med. 2012 Mar 6;156(5):350-9.
Andersohn F, et al. Cyclooxygenase-2 Selective Nonsteroidal Anti-Inflammatory Drugs and the **Risk of Ischemic Stroke**. A Nested Case-Control Study. Stroke. 2006 May 25; [Epub ahead of print] Current use of rofecoxib (OR=1.71; 95% CI, 1.33 to 2.18), etoricoxib (OR=2.38; 95% CI, 1.10 to 5.13), but not of celecoxib (OR=1.07; 95% CI, 0.79 to 1.44) was associated with a significantly increased risk of ischemic stroke. For rofecoxib and etoricoxib, ORs tended to increase with higher daily dose and longer duration of use and were also elevated in patients without major stroke risk factors. "From the non-selective NSAIDs, diclofenac, but not ibuprofen or naproxen, was also associated with a slightly increased risk of ischemic stroke," Dr. Andersohn said.
Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs & risk of **acute myocardial infarction**. Circulation. 2006 Apr 25;113(16):1950-7. Epub 2006 Apr 17. Current use of etoricoxib was associated with a 2.09-fold (95% confidence interval [CI], 1.10 to 3.97) risk of AMI compared with no use of NSAIDs during the prior year. Current use of rofecoxib (RR=1.29; 95% CI, 1.02 to 1.63), celecoxib (RR=1.56; 95% CI, 1.22 to 2.00), and diclofenac (RR=1.37; 95% CI, 1.17 to 1.59) also significantly increased the AMI risk. For current use of valdecoxib, the RR was 4.60 (95% CI, 0.61 to 34.51). RRs appeared to increase with higher daily doses of COX-2 inhibitors and were also increased in patients without major cardiovascular risk factors.
Andrew T. Chan, MD, MPH; Edward L. et al. Long-term Use of Aspirin and Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Cancer JAMA. 2005;294:914-923. CONCLUSIONS: Regular, long-term aspirin use reduces risk of colorectal cancer. Nonaspirin NSAIDs appear to have a similar effect. However, a significant benefit of aspirin is not apparent until more than a decade of use, with maximal risk reduction at doses greater than 14 tablets per week. These results suggest that optimal chemoprevention for colorectal cancer requires long-term use of aspirin doses substantially higher than those recommended for prevention of cardiovascular disease, but the dose-related risk of gastrointestinal bleeding must also be considered. (InfoPOEMs: Regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), especially more than 14 doses per week for at least 10 years, reduces the risk of colon cancer while also increasing the risk of a major gastrointestinal bleeding event. All-cause mortality is not affected by regular use. We need additional methods (gene testing?) to determine who is at high risk of colorectal cancer before making specific recommendations for prevention. (LOE = 2b))
Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs. An update for clinicians. A scientific statement from the **American Heart Association**. Circulation 2007; DOI:10.1161/CIRCULATIONAHA.106.181424. Available at: http://circ.ahajournals.org.
Anzellotti P, Capone ML, Jeyam A, et al. Low-dose **naproxen interferes with the antiplatelet effects of aspirin** in healthy subjects: Recommendations to minimize the functional consequences. Arthritis Rheum. 2010 Dec 2.
Are, Chaitanya, Turagam, Mohit, Aucar, John A., Greenberg, Eugene. **Meloxicam-induced enteropathy** of the small bowel. CMAJ 2011 183: 577-580
Asgari MM, Chren MM, Warton EM, Friedman GD, White E. Association Between Nonsteroidal Anti-inflammatory Drug Use and **Cutaneous Squamous Cell Carcinoma**. Arch Dermatol. 2010 Feb 15.
Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of **psoriatic arthritis**: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2011 Jul 28.
Aspirin for cancer: Rothwell PM, Price JF, Fowkes FGR, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefi ts in 51 randomised controlled trials. Lancet 2012; online March 21.
Rothwell PM, Wilson M, Price JF, Belch JFF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012; online March 21. DOI:10.1016/S0140-6736(12)60209-8.
Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncology 2012; online March 21. DOI:10.1016/S1470-2045(12)70112-2.
Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of **aspirin on colorectal cancer** incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010 Oct 21.
Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily **aspirin on long-term risk of death due to cancer**: analysis of individualpatient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41.
Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study (**WHS**): a randomized controlled trial. JAMA 2005; 294: 47–55. (no effect)
Sturmer T, Glynn RJ, Lee IM, Manson JE, Buring JE, Hennekens CH. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study (**PHS**). Ann Intern Med 1998; 128: 713–20. (no effect)
Babb, Malaika, Koren, Gideon, Einarson, Adrienne. Treating **pain during pregnancy**. Can Fam Physician 2010 56: 25-27.

TOP

Bäck M, Yin L, Ingelsson E. **Cyclooxygenase-2 inhibitors** and cardiovascular risk in a nationwide cohort study after the withdrawal of rofecoxib. Eur Heart J 2011. (increased risk of developing atrial fibrillation)

Bandolier. Avocado/soybean unsaponifiables for OA. April 2004;122-23. Web site: http://www.jr2.ox.ac.uk/bandolier/band122/b122-3.html. The limited data to date support the safety and possible efficacy of ASU for osteoarthritis of the knee. More and longer studies are needed before we can recommend this to our patients without hesitation. (LOE = 1b-)

Barkhuizen A, et al. Celecoxib is efficacious and well tolerated in treating signs and symptoms of **ankylosing spondylitis**. J Rheumatol. 2006 Sep;33(9):1805-12.

Bakkeheim E, Mowinckel P, Carlsen KH, Håland G, Carlsen KC. Paracetamol (**acetaminophen**) in early infancy: the risk of childhood allergy and asthma. Acta Paediatr. 2011 Jan;100(1):90-6. doi: 10.1111/j.1651-2227.2010.01942.x.

Barkin RL, Beckerman M, Blum SL, et al. Should nonsteroidal anti-inflammatory drugs **(NSAIDs) be prescribed to the older adult**? Drugs Aging. 2010 Oct 1;27(10):775-89. Prescribing

Barkun AN, Bardou M, et al. and for the **International Consensus** Upper Gastrointestinal Bleeding Conference Group. Management of Patients With **Nonvariceal Upper Gastrointestinal Bleeding**. Ann Intern Med January 19, 2010 152:101-113.

Baron JA, et al. A randomized trial of **aspirin to prevent colorectal adenomas**. N Engl J Med. 2003 Mar 6;348(10):891-9.

Baron JA, Sandler RS, Bresalier RS, et al. Cardiovascular events associated with **rofecoxib**: final analysis of the **APPROVe** trial. Lancet. 2008 Oct 13. [Epub ahead of print] Use of rofecoxib is associated with increased rates of APTC events. Study data are compatible with an early increase in risk that persists for one year after stopping treatment.

Bavbek S, et al. Safety of **Meloxicam** in Aspirin-**Hypersensitive** Patients with Asthma and/or Nasal Polyps. A Challenge-Proven Study. Int Arch Allergy Immunol. 2006 Oct 2;142(1):64-69 [Epub ahead of print]

Bavry AA, Khaliq A, Gong Y, et al. **Harmful effects of NSAIDs** among patients with hypertension and coronary artery disease. Am J Med 2011; 124:614-620.

Bellamy N, et al. **Viscosupplementation** for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD005321.

Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. **Reye's syndrome** in the United States from 1981 through 1997. N Engl J Med. 1999 May 6;340(18):1377-82.

Berman BM, et al. Effectiveness of **acupuncture** as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. Ann Intern Med. 2004 Dec 21;141(12):901-10. Summary for patients in: Ann Intern Med. 2004 Dec 21;141(12):I20.

Bhatt DL, Scheiman J, Abraham NS, et al. **ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID** use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol***.** 2008; *Circulation*. 2008; DOI: DOI: 10.1161/CIRCULATIONAHA.108.191087. Available at: http://circ.ahajournals.org http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.191087

Bijlsma Johannes W J, Berenbaum Francis, Lafeber Floris P J G. **Osteoarthritis**: an update with relevance for clinical practice. Lancet 2011; 377: 2115–26.

Bingham CO 3rd, Eet al. Efficacy and safety of **etoricoxib** 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. Rheumatology (Oxford). 2006 Aug 27.

Biswal S, Medhi B, Pandhi P. Longterm efficacy of **topical nonsteroidal antiinflammatory** drugs in knee osteoarthritis: metaanalysis of randomized placebo controlled clinical trials. J Rheumatol. 2006 Sep;33(9):1841-4.

Braun J, van den Berg R, Baraliakos X, et al. **2010 update of the ASAS/EULAR recommendations** for the management of **ankylosing spondylitis**. Ann Rheum Dis 2011;70:896-904 doi:10.1136/ard.2011.151027.

Burmester Gerd, Lanas Angel, Biasucci Luigi, et al. The appropriate use of **non-steroidal anti-inflammatory drugs** (NSAIDs)in rheumatic disease: opinions of a multidisciplinary **European expert panel**. Ann Rheum Dis 2011;70:818-822 Online: 10 Sept 2010.

Butler GJ, Neale R, Green AC, Pandeya N, Whiteman DC. Nonsteroidal anti-inflammatory drugs and the risk of **actinic keratoses and squamous cell** cancers of the skin. J Am Acad Dermatol. 2005 Dec;53(6):966-72. Epub 2005 Oct 19.

Cannon CP, et al.; **MEDAL** Steering Committee. Clinical trial design and patient demographics of the Multinational **Etoricoxib and Diclofenac** Arthritis Long-term (MEDAL) study program: cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. Am Heart J. 2006 Aug;152(2):237-45.

Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with **etoricoxib and diclofenac** in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (**MEDAL**) programme: a randomised comparison. Lancet 2006: DOI:10.1016/S0140-6736(06)69666-9. Rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib are similar to those in patients on diclofenac with long-term use of these drugs.

Capone ML, Sciulli MG, Tacconelli S, Grana M, Ricciotti E, Renda G, Di Gregorio P, Merciaro G, Patrignani P. Pharmacodynamic interaction of **naproxen with low-dose aspirin** in healthy subjects. J Am Coll Cardiol. 2005 Apr 19;45(8):1295-301.

Cardiovascular and Cerebrovascular Events in the Randomized, Controlled **Alzheimer's** Disease Anti-Inflammatory Prevention Trial (**ADAPT**). PLoS Clin Trials. 2006 Nov 17;1(7):e33 [Epub ahead of print] For celecoxib, ADAPT data do not show the same level of risk as those of the APC trial. The data for **naproxen**, although not definitive, are suggestive of increased cardiovascular and cerebrovascular risk. (Nissen SE. ADAPT: The Wrong Way to Stop a Clinical Trial. PLoS Clin Trials. 2006 Nov 17;1(7):e35 [Epub ahead of print])

Carmo KB, Evans N, Paradisis M. Duration of indomethacin treatment of the **preterm patent ductus arteriosus** as directed by echocardiography. J Pediatr. 2009 Dec;155(6):819-822.e1. Epub 2009 Jul 29.

Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. **Cyclooxygenase inhibitors and the antiplatelet effects of aspirin**. N Engl J Med. 2001 Dec 20;345(25):1809-17.

Chan AT, et al. Nonsteroidal Antiinflammatory Drugs, Acetaminophen, and the Risk of **Cardiovascular Events**. Circulation. 2006 Mar 13; [Epub ahead of print]

Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of **colorectal cancer**. JAMA. 2009 Aug 12;302(6):649-58. Regular aspirin use after the diagnosis of colorectal cancer is associated with lower risk of colorectal cancer-specific and overall mortality, especially among individuals with tumors that overexpress COX-2.

Chan FKL, et al Clopidogrel versus **Aspirin and Esomeprazole** to Prevent Recurrent Ulcer Bleeding. N Engl J Med 2005;352:238-44. (InfoPOEMs: For patients with a history of bleeding peptic ulcer, the combination of aspirin and a proton pump inhibitor twice a day was safer in terms of bleeding side effects than clopidogrel. While esomeprazole was used in this study, generic omeprazole 20 mg give twice a day provides nearly the same degree of acid suppression at a much lower cost. This study calls into question the overall safety of clopidogrel, which has been promoted as not increasing the risk of bleeding significantly. (LOE = 1b))

Chan FK, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med. 2001 Mar 29;344(13):967-73. CONCLUSIONS: Among patients with H. pylori infection and a history of upper gastrointestinal bleeding who are taking low-dose aspirin, the eradication of H. pylori is equivalent to treatment with omeprazole in preventing recurrent bleeding. Omeprazole is superior to the eradication of H. pylori in preventing recurrent bleeding in patients who are taking other NSAIDs.

Chan FK, Wong VW, Suen BY, et al. Combination of cyclo-oxygenase-2 inhibitor **(celecoxib 200mg bid) and proton-pump inhibitor (esomeprazole 20mg bid)** for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet. 2007 May 12;369(9573):1621-6. The 13-month cumulative incidence of the primary endpoint was 0% in the combined-treatment group and 12 (8.9%) in the controls (95% CI difference, 4.1 to 13.7; p=0.0004). n=441 12months. Patients at very high risk for recurrent ulcer bleeding who need anti-inflammatory analgesics should receive combination treatment with a COX 2 inhibitor and a PPI. Our findings should encourage guideline committees to review their recommendations for patients at very high risk of recurrent ulcer bleeding.

Chan CC, Reid CM, Aw TJ, Liew D, Haas SJ, Krum H. Do COX-2 inhibitors raise blood pressure more than nonselective NSAIDs and placebo? An updated meta-analysis. J Hypertens. 2009 Nov 2. [Epub ahead of print] However, this response was heterogeneous, with markedly raised BP associated with rofecoxib and etoricoxib, whereas celecoxib, valdecoxib and lumiracoxib appeared to have little BP effect.

Chan Francis KL, Lanas Angel, Scheiman James, et al. **Celecoxib versus omeprazole and diclofenac** in patients with osteoarthritis and rheumatoid arthritis (**CONDOR**): a randomised trial, The Lancet, Online 16 June 2010, ISSN 0140-6736, DOI:10.1016/S0140-6736(10)60673-3.

Chang CH, Shau WY, Kuo CW, Chen ST, Lai MS. **Increased Risk of Stroke** Associated With Nonsteroidal Anti-Inflammatory Drugs. A Nationwide Case-Crossover Study. Stroke. 2010 Jul 29.

Chen H, Jacobs E, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ, Ascherio A. **Nonsteroidal antiinflammatory** drug use and the risk for Parkinson's disease. Ann Neurol. 2005 Dec;58(6):963-7.

Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al. **Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs** (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2008 Apr;12(11):1-278, iii.

Cho E, Curhan G, Hankinson SE, Kantoff P, Atkins MB, Stampfer M, Choueiri TK. Prospective evaluation of analgesic use and **risk of renal cell cancer**. Arch Intern Med. 2011 Sep 12;171(16):1487-93.

Cimbollek S, Quiralte J, Avila R. COX-2 inhibitors in patients with **sensitivity to nonselective NSAIDs**. N Engl J Med. 2009 Nov 26;361(22):2197-8.

Claridge LC, Eksteen B, Smith A, Shah T, Holt AP. Acute **liver failure after administration of paracetamol (acetaminophen)** at the maximum recommended daily dose in adults. BMJ. 2010 Dec 2;341:c6764. doi: 10.1136/bmj.c6764.

Colak T, Ipek T, Kanik A, Ogetman Z, Aydin S. Efficacy of **topical nonsteroidal (diclofenac) antiinflammatory drugs in mastalgia** treatment. J Am Coll Surg. 2003 Apr;196(4):525-30.

Cook NR, Lee IM, Gaziano JM, et al. Low-dose **aspirin in the primary prevention of cancer**: the Women's Health Study (**WHS**): a randomized controlled trial. JAMA. 2005;294:47-55.

Cooper K, Squires H, Carroll C, et al. **Chemoprevention of colorectal cancer**: systematic review and economic evaluation. Health Technol Assess. 2010 Jun;14(32):1-206. (Especially aspirin & celecoxib reviewed)

Corman SL, Fedutes BA, Ansani NT. Impact of **nonsteroidal antiinflammatory drugs on the cardioprotective effects of aspirin**. Ann Pharmacother. 2005 Jun;39(6):1073-9. Epub 2005 May 3.

Cox-2 inhibitors & NSAIDS: **Drug Class Review Nov 2006** Oregon Health & Science University http://www.ohsu.edu/drugeffectiveness/reports/documents/NSAIDS%20Final%20Report%20Update%203.pdf

Craig DG, Bates CM, Davidson JS, et al.. **Staggered overdose pattern and delay** to hospital presentation are associated with adverse outcomes following **paracetamol (acetaminophen)**-induced hepatotoxicity. Br J Clin Pharmacol. 2011 Nov 22.

Curhan SG, Eavey R, Shargorodsky J, Curhan GC. Analgesic use and the risk of **hearing loss** in men. Am J Med. 2010 Mar;123(3):231-7.

Dart RC, et al. **Acetaminophen poisoning**: an evidence-based consensus guideline for out-of-hospital management. Washington (DC): American Association of Poison Control Centers; 2005.http://www.aapcc.org/FinalizedPMGdlns/APAP%20-%20final%20guideline%209.9.05.pdf

De Caterina Raffaele; Ruigomez Ana; Rodriguez Luis Alberto Garcia. Long-term Use of Anti-inflammatory Drugs (**NSAIDS**) and Risk of **Atrial Fibrillation**. Arch Intern Med. 2010;170(16):1450-1455.

De Silva V, El-Metwally A, Ernst E, et al. Evidence for the efficacy of **complementary and alternative medicines in the management of osteoarthritis**: a systematic review. Rheumatology (Oxford). 2011 May;50(5):911-20.

den Hertog HM, van der Worp HB, et al.; on behalf of the PAIS investigators. The Paracetamol (**Acetaminophen**) In **Stroke (PAIS)** trial: a multicentre, randomised, placebo-controlled, phase III trial. Lancet Neurol. 2009 May;8(5):434-440. Epub 2009 Mar 16.

Derry S, Moore RA. Single dose oral **aspirin for acute postoperative pain** in adults. Cochrane Database Syst Rev. 2012 Apr 18;4:CD002067. Aspirin is an effective analgesic for acute pain of moderate to severe intensity. High doses are more effective, but are associated with increased adverse events, including drowsiness and gastric irritation. The pain relief achieved with aspirin was very similar milligram for milligram to that seen with paracetamol.

Diener HC, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalagia. 2006 May;26(5):537-47.

Din Farhat V N, Theodoratou Evropi, Farrington Susan M, Effect of **aspirin and NSAIDs on risk and survival from colorectal cancer**. Gut gut.2009.203000Published Online First: 15 September 2010 doi:10.1136/gut.2009.203000.

Doherty M, Hawkey C, Goulder M, et al.A randomised controlled trial of **ibuprofen, paracetamol or a combination** tablet of ibuprofen/paracetamol in community-derived people with knee pain. Ann Rheum Dis. 2011 Sep;70(9):1534-41.

Dougados M, Baeten D. **Spondyloarthritis**. Lancet. 2011 Jun 18;377(9783):2127-37.

Douglas L, Akil M. Sodium in soluble **paracetamol** may be linked to raised blood pressure. BMJ. 2006 May 13;332(7550):1133. (some forms of acetaminophen may have high sodium content)

Drendel AL, Lyon R, Bergholte J, et al. Outpatient pediatric **pain** management practices for **fractures**. Pediatr Emerg Care. 2006 Feb;22(2):94-9. Most children with fractures have the "worst" pain in the first 48 hours after injury and used analgesia for 3 days after injury. There are noteworthy functional limitations for both children and their caregivers. Ibuprofen and acetaminophen with codeine are the analgesics most commonly used, with no clear superiority.

Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK. A randomized clinical trial of **ibuprofen** versus acetaminophen with codeine for acute pediatric arm fracture pain. Ann Emerg Med. 2009 Oct;54(4):553-60.

Driver Jane A, Logroscino Giancarlo, Lu Linda, et al. Use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of **Parkinson's disease**: nested case-control study. BMJ 2011;342:doi:10.1136/bmj.d198 (20 Jan 2011) –no association found

Drugs in Pregnancy and Lactation. 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Philadelphia, PA: 2011.

Eliassen AH, Chen WY, Spiegelman D, Willett WC, Hunter DJ, Hankinson SE. Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and **risk of breast cancer** among premenopausal women in the Nurses' Health Study II. Arch Intern M

TOP

26;169(2):115-21; discussion 121. These data **suggest** that the use of aspirin, other NSAIDs, and acetaminophen is not associated with a reduced risk of breast cancer among premenopausal women.
Elmunzer BJ, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the **prevention of post-ERCP pancreatitis**. Gut. 2008 Sep;57(9):1262-7.
Elmunzer BJ, Scheiman JM, Lehman GA, et al. U.S. Cooperative for Outcomes Research in Endoscopy (**USCORE**). A randomized trial of rectal **indomethacin** to **prevent post-ERCP pancreatitis**. N Engl J Med. 2012 Apr 12;366(15):1414-22.
Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. **Acetaminophen** Use and the **Risk of Asthma** in Children and Adults: A Systematic Review and Metaanalysis. Chest. 2009 Aug 20. [Epub ahead of print]
FDA- **Acetaminophen and Liver Injury**: Q & A for Consumers 2009 http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM172664.pdf
FDA Dec/09 , Endo, & Novartis revised the Hepatic Effects section of the Prescribing Information to add new warnings and precautions about the potential for elevation in liver function tests during treatment with all products (**including diclofenac gel**) on **diclofenac** sodium. In postmarketing reports, cases of drug-induced **hepatotoxicity** have been reported in the first month but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.
FDA June/12 cautioned late last week against using **Reumofan Plus**, a dietary supplement marketed as a "natural" pain reliever for arthritis, osteoporosis, and other conditions. The drug, which is made in Mexico but available online, contains unlabeled and potentially harmful pharmaceutical ingredients: diclofenac, methocarbamol & sometimes dexamethasone.
Felson DT. Clinical practice. **Osteoarthritis of the knee**. N Engl J Med. 2006 Feb 23;354(8):841-8.
Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of **aspirin on long-term risk of colorectal cancer**: consistent evidence from randomised and observational studies. Lancet. 2007 May 12;369(9573):1603-13. Use of 300 mg or more of aspirin a day for about 5 years is effective in primary prevention of colorectal cancer in randomised controlled trials, with a latency of about 10 years, which is consistent with findings from observational studies. Long-term follow-up is required from other randomised trials to establish the effects of lower or less frequent doses of aspirin.
Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. Arch Intern Med 2007; 167:394-399. The frequency of **nonnarcotic analgesic** use is independently associated with a moderate increase in the risk of incident **hypertension**. Given the widespread use of these medications and the high prevalence of hypertension, these results may have important public health implications.
Forestier R, Desfour H, Tessier JM, et al. **Spa therapy** in the treatment of knee osteoarthritis: a large randomised multicentre trial. Ann Rheum Dis. 2010 Apr;69(4):660-5. Epub 2009 Sep 3.
Fosbøl EL, Folke F, Jacobsen S, et al. Cause-Specific Cardiovascular Risk Associated With Nonsteroidal Antiinflammatory Drugs Among Healthy Individuals. Circ Cardiovasc Qual Outcomes. 2010 Jun 8. (**Diclofenac & rofecoxib**)
Foster NE, Thomas E, Barlas P, Hill JC, Young J, Mason E, Hay EM. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. BMJ. 2007 Sep 1;335(7617):436. Epub 2007 Aug 15. The addition of **acupuncture** to a course of advice and exercise for osteoarthritis of the knee delivered by physiotherapists provided no additional improvement in pain scores.
Fransen M, et al. HIPAID Collaborative Group. Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial. BMJ. 2006 Sep 9;333(7567):519. Epub 2006 Aug 2. These data do not support the use of routine prophylaxis with NSAIDs in patients undergoing **total hip replacement surgery**.
Friday JH, Kanegaye JT, McCaslin I, Zheng A, Harley JR. **Ibuprofen** provides analgesia equivalent to **acetaminophen-codeine** in the treatment of acute pain in children with extremity injuries: a randomized clinical trial. Acad Emerg Med. 2009 Aug;16(8):711-6. Epub 2009 Jul 14. Acute pain relief from ibuprofen is equivalent to that of acetaminophen-codeine for children presenting to the emergency department with extremity injury. More than half the children in this study were consequently found to have fractures. (LOE = 1b)
Frithsen IL, Simpson WM Jr. Recognition and management of acute medication **poisoning**. Am Fam Physician. 2010 Feb 1;81(3):316-23.
Gatoulis SC, Voelker M, Fisher M. Assessment of the Efficacy and Safety Profiles of **Aspirin 1gm and Acetaminophen With Codeine**: Results From 2 Randomized, Controlled Trials in Individuals With Tension-Type Headache and Postoperative Dental Pain. Clin Ther. 2011 Dec 12.
Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of **steroid injections** for shoulder and elbow tendonitis: a meta-analysis of randomized controlled trials. Ann Rheum Dis. 2009 Dec;68(12):1843-9. Epub 2008 Dec 3. In the first 3 months of tendinitis of either the elbow or shoulder, injected corticosteroids are more effective than placebo or physical therapy, but no more effective than treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). In the longer term they are no more effective than any treatment. What hasn't been studied is the effectiveness of steroid injections in patients for whom NSAID treatment isn't effective, since this is the usual progression of treatment of these painful conditions. (LOE = 1a-)
Gislason GH, et al. **Risk of Death or Reinfarction** Associated With the Use of Selective Cyclooxygenase-2 Inhibitors and Nonselective Nonsteroidal Antiinflammatory Drugs After Acute Myocardial Infarction. Circulation. 2006 Jun 19; [Epub ahead of print] For any use of rofecoxib, celecoxib, ibuprofen, diclofenac, and other NSAIDs, the hazard ratios and 95% confidence intervals for death were 2.80 (2.41 to 3.25; for rofecoxib), 2.57 (2.15 to 3.08; for celecoxib), 1.50 (1.36 to 1.67; for ibuprofen), 2.40 (2.09 to 2.80; for diclofenac), and 1.29 (1.16 to 1.43; for other NSAIDS); there were dose-related increases in risk of death for all of the drugs. There were trends for increased risk of rehospitalization for MI associated with the use of both the selective COX-2 inhibitors and the nonselective NSAIDs. CONCLUSIONS: Selective COX-2 inhibitors in all dosages and nonselective NSAIDs in high dosages increase mortality in patients with previous MI and should therefore be used with particular caution in these patients.
Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs) in chronic **heart failure**. Arch Intern Med. 2009 Jan 26;169(2):141-9.
Gleason JM, Slezak JM, Jung H, et al. Regular Nonsteroidal Anti-Inflammatory Drug (**NSAIDs**) Use and **Erectile Dysfunction**. J Urol. 2011 Feb 18.
Gokmen T, Erdeve O, Altug N, et al. Efficacy and safety of oral versus intravenous Ibuprofen in very low birth weight preterm infants with patent ductus arteriosus. J Pediatr. 2011 Apr;158(4):549-554.e1.
Goldstein JL, Johanson JF, et al. Healing of gastric ulcers with **esomeprazole versus ranitidine** in patients who continued to receive NSAID therapy: a randomized trial. Am J Gastroenterol. 2005 Dec;100(12):2650-7.
Goldstein JL, Cryer B, Amer F, Hunt B. Celecoxib plus aspirin versus naproxen and lansoprazole plus aspirin: a randomized, double-blind, endoscopic trial. Clin Gastroenterol Hepatol. 2007 Oct;5(10):1167-74. n=854 In patients with osteoarthritis taking low-dose aspirin, the use of celecoxib or naproxen plus lansoprazole resulted in similar rates of gastroduodenal ulceration.
Goldstein LH, Berlin M, Berkovitch M, Kozer E. Effectiveness of oral vs rectal acetaminophen: a meta-analysis. Arch Pediatr Adolesc Med. 2008 Nov;162(11):1042-6. Among 4 small studies, oral and rectal acetaminophen for fever control were comparable in effectiveness. The authors could only find 1 study comparing **oral and rectal acetaminophen** for pain. It appeared that oral administration was more effective, but the effect may not have been clinically meaningful. The authors don't report on adverse effects. (LOE = 1a-)
Goldstein JL, Chan FK, Lanas A, Wilcox CM, Peura D, Sands GH, Berger MF, Nguyen H, Scheiman JM. **Haemoglobin decreases in NSAID** users over time: an analysis of two large outcome trials. Aliment Pharmacol Ther. 2011 Aug 2.
González ELM et al. **Variability** among nonsteroidal antiinflammatory drugs in risk of upper **gastrointestinal bleeding**. Arthritis Rheum 2010 Jun; 62:1592.
Gouyon JB, Kibleur Y. Efficacy and tolerability of enteral formulations of **ibuprofen** in the treatment of **patent ductus arteriosus** in preterm infants. Clin Ther. 2010 Sep;32(10):1740-8.
Gossec L, Smolen JS, Gaujoux-Viala C, et al. European League Against Rheumatism (**EULAR**) recommendations for the management of **psoriatic arthritis** with pharmacological therapies. Ann Rheum Dis. 2011 Sep 27.
Graham GG, Scott KF, Day RO. Tolerability of **paracetamol**. Drug Saf. 2005;28(3):227-40.
Graham DJ, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet. 2005 Feb 5-11;365(9458):475-81.
Graham DY, Agrawal NM, Campbell DR, et al. NSAID-Associated Gastric Ulcer Prevention Study Group. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of **misoprostol vs lansoprazole**. Arch Intern Med. 2002 Jan 28;162(2):169-75.
Hammerman C et al. **Ductal closure with paracetamol** (acetaminophen): a surprising new approach to patent ductus arteriosus treatment. Pediatrics. 2011 Dec;128(6):e1618-21.
Harnden A, Takahashi M, Burgner D. **Kawasaki disease**. BMJ. 2009 May 5;338:b1514. doi: 10.1136/bmj.b1514.
Harris RE, Beebe-Donk J, Alshafie GA. Reduction in the risk of human **breast cancer** by selective cyclooxygenase-2 (COX-2) inhibitors. BMC Cancer. 2006 Jan 30;6:27.
Hay EM, et al. Effectiveness of community **physiotherapy** and enhanced **pharmacy review** for knee pain in people aged over 55 presenting to primary care: pragmatic randomized trial. BMJ. 2006 Oct 20; [Epub ahead of print] Evidence based care for older adults with knee pain, delivered by primary care physiotherapists and pharmacists, resulted in short term improvements in health outcomes, reduced use of non-steroidal anti-inflammatory drugs, and high patient satisfaction.
Hay AD, Costelloe C, Redmond NM, et al. Paracetamol plus ibuprofen for the treatment of fever in children (**PITCH**): randomised controlled trial. BMJ. 2008 Sep 2;337:a1302. doi: 10.1136/bmj.a1302. Parents, nurses, pharmacists, and doctors wanting to use medicines to supplement physical measures to maximise the time that children spend without fever should use **ibuprofen first** and consider the relative benefits and risks of using paracetamol plus ibuprofen over 24 hours.
Hawkey CJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. **Omeprazole** versus Misoprostol for NSAID-induced Ulcer Management (**OMNIUM**) Study Group. N Engl J Med. 1998 Mar 12;338(11):727-34.
Health Canada Prohits sale of Bextra http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_134_e.html
Health Canada June/06 two documents as part of its ongoing evaluation of COX-2-selective drugs: its official comments on the advice provided by the COX-2 Expert Advisory Panel and a report on the Department's scientific review of certain COX-2s. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-consult/cox2/index_e.html
Health Canada Aug/07 reports that the Therapeutic Goods Administration (TGA), the federal regulatory authority in Australia, recently withdrew market authorization for **Prexige due to eight reports of serious liver adverse events** in Australia linked to the drug, including two deaths and two liver transplants. These adverse events were primarily with use of 200 mg and 400 mg doses daily.
Health Canada Sept/07 reports that **Qiangli Zhuanggutongbiling** has reportedly been used for joint pain and stiffness. It was found to contain the undeclared prescription drugs prednisolone acetate, cortisone acetate, piroxicam, and diclofenac.
Health Canada Sept/07: **Khun-Phra** is a health product promoted for pain relief that has been found to contain the undeclared drugs dexamethasone, prednisolone, phenylbutazone, diazepam, cyproheptadine and mebhydrolin.. **Asam Urat Flu Tulang, PJ Dewandaru** is a health product promoted to treat joint pain, rheumatism and arthritis. It has been found to contain the undeclared drugs dexamethasone, diclofenac and acetaminophen.
Health Canada Oct/07 Foreign Product Alerts: ***Zhen Feng Da Brand Xi Tong Wan*** is promoted as a pain reliever. Lot #060908 has been found to contain undeclared indomethacin, a prescription anti-inflammatory drug that should only be taken under the guidance of a health professional. ***Wellring Brand Yin Qiao Jie Du*** is a health product promoted to treat cold and flu symptoms. Lot#51005 has been found to contain undeclared acetaminophen. ***Gu Ci Dan*** and ***Xu Log Bou*** are promoted as pain relievers and have been found to contain indomethacin.
Health Canada Oct/07 is advising consumers that it has stopped the sale of the anti-inflammatory drug **Prexige** (lumiracoxib) in Canada and will cancel the drug's market authorization due to the potential for serious liver-related adverse events. (2 new severe cases in Canada)
Health Canada July/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **3rd Generation In Homoeopathy Arthrit Indica Tablet**. The product is labelled for "intense joint pain." The Health Sciences Authority of Singapore has warned consumers not to use the product because it contains **nimesulide**, a pharmaceutical ingredient that has been associated with liver damage.
Health Canada Aug/08 is advising consumers not to use foreign health products due to concerns against the use of **AA Qu Feng Shu Jin Wan** because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. **Obat Asam Urat** and **Asam Urat** both contained dexamethasone, phenylbutazone and piroxicam.
Health Canada June/09 is informing Canadian health care professionals and consumers of recent restrictions regarding the use of the prescription drug piroxicam. Health Canada has conducted a safety review and concluded that **piroxicam** should no longer be used to treat short-term pain and inflammation due to an increased risk of serious skin reactions and gastrointestinal problems relative to other similar drugs.
Health Canada July/09 is warning consumers not to use the unauthorized health product labelled as **Specific-Formula Arthro-Ace** as it was found to contain undeclared dexamethasone and may cause serious health effects.
Health Canada July/09 is warning that the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **Air Ikan Haruan** after it was found to contain undeclared dexamethasone. The Hong Kong Department of Health warned consumers not to buy or use the product **Neovidan** after it was found to contain undeclared prednisolone and mefenamic acid.
Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine, while **Cao Gen Bai Lin Wan** contains undeclared dexamethasone and
Health Canada Aug/10 **Huo Luo Jing Dan** The Singapore Health Sciences Authority warned consumers not to buy or consume Huo Luo Jing Dan after it was found to contain undeclared indomethacin, dexamethasone and prednisolone.

TOP

Health Canada Oct/11 **Huo Li Bao and Ren Sem Tu Chon Chin Kuo Pill** - The Singapore Health Sciences Authority warned that these Chinese pain-relief products contain prescription and/or over-the-counter drugs (furosemide, piroxicam, chlorpheniramine, and/or dexamethasone).
Health Canada Dec/11 is advising Canadians that Vita Health's product, "**Compliments Muscle and Back Pain Relief Regular Strength**" contains a significant labelling error in the French dosing directions that may pose serious risks to children (less than 12 years of age).
Heard KJ, Green JL, Dart RC. Serum alanine **aminotransferase elevation during 10 days of acetaminophen** use in nondrinkers. Pharmacotherapy. 2010 Aug;30(8):818-22.
Helin-Salmivaara A, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. Eur Heart J. 2006 Jul;27(14):1657-63. Epub 2006 May 26.
Huerta C, Varas-Lorenzo C, Castellsague J, Garcia Rodriguez LA. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for **heart failure** in the general population. Heart. 2006 Nov;92(11):1610-5. Epub 2006 May 22.
Hill KP, Ross JS, Egilman DS, Krumholz HM. The **ADVANTAGE seeding trial**: a review of internal documents. (Vioxx marketing trial) Ann Intern Med. 2008 Aug 19;149(4):251-8.
Hinz B, Brune K. **Paracetamol and cyclooxygenase inhibition**: is there a cause for concern? Ann Rheum Dis. 2012 Jan;71(1):20-5.
Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking **cyclo-oxygenase-2 inhibitors or conventional** non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ. 2005 Dec 3;331(7528):1310-6.
CONCLUSION: No consistent evidence was found of enhanced safety against gastrointestinal events with any of the new cyclo-oxygenase-2 inhibitors compared with non-selective non-steroidal anti-inflammatory drugs. The use of ulcer healing drugs reduced the increased risk of adverse gastrointestinal outcomes with all groups of non-steroidal anti-inflammatory drugs, but for diclofenac the increased risk remained significant.
Ho JM, Juurlink DN. Considerations when prescribing **trimethoprim-sulfamethoxazole**. CMAJ. 2011 Oct 11. (NSAID DIs)
Holmes, Michelle D., Chen, Wendy Y., Li, Lisa, et al. **Aspirin** Intake and Survival **After Breast Cancer**. J Clin Oncol 2010 0: JCO.2009.22.7918.
Hooper L, Brown TJ, Elliott R, et al. The effectiveness of **five strategies for the prevention of gastrointestinal toxicity** induced by non-steroidal anti-inflammatory drugs: systematic review. BMJ. 2004 Oct 23;329(7472):948. Epub 2004 Oct 8. CONCLUSIONS: Misoprostol, COX-2 specific and selective NSAIDs, and probably proton pump inhibitors significantly reduce the risk of symptomatic ulcers, and misoprostol and probably COX-2 specifics significantly reduce the risk of serious gastrointestinal complications, but data quality is low. More data on H2 receptor antagonists and proton pump inhibitors are needed, as is better reporting of rare but important outcomes.
Hudson N, Taha AS, Russell RI, et al. **Famotidine** for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration. Gastroenterology. 1997 Jun;112(6):1817-22.
Hughes GJ, Patel PN, Saxena N.. Effect of **acetaminophen on international normalized ratio** in patients receiving warfarin therapy. Pharmacotherapy 2011 June;31(6):591–597.
Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating **pain to reduce behavioural disturbances** in residents of nursing homes with dementia: cluster randomised clinical trial. BMJ 2011;343;d4065. (**70% on 3g/day acetaminophen**)
Irwin RS, et al. American College of Chest Physicians (ACCP). **Diagnosis and management of cough** executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):1S-23S. http://www.chestjournal.org/cgi/content/full/129/1_suppl/1S
Iversen MD, Hammond A, Betteridge N. **Self-management** of rheumatic diseases: state of the art and future perspectives. Ann Rheum Dis 2010; 69: 955–63.
James LP, et al. Pediatric Acute Liver Failure Study Group. Detection of **acetaminophen** protein adducts in children with acute **liver failure** of indeterminate cause. Pediatrics. 2006 Sep;118(3):e676-81.
James ND, Sydes MR, Mason MD, et al. **Celecoxib plus hormone therapy versus hormone** therapy alone for hormone-sensitive **prostate cancer**: first results from the STAMPEDE multiarm, multistage, randomised controlled trial. Lancet Oncol 2012; online March 26.
Jaturapatporn D, Isaac MG, McCleery J, et al. Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of **Alzheimer`s disease**. Cochrane Database Syst Rev. 2012 Feb 15;2:CD006378. Based on the studies carried out so far, the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven. Therefore, these drugs cannot be recommended for the treatment of AD.
Jick H, et al. Nonsteroidal antiinflammatory drugs and **acute myocardial infarction** in patients with no major risk factors. Pharmacotherapy. 2006 Oct;26(10):1379-87. Extensive use of rofecoxib, celecoxib, and diclofenac increases the risk of acute myocardial infarction, but similar use of ibuprofen and naproxen does not.
Jickling G, Heino A, Ahmed SN. **Acetaminophen toxicity** with concomitant use of **carbamazepine**. Epileptic Disord. 2009 Dec 9.
Johnson MT, McCammon CA, Mullins ME, Halcomb SE. Evaluation of a **Simplified N-Acetylcysteine Dosing Regimen** for the Treatment of Acetaminophen Toxicity (June). Ann Pharmacother. 2011 May 17.
Jordan KM, Arden NK, Doherty M, et al. **EULAR** Recommendations 2003: an evidence based approach to the management of knee **osteoarthritis**: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003; 62: 1145–55.
Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to **acetaminophen and asthma** in children. Obstet Gynecol. 2009 Dec;114(6):1295-306.
Kastelein F et al. Probar-study Group. Nonsteroidal Anti-Inflammatory Drugs and Statins Have **Chemopreventative Effects in Patients With Barrett's Esophagus**. Gastroenterology. 2011 Dec;141(6):2000-8
Kearney PM, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of **atherothrombosis**? Meta-analysis of randomised trials. BMJ. 2006 Jun 3;332(7553):1302-8. Selective COX 2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but high dose naproxen is not associated with such an excess.
Kerry S. Kuehl, Review of the efficacy and tolerability of the **diclofenac epolamine topical** patch 1.3% in patients with acute pain due to soft tissue injuries, Clinical Therapeutics, Volume 32, Issue 6, June 2010, Pages 1001-1014.
Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS. Non-steroidal anti-inflammatory drugs for the **common cold**. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006362.
Kirkley A, et al. A Randomized Trial of **Arthroscopic Surgery** for Osteoarthritis of the Knee. N Engl J Med. 2008 Sep 11;359(11):1097-1107. Arthroscopic surgery for osteoarthritis of the knee provides no additional benefit to optimized physical and medical therapy.
Konstan MW, Schluchter MD, Xue W, Davis PB. Clinical use of Ibuprofen is associated with slower FEV1 decline in children with **cystic fibrosis**. Am J Respir Crit Care Med. 2007 Dec 1;176(11):1084-9. Epub 2007 Sep 13. Slower rates of FEV(1) decline are seen in children and adolescents with cystic fibrosis who are treated with ibuprofen. The apparent benefits of ibuprofen therapy outweigh the small risk of gastrointestinal bleeding.
Kuo HW, Tsai SS, Tiao MM, Liu YC, Lee IM, Yang CY. Analgesic use and the **risk for progression of chronic kidney disease**. Pharmacoepidemiol Drug Saf. 2010 Jul;19(7):745-51.
Kurmis AP, Kurmis TP, O'Brien JX, Dalén T. The effect of nonsteroidal anti-inflammatory drug administration on **acute phase fracture-healing**: a review. J Bone Joint Surg Am. 2012 May 2;94(9):815-23.
Kurth T, Hennekens CH, Stürmer T, Sesso HD, Glynn RJ, Buring JE, Gaziano JM. Analgesic use and risk of **subsequent hypertension** in apparently healthy men. Arch Intern Med. 2005 Sep 12;165(16):1903-9.
Lackner JE, et al. Correlation of leukocytospermia with clinical infection and the positive effect of antiinflammatory (**valdecoxib**) treatment on **semen** quality. Fertil Steril. 2006 Sep;86(3):601-5. Epub 2006 Jun 16.
Lai KC, Chu KM, Hui WM, et al. Celecoxib compared with **lansoprazole and naproxen** to prevent gastrointestinal ulcer complications. Am J Med. 2005 Nov;118(11):1271-8. (InfoPOEMs: In patients at high risk for recurrent peptic ulcer with nonsteroidal anti-inflammatory drug therapy, celecoxib was no more effective than the combination of naproxen (Naprosyn) and lansoprazole (Prevacid) in preventing serious adverse effects and was more likely to cause dyspepsia symptoms. The benefit of COX-2 inhibitors in preventing serious gastrointestinal adverse events is likely overstated. (LOE = 1b-))
Lai KC, Lam SK, et al. **Lansoprazole** for the prevention of recurrences of ulcer complications from long-term **low-dose aspirin** use. N Engl J Med. 2002 Jun 27;346(26):2033-8.
Laine L, Kivitz AJ, Bello AE, et al. Double-blind randomized trials of single-tablet **ibuprofen/high-dose famotidine vs. ibuprofen** alone for reduction of gastric and duodenal ulcers. Am J Gastroenterol. 2012 Mar;107(3):379-86.
Lands LC, Milner R, Cantin AM, Manson D, Corey M. High-dose **ibuprofen in cystic fibrosis**: Canadian safety and effectiveness trial. J Pediatr. 2007 Sep;151(3):249-54. Epub 2007 Jun 26.
Lane NE. Clinical practice. **Osteoarthritis of the hip**. N Engl J Med. 2007 Oct 4;357(14):1413-21.
Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the **American College of Gastroenterology. Guidelines** for **prevention of NSAID-related ulcer** complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. Epub 2009 Feb 24.
Larson AM, et al, and the Acute Liver Failure Study Group. **Acetaminophen-Induced Acute Liver Failure**: Results of a US Muticenter, Prospective Study. Hepatology; Dec 2005. (of 662 consecutive acute liver failure pts over 6yrs: 42% from acetaminophen liver injury; 48% were unintentional overdoses; only 65% of pts survived) (Benson GD, Koff RS, Tolman KG. The therapeutic use of acetaminophen in patients **with liver disease**. Am J Ther. 2005 Mar-Apr;12(2):133-41. & Oviedo J, Wolfe MM. Alcohol, acetaminophen, & toxic effects on the liver. Arch Intern Med. 2002 May 27;162(10):1194-5.) (Mahadevan SB, McKiernan PJ, Davies P, Kelly DA. Paracetamol-induced hepatotoxicity in children. Arch Dis Child. 2006 Mar 17; [Epub ahead of print]) (Watkins PB, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):87-93.) (Kuffner EK, Green JL, Bogdan GM, Knox PC, Palmer RB, Heard K, Slattery JT, Dart RC. The effect of acetaminophen (four grams a day for three consecutive days) on hepatic tests in alcoholic patients--a multicenter randomized study. BMC Med. 2007 May 30;5:13. Alcoholic patients treated with the maximum recommended daily dose of acetaminophen for 3 consecutive days did not develop increases in serum transaminase or other measures of liver injury. Treatment of pain or fever for 3 days with acetaminophen appears safe in newly-abstinent alcoholic patients, such as those presenting for acute medical care.) (Heard K, Green JL, Bailey JE, Bogdan GM, Dart RC. A randomized trial to determine the change in alanine aminotransferase during 10 days of paracetamol (acetaminophen) administration in subjects who consume moderate amounts of alcohol. Aliment Pharmacol Ther. 2007 Jul 15;26(2):283-90. Therapeutic dosing of paracetamol administered for 10 days appears to elevate serum ALT in moderate drinkers, but does not produce clinically evident liver injury.)
Latimer Nicholas, Lord Joanne, Grant Robert L, et al., on behalf of the National Institute for Health and Clinical Excellence Osteoarthritis Guideline Development Group. **Cost effectiveness** of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. BMJ 2009;339:b2538, doi: 10.1136/bmj.b2538
Lavonas, Eric J., Reynolds, Kate M., Dart, Richard C. **Therapeutic Acetaminophen** Is **Not Associated With Liver Injury in Children**: A Systematic Review. Pediatrics 2010 0: peds.2009-3352
Lee WM. **Acetaminophen and the U.S. Acute Liver Failure** Study Group: lowering the risks of hepatic failure. Hepatology. 2004 Jul;40(1):6-9.
Levesque LE, Brophy JM, Zhang B. Time variations in the risk of **myocardial infarction** among elderly users of COX-2 inhibitors. CMAJ. 2006 May 23;174(11):1563-9. Epub 2006 May 2. A small proportion of patients using rofecoxib for the first time had their first MI shortly after starting the drug. This risk did not increase with the length of treatment and returned to baseline shortly after treatment was discontinued. More research is needed to identify those most susceptible to cardiotoxicity mediated by COX-2 inhibitor therapy.
Liao LM, Vaughan TL, Corley DA, et al. Nonsteroidal Anti-inflammatory Drug Use **Reduces Risk of Adenocarcinomas of the Esophagus** and Esophagogastric Junction in a Pooled Analysis. Gastroenterology. 2012 Mar;142(3):442-452.e5
Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during **pregnancy and risk of miscarriage**: population based cohort study. BMJ. 2003 Aug 16;327(7411):368.
Liccardi G, et al. Safety of celecoxib in patients with adverse **skin reactions** to acetaminophen (paracetamol) and other non-steroidal anti-inflammatory drugs. J Investig Allergol Clin Immunol. 2005;15(4):249-53.
Lin J, Zhang W, Jones A, Doherty M. Effi cacy of **topical non-steroidal** anti-infl ammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ 2004; 329: 324–26.
Lipman GS, Kanaan NC, Holck PS, et al. **Ibuprofen Prevents Altitude Illness**: A Randomized Controlled Trial for Prevention of Altitude Illness With Nonsteroidal Anti-inflammatories. Ann Emerg Med. 2012 Mar 20.
Loke YK, Trivedi AN, Singh S. Meta-analysis: Gastrointestinal bleeding due to interaction between **selective serotonin uptake inhibitors** and non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther. 2007 Oct 5; [Epub ahead of print]
Lotrionte M, Biondi-Zoccai G, Imazio M, et al. International collaborative systematic review of controlled clinical trials on pharmacologic treatments for **acute pericarditis** and its recurrences. Am Heart J. 2010 Oct;160(4):662-70.
Lynde, Carrie B, Pierscianowski, Tadeusz A, Pratt, Melanie D. **Allergic contact dermatitis** caused by diclofenac cream. CMAJ 2009 0: cmaj.081784
Lyrtzis C, Natsis K, Papadopoulos C, et al. Efficacy of **Paracetamol** Versus Diclofenac for Grade II Ankle Sprains. Foot Ankle Int. 2011 Jun;32(6):571-5.
Madden T, Proehl S, Allsworth JE, et al. **Naproxen** or estradiol for bleeding and **spotting with the levonorgestrel intrauterine system**: a randomized controlled trial. Am J Obstet Gynecol. 2012 Feb;206(2):129.e1-8.
Mamdani M, Warren L, Kopp A, Paterson JM, Laupacis A, Bassett K, Anderson GM. Changes in rates of upper gastrointestinal hemorrhage after the introduction of **cyclooxygenase-2 inhibitors** in British Columbia and Ontario. CMAJ. 2006 Dec

TOP

5;175(12):1535-8. (InfoPOEMs: Although COX-2 inhibitors may be slightly less likely to cause gastrointestinal (GI) complications, the overall increase in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) seen after their introduction appears to have led to an overall increase in the number of GI complications in the population (not to mention the thousands of cardiovascular deaths attributed to this class of drugs). Although physicians complain about prescribing restrictions, sometimes for good reason, in this case they seem to be of benefit. (LOE = 2c))

Marjoribanks J, Proctor M, Farquhar C, Derks RS. Nonsteroidal anti-inflammatory drugs for **dysmenorrhoea**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD001751.

Massey T, Derry S, Moore RA, McQuay HJ. **Topical NSAIDs** for acute pain in adults. Cochrane Database Syst Rev. 2010 Jun 16;6:CD007402. Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs, when used to treat acute musculoskeletal conditions. NNT=4.5 (3.9-5.3) for ≥50% reduction in pain.

Masuda I, Matsuo T, Okamoto K, et al. Two cases of corneal perforation after oral administration of nonsteroidal anti-inflammatory drugs: oral NSAID-induced **corneal damage**. Eur J Ophthalmol. 2009 Dec 12. [Epub ahead of print]

McBride John T.. The Association of **Acetaminophen and Asthma** Prevalence and Severity. Pediatrics 2011; peds.2011-1106; published ahead of print November 7, 2011, doi:10.1542/peds.2011-1106

McCormack PL. **Celecoxib**: a review of its use for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Drugs. 2011 Dec 24;71(18):2457-89. doi: 10.2165/11208240-000000000-00000.

McGettigan P, Henry D. Cardiovascular Risk and Inhibition of Cyclooxygenase: A Systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2. JAMA. 2006 Sep 12; [Epub ahead of print] A dose-related risk was evident with rofecoxib, summary relative risk with 25 mg/d or less, 1.33 (95% confidence interval [CI], 1.00-1.79) and 2.19 (95% CI, 1.64-2.91) with more than 25 mg/d. The risk was elevated during the first month of treatment. Celecoxib was not associated with an elevated risk of vascular occlusion, summary relative risk 1.06 (95% CI, 0.91-1.23). Among older nonselective drugs, diclofenac had the highest risk with a summary relative risk of 1.40 (95% CI, 1.16-1.70). The other drugs had summary relative risks close to 1: naproxen, 0.97 (95% CI, 0.87-1.07); piroxicam, 1.06 (95% CI, 0.70-1.59); and ibuprofen, 1.07 (95% CI, 0.97-1.18). CONCLUSIONS: This review confirms the findings from randomized trials regarding the risk of cardiovascular events with rofecoxib and suggests that celecoxib in commonly used doses may not increase the risk, contradicts claims of a protective effect of naproxen, and raises serious questions about the safety of diclofenac, an older drug. (InfoPOEMs: Rofecoxib (Vioxx), diclofenac (Voltaren, Cataflam), and indomethacin (Indocin) are associated with a significant increased risk of CVD. It is likely that all NSAIDs carry some risk, but the risks may vary between medicines. Current evidence does not point to an increased risk for low dose (over the counter) ibuprofen and this remains safe to use at recommended doses. (LOE = 2a-))

McGettigan P, Henry D. **Cardiovascular risk with nonsteroidal anti-inflammatory drugs**: systematic review of population-based controlled observational studies. PLoS Med 2011; DOI:10.1371/journal.pmed.1001098. (High CV risk with rofecoxib & diclofenac)

Medical Letter: Treatment guidelines. **Drugs for Pain**. April 2007; **April 2010**.

Medical Letter. Off-Label Use of **Ketorolac** for Athletic Injuries (IM into injured muscles). May 14, 2012.

Mehlisch Donald R., Aspley Sue, Daniels Stephen E., et al., Comparison of the analgesic efficacy of concurrent **ibuprofen and paracetamol** with ibuprofen or paracetamol alone in the management of moderate to severe acute postoperative dental pain in adolescents and adults: A randomized, double-blind, placebo-controlled, parallel-group, single-dose, two-center, modified factorial study, Clinical Therapeutics, Volume 32, Issue 5, May 2010, Pages 882-895.

Meurin Philippe, Tabet JY, Thabut Gabriel, et al. and for the French Society of Cardiology. Nonsteroidal Anti-inflammatory Drug Treatment for Postoperative **Pericardial Effusion**: Multicenter Randomized, Double-Blind Trial (**POPE**). Ann Intern Med Feb 2, 2010 152:137-143.

Mindikoglu AL, Magder LS, et al. Outcome of **liver transplantation** for drug-induced acute liver failure in the United States: analysis of the united network for organ sharing database. Liver Transpl. 2009 Jul;15(7):719-29. The 4 leading implicated drug groups were acetaminophen (n = 265; **40%**), antituberculosis drugs (n = 50; 8%), antiepileptics (n = 46; 7%), & antibiotics (n = 39; 6%). Being on life support, DIALF due to antiepileptics (at age < 18), and elevated serum creatinine were independent pretransplant predictors of poor survival after LT for DIALF.

Messier SP, et al. **Exercise and dietary** weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum. 2004 May;50(5):1501-10.

Moon KW, Kim J, Kim JH, et al. Risk factors for acute kidney injury by non-steroidal anti-inflammatory drugs in patients with hyperuricaemia. Rheumatology (Oxford). 2011 Oct 22. (Low GFR and **low serum albumin**)

Nakhai-Pour HR, Broy P, Sheehy O, Bérard A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during **pregnancy and the risk of spontaneous abortion**. CMAJ. 2011 Sep 6.

Najafi N, Van de Velde A, Poelaert J. Potential risks of **hemolysis** after short-term administration of analgesics in children with **glucose-6-phosphate dehydrogenase deficiency**. J Pediatr. 2011 Dec;159(6):1023-8.

Ng FH, Wong SY, Lam KF, et al. **Famotidine 40mg bid is inferior to pantoprazole 20mg od** in preventing recurrence of **aspirin-related** peptic ulcers or erosions. Gastroenterology. 2010 Jan;138(1):82-8. n=160 Epub 2009 Nov 11.

Ni X, Ma J, Zhao Y, et al. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and **ovarian cancer**. Br J Clin Pharmacol. 2012 Apr 3.

NICE Guidelines for the care and management of Osteoarthritis in Adults Feb, 2008. http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11926

Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. **Hyperkalaemia**. BMJ. 2009 Oct 23;339:b4114. doi: 10.1136/bmj.b4114.

Ofori B, et al. Risk of **congenital anomalies** in pregnant users of non-steroidal anti-inflammatory drugs: a nested case-control study. Birth Defects Res B Dev Reprod Toxicol. 2006 Aug 23; [Epub ahead of print] Our study suggests that women prescribed NSAIDs during early pregnancy may be at a greater risk of having children with congenital anomalies, specifically cardiac septal defects.

Ohlsson A, Walia R, Shah SS. **Ibuprofen for the treatment of patent ductus arteriosus** in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2010 Apr 14;4:CD003481. Ibuprofen is effective in closing a PDA. Ibuprofen is as effective as indomethacin in closing a PDA and reduces the risk of NEC and transient renal insufficiency.

Olsen Anne-Marie Schjerning, Fosbøl Emil L., Lindhardsen Jesper, et al. Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent **Myocardial Infarction** in Patients With Prior Myocardial Infarction: A Nationwide Cohort Study. Circulation published May 9, 2011, doi:10.1161/CIRCULATIONAHA.110.004671

Orchard J, Kountouris A. The management of **tennis elbow**. BMJ. 2011 May 10;342:d2687. doi: 10.1136/bmj.d2687.

Patel RA, Gallagher JC. **Drug Fever**. Pharmacotherapy. 2010 Jan;30(1):57-69.

Paul IM, Sturgis SA, Yang C, et al. Efficacy of standard doses of **Ibuprofen** alone, **alternating, and combined with acetaminophen** for the treatment of febrile children. Clin Ther. 2010 Dec;32(14):2433-40.

Pharmacist's Letter Oct 2006. Alternative or **Off-label** Routes of Drug Administration. (Oral administration of: N-acetylcysteine Mucomyst)

Pharmacist's Letter Oct 2006. **Cardiovascular Risks** of NSAIDs and Cox-2 Inhibitors.

Pharmacist's Letter. Can Individuals with **Aspirin Sensitivity Take NSAIDs**? Oct 2010.

Psaty BM and Potter JD. Risks and benefits of celecoxib to prevent recurrent **adenomas**. N Engl J Med 2006; 355:950-952.

Psaty BM, Weiss NS. NSAID trials and the **choice of comparators**--questions of public health importance. N Engl J Med. 2007 Jan 25;356(4):328-30.

Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic **paracetamol administration at time of vaccination** on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet. 2009 Oct 17;374(9698):1339-50.

Purssell E. Systematic review of studies comparing **combined treatment with paracetamol (acetaminophen) and ibuprofen**, with either drug alone. Arch Dis Child. 2011 Dec;96(12):1175-9.

Rebordosa C, Kogevinas M, Horváth-Puhó E,et al. **Acetaminophen use during pregnancy**: effects on risk for congenital abnormalities. Am J Obstet Gynecol. 2008 Feb;198(2):178.e1-7. Acetaminophen is not associated with an increased prevalence of congenital abnormalities overall or with any specific group of major abnormalities.

Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for Upper and Lower GI Events Associated With Traditional NSAIDs and Acetaminophen Among the Elderly in Quebec, Canada. Am J Gastroenterol. 2008 Apr;103(4):872-82. Epub 2008 Mar 26. Among elderly patients requiring analgesic/anti-inflammatory treatment, use of the combination of a **NSAID and acetaminophen may increase the risk of GI bleeding** compared with either agent alone.

Ray WA, Varas-Lorenzo C, Chung CP, et al. **Cardiovascular risks** of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes. 2009 May;2(3):155-63. Epub 2009 May 5. (**Naproxen** good CV safety)

Ringdahl E, Pandit S. **Treatment of Knee Osteoarthritis**. Am Fam Physician. 2011;83(11):1287-1292.

Risser A, Donovan D, Heintzman J et al. **NSAID Prescribing Precautions**. Am Fam Physician. 2009;80(12):1371–1378.

Roddy E, Zhang W, Doherty M. **Aerobic walking or strengthening exercise** for osteoarthritis of the knee? A systematic review. Ann Rheum Dis. 2005 Apr;64(4):544-8 & ACP Journal Club .

Ross Joseph S.; Madigan David; Hill Kevin P.; et al. Pooled Analysis of **Rofecoxib** Placebo-Controlled Clinical Trial Data: Lessons for Postmarket Pharmaceutical Safety Surveillance. Arch Intern Med. 2009;169(21):1976-1985.

Ross Joseph S.; Madigan David; Konstam Marvin A.; et al. Persistence of **Cardiovascular Risk After Rofecoxib Discontinuation**. Arch Intern Med. 2010;170(22):2035-2036.

Rostom A, et al; U.S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for **primary prevention of colorectal cancer**: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007 Mar 6;146(5):376-89. Review. Summary for patients in: Ann Intern Med. 2007 Mar 6;146(5):I35. Cyclooxygenase-2 inhibitors and NSAIDs reduce the incidence of colonic adenomas. Nonsteroidal anti-inflammatory drugs also reduce the incidence of CRC. However, these agents are associated with important cardiovascular events and gastrointestinal harms. The balance of benefits to risk does not favor chemoprevention in average-risk individuals. (InfoPOEMs: The US Preventive Services Task Force recommends against routine use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent colorectal cancer. The beneficial decrease in colorectal adenoma, cancer incidence, and possibly cancer-related mortality is more than offset by the harm associated with their use. Ulcers leading to gastrointestinal bleeding, renal impairment, and an increase in cardiovascular events are the main problems. (LOE = 1a))

Rostom A, Muir K, Dube C, Jolicoeur E, Boucher M, Joyce J, Tugwell P, Wells GW. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. Clin Gastroenterol Hepatol. 2007 Jul;5(7):818-28, 828.e1-5; quiz 768. Epub 2007Jun 6. **COX-2s appear to offer greater upper GI safety** and are better tolerated than nonselective NSAIDs. The co-administration of acetylsalicylic acid might reduce the safety advantage of COX-2s over that of nonselective NSAIDs.

Rostom A, Moayyedi P, Hunt R; CAG Consensus Group. **Canadian consensus guidelines** on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. Aliment Pharmacol Ther. **2009** Mar 1;29(5):481-96 {Recommendations based on personal opinion: *Low GI & low CV risk* ⇨ traditional NSAID; *low GI & high CV risk* ⇨ naproxen; *high GI & low CV risk* ⇨ COXIB plus PPI standard dose; *high GI & high CV risk* ⇨ careful assessment to priorize risks (consider alternatives) ; prescribe lowest dose for shortest time possible.}

Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of **aspirin on colorectal cancer** incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010 Oct 21.

Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily **aspirin on long-term risk of death due to cancer**: analysis of individualpatient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41.

Roumie CL, Mitchel EF Jr, Kaltenbach L, Arbogast PG, Gideon P, Griffin MR. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. Stroke. 2008 Jul;39(7):2037-45. Epub 2008 Apr 24. Our results indicate an increased risk of stroke with current use of two highly selective coxibs, rofecoxib and valdecoxib, also shown to increase cardiovascular risk. These results also provide some reassurance about other specific NSAIDs regarding stroke risk.

Samii A, Etminan M, Wiens MO, Jafari S. NSAID use and the risk of **Parkinson's disease**: systematic review and meta-analysis of observational studies. Drugs Aging. 2009;26(9):769-79.

Savino, Francesco, Lupica, Maria Maddalena, Tarasco, Valentina, et al. Fulminant **Hepatitis After 10 Days of Acetaminophen** Treatment at Recommended Dosage in an Infant. Pediatrics 2011 127: e494-e497.

Sawhney MS, McDougall H, Nelson DB, Bond JH. **Fecal Occult Blood Test** in Patients on Low-Dose Aspirin, Warfarin, Clopidogrel, or Non-steroidal Anti-inflammatory Drugs. Dig Dis Sci. 2010 Mar 3. [Epub ahead of print] Anticoagulants and antiplatelet medications lower the positive-predictive-value of FOBT for advance colonic neoplasia and should be stopped if clinically feasible prior to stool collection.

Sawitzke AD, Shi H, Finco MF, Dunlop DD, et al.. Clinical efficacy and safety of **glucosamine, chondroitin sulphate, their combination, celecoxib or placebo** taken to treat osteoarthritis of the knee: 2-year results from **GAIT**. Ann Rheum Dis. 2010 Jun 4.

Scharf HP, et al. Acupuncture and knee osteoarthritis: a three-armed randomized trial. Ann Intern Med. 2006 Jul 4;145(1):12-20. Compared with physiotherapy and as-needed anti-inflammatory drugs, addition of either TCA or sham acupuncture led to greater improvement in WOMAC score at 26 weeks.

TOP

OPIOID ANALGESIC: COMPARISON CHART

Extras:

- Buprenorphine Transdermal System (BuTrans Patch) Q&A – Aug 2010: http://www.rxfiles.ca/rxfiles/uploads/documents/BuTrans-QandA.pdf
- Fentanyl Nasal Spray (LAZANDA): available in USA, for cancer related breakthrough pain; 100ug/100mcL, 400ug/100mcL; time to onset =11 minutes; always start at 100ug spray, allow 2 hrs between doses, stepwise ↑ in dosage, max 4 doses in 24hrs.
- Fentanyl Sublingual Tablet (PALADIN, ProStrakan in USA): 100, 200, 300, 400, 600, 800 ug.
- Hydrocodone + Ibuprofen (REPREXAIN, VICOPROFEN, others): available in USA. (5/200, 7.5/200, 10/200 mg)
- Methadone injection (IV): available via special access program (SAP) in Canada
- Morphine + naltrexone (EMBEDA): available in USA; naltrexone added to ↓ abuse risk.
- Oxycodone: new products USA: (OXECTA), (ROXYCODONE)
- Oxycodone + Ibuprofen (COMBUNOX): available in USA. (5 / 400 mg)
- Oxymorphone (OPANA, OPANA ER): available in USA; IM, rectal, & recently oral; 3x more potent than oral morphine; avoid alcohol as ↑↑↑ peak concentrations. (IR tabs: 5,10mg; e.g 5mg q4-6h prn. ER tabs: 5, 7.5, 10,15,20,30, 40mg; e.g. 10mg q12h).
- Tapentadol (NUCYNTA): available in USA; weak mu agonist; ↑ noradrenalin (e.g. also known as norepinephrine); may have ↓ GI effects but similar CNS effects to other opioids. (50-75,100mg tabs e.g. 50mg q4-6h prn.)
- See also RxFiles Substance Abuse Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Substance-Abuse.pdf (sections: 4- Addiction screening; 5-Universal Precautions in Pain Medicine; 6-Red Flags for Aberrant Rx Drug Use)

Fentanyl Patches: "Attempting to give 1/2 patch"

The rate of medication delivery from Duragesic® patches is in proportion to the surface area of drug reservoir in contact with the skin. Prior to the availability of the 12.5 mcg/hr strength, the following procedure was occasionally used to achieve this rate:

1. An occlusive dressing like Opsite was put on the skin.
2. A 25 mcg/hr patch was then applied on top with half on the skin and half on the dressing.

This approach lacks documentation and can not be routinely recommended.

Fentanyl / Opioid Patch Exchange Tool: http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Patch-Exchange-Disposal-Tool.pdf

Opioid Intolerance:

- **Pseudoallergy** (**COMMON**! – may use non-opioid, lower opioid dose, alternate opioid even from same class, addition of H1 $_{\text{diphenhydramine}}$ +/- H2 $_{\text{ranitiidine}}$ blocker.
  - Flushing, itching, hives, sweating, and/or mild hypotension
  - Itching, flushing or hives at injection site only
- **Potential true opioid allergy** (**RARE**! - would require change to non-opioid or opioid from different chemical class – see below)
  - Severe hypotension
  - Skin reaction other than (Flushing, itching, hives)
  - Breathing, speaking, swallowing difficulties
  - Swelling of the face, lips, mouth, tongue, pharynx or larynx

Opioid Chemical Class

1. **Phenylpiperidines**: meperidine, fentanyl, sufentanil, remifentanil
2. **Diphenylheptanes**: methadone, propoxyphene
3. **Morphine group**: morphine, codeine, hydromorphone, nalbuphine, butorphanol, levorphanol, pentazocine

New Drugs {Not yet in Canada)

- **Oral Oxymorphone**
  i. (Opana, Opana ER): **Potency** is about 10x more potent than morphine! Caution!. [Immediate release: 5, 10mg tabs; Extended release; 5, 10, 20, 40 mg tabs]

Additional References & Links:

- **Canadian Opioids in CNCP Guidelines**: http://nationalpaincentre.mcmaster.ca/index.html
- **Responsible Physician Opioid Prescribing Resources (USA) Links:** http://www.responsibleopioidprescribing.org
- Health Canada – Company – Dosage Conversion Guidelines for Fentanyl; Revised Mar 2010: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2010/fentanyl_2_hpc-cps-eng.pdf
- **Opioid Manager Tool**: Point of care tool summarizing Canadian Guidelines:
  - **From CEP**: http://www.effectivepractice.org/index.cfm?pagePath=CEP_TOOLS/Opioid_Manager&id=23515
  - **From NPC:** http://nationalpaincentre.mcmaster.ca/opioidmanager/
- Tramadol warning (FDA): http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213264.htm

Treatment Agreements:

Medscape discussion on use in primary care. http://www.medscape.com/viewarticle/711659?src=mp&spon=30&uac=93517FV

Canadian Guideline sample at http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b05.html

RxFiles 1 page version at http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.pdf ; Customizable MS-Word versionhttp://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.doc

RxFiles 2 page version at: ♦customizable MS Word: http://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.docx ♦pdf: http://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.pdf

TOP

[1] Ballantyne JC, Mao J. Opioid Therapy for Chronic Pain. N Engl J Med. 2003 Nov 13;349(20):1943-1953.
[2] Micromedex 2010
[3] Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2008.
[4] Drugs in Pregnancy & Lactation 9th edition, 2011.
[5] Morrison, R. Sean, Meier, Diane E., Palliative Care. N Engl J Med 2004 350: 2582-2590.
[6] Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005 Mar 31;352(13):1324-34. (InfoPOEMs: The combination of gabapentin & morphine provides a small but clinically unimportant benefit over either drug alone. Tricyclic antidepressants have been shown in other studies to be as effective as gabapentin & much less expensive, but were not studied in this trial. (LOE = 1b))
[7] Health Canada Aug 2005 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_84_e.html (Long-Acting Opioids and a New Type of Alcohol Warning. Pharmacit's Letter. Dec 2005).
[8] Other Opioid Conversion (e.g. tramadol): http://databaseinnovationsdraft.com/OpioidConversionChart2007.pdf

Additional references:

Agthe AG, Kim GR, Mathias KB, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. Pediatrics. 2009 May;123(5): e849-56. Epub 2009 Apr 27.

Amato L, Minozzi S, Davoli M, Vecchi S, Ferri MM, Mayet S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD005031. Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, results at follow-up and compliance. Although a treatment, like detoxification, that exclusively attenuates the severity of opiate withdrawal symptoms can be at best partially effective for a chronic relapsing disorder like opiate dependence, this type of treatment is an essential step prior to longer-term drug-free treatment and it is desirable to develop adjunct psychosocial approaches that might make detoxification more effective.

Amato L, Minozzi S, Davoli M, et al. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database Syst Rev. 2011 Sep 7;9:CD005031. Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, participants abstinent at follow-up and clinical attendance.

Analgesic options for patients with allergic-type opioid reactions. Pharmacist's Letter/Prescriber's Letter 2006;22(2):220201.

Anand, Kanwaljeet J.S., Willson, Douglas F., Berger, John, et al., for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network, Tolerance and Withdrawal From Prolonged Opioid Use in Critically Ill Children. Pediatrics 2010 0: peds.2009-0489.

Ansermot Nicolas; Albayrak Ozgur; Schlapfer Jurg; et al. Substitution of (R,S)-Methadone by (R)-Methadone: Impact on QTc Interval. Arch Intern Med. 2010;170(6):529-536.

APS-Opioid Treatment Guidelines Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain Feb/09 http://download.journals.elsevierhealth.com/pdfs/journals/1526-5900/PIIS1526590008008316.pdf
(Chou R, Fanciullo GJ, Fine PG, et al. American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009 Feb;10(2):113-30.)

Australian Prescriber: Caution with Codeine: http://www.australianprescriber.com/magazine/34/5/133/5. { Codeine is a weak opioid analgesic. It has to be converted to morphine, but there is significant inter-individual variation in its pharmacokinetics which results in variable effectiveness. Codeine's efficacy in clinical trials is generally modest and while its adverse events are usually mild, serious adverse events, including death, have occurred. Tolerance and drug dependence can occur. There is a risk of toxicity especially if combination products containing codeine and other drugs are misused. Treatment with simple analgesics, or other opioids if required, provides a more predictable response.}

Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2007; 15: 957–65.

Babb, Malaika, Koren, Gideon, Einarson, Adrienne. Treating pain during pregnancy. Can Fam Physician 2010 56: 25-27.

Bohnert Amy S. B., Valenstein Marcia, Bair Matthew J., et al. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. JAMA. 2011;305(13): 1315-1321.doi:10.1001/jama.2011.370. (Opioid overdose is now the second most common cause of unintentional death in the US, after motor vehicle crashes, write two observers)

Braden Jennifer Brennan; Russo Joan; Fan Ming-Yu; et al. Emergency Department Visits Among Recipients of Chronic Opioid Therapy. Arch Intern Med. 2010;170(16):1425-1432.

Brands Bruna, Paglia-Boak Angela, Sproule Beth A., et al. Nonmedical use of opioid analgesics among Ontario students. Can Fam Physician 2010 56: 256 -262.

Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:x.ex-x.ex. PII: S0002-9378(10)02524-X doi:10.1016/j.ajog.2010.12.039.

Carise D, Dugosh KL, McLellan AT, et al. Prescription OxyContin Abuse Among Patients Entering Addiction Treatment. Am J Psychiatry. 2007 Nov;164(11):1750-6.

CDC June/10 About one fifth of US high school students reported ever having used prescription drugs not prescribed to them, such as OxyContin, Percocet, Vicodin, Adderall, Ritalin, and Xanax. The CDC reports the first assessment of such use within the National Youth Risk Behavior Survey. In addition, prescription drug abuse was more common among white than Hispanic or black students. The agency highlighted these findings from the 2009 survey in the context of an ongoing national trend toward higher rates of nonsuicide-related overdoses and deaths associated with prescription drug abuse. 2009 National Youth Risk Behavior Survey (Free PDF)CDC news release (Free)
2007 *MMWR* article on unintentional poisoning deaths (Free)

CDC: Centers for Disease Control and Prevention (CDC). Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. MMWR Morb Mortal Wkly Rep. 2010 Jun 18;59(23):705-9. This report describes the results of that review, which showed that the estimated number of ED visits for nonmedical use of opioid analgesics increased 111% during 2004-2008 (from 144,600 to 305,900 visits) and increased 29% during 2007-2008. The highest numbers of ED visits were recorded for oxycodone, hydrocodone, and methadone, all of which showed statistically significant increases during the 5-year period. The estimated number of ED visits involving nonmedical use of benzodiazepines increased 89% during 2004-2008 (from 143,500 to 271,700 visits) and 24% during 2007-2008.

CDC Grand Rounds: Prescription Drug Overdoses — a U.S. Epidemic.Weekly. January 13, 2012 / 61(01);10-13.This is another in a series of occasional MMWR reports titled CDC Grand Rounds. These reports are based on grand rounds presentations at CDC on high-profile issues in public health science, practice, and policy. *http://www.cdc.gov/about/grand-rounds*.

Chapman E, Leipsic J, Satkunam N, Churg A. Pulmonary alveolar proteinosis as a reaction to fentanyl patch smoke. Chest. 2012 May;141(5):1321-3.

Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009 Aug 20;361(8):827-8.

TOP

Clary PL, Lawson P. Pharmacologic Pearls for End-of-Life Care. Am Fam Physician. 2009 Jun 15;79(12):1059-65.
Cleary BJ, Donnelly JM, Strawbridge JD, et al. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol. 2010 Dec 7.
Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing. 2011 Jan;40(1):23-9.
Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010 Oct 26;341:c5475. doi: 10.1136/bmj.c5475.
Cupp M. Analgesics in pregnancy and lactation. Pharmacists Letter. February 2012.
Dhalla, Irfan A., Mamdani, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. CMAJ 2009 181: 891-896
Dhalla, Irfan A., Mamdani, Muhammad M., Gomes, Tara, et al. Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario. Can Fam Physician 2011 57: e92-96.
Dunn KM., Saunders KW., Rutter CM., et al. Opioid Prescriptions for Chronic Pain and Overdose: A Cohort Study. *Ann Intern Med* January 19, 2010 152:85-92.
Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005 Jun 22;293(24):3043-52. CONCLUSIONS: Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrate significant efficacy of opioids over placebo for neuropathic pain, which is likely to be clinically important. Reported adverse events of opioids are common but not life-threatening. Further RCTs are needed to establish their long-term efficacy, safety (including addiction potential), and effects on quality of life.
Ehret GB, et al. Drug-Induced Long QT Syndrome in Injection Drug Users Receiving Methadone: High Frequency in Hospitalized Patients and Risk Factors. Arch Intern Med. 2006 Jun 26;166(12):1280-7.
FDA July/09 notified healthcare professionals that it is taking several actions to reduce the risk of overdose in patients using pain medications that contain propoxyphene because of data linking propoxyphene and fatal overdoses. The agency will require manufacturers of propoxyphene-containing products to strengthen the label, including the boxed warning, emphasizing the potential for overdose when using these products and to provide a medication guide to patients stressing the importance of using the drugs as directed.
FDA Nov/10 is requesting that manufacturers of the painkiller propoxyphene pull the drug from the market because of concerns over cardiotoxicity. (Propoxyphene is marketed alone as Darvon and combined with acetaminophen as Darvocet.) The agency's request is based on data showing that, even when taken at therapeutic doses, the drug can lead to potentially dangerous changes in the heart's electrical activity, including prolonged PR and QT intervals and widened QRS complex. The FDA advises clinicians to stop prescribing propoxyphene and to ask current users to discontinue the drug. FDA's MedWatch alert (Free)
Feeney Colin, Ani Chizobam, Sharma Naini, et al. Morphine-Induced Cardiogenic Shock. Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1Q022. Ann Pharmacother ;45:e30.
Fiellin DA, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med. 2006 Jul 27;355(4):365-74. (InfoPOEMs: More intensive counseling and more frequent medication dispensing does not improve outcomes for treatment of opioid dependence in the primary care setting. (LOE = 1b))
Finkel JC, et al. Ketamine as an adjuvant for treatment of cancer pain in children and adolescents. J Pain. 2007 Jun;8(6):515-21. Epub 2007 Apr 16. In many children with advanced stages of cancer, pain control remains inadequate. We used subanesthetic doses of ketamine to treat 11 children & adolescents who were on high doses of opioids and had uncontrolled cancer pain. In the majority of patients, ketamine appeared to improve pain control and to have an opioid-sparing effect.
Fischer B, Rehm J. Deaths related to the use of prescription opioids. CMAJ. 2009 Dec 8;181(12):881-2. Epub 2009 Dec 7.
Foral PA, Malesker MA, Huerta G, Hilleman DE. Nebulized opioids use in COPD. Chest. 2004 Feb;125(2):691-4.
Fortuna RJ, Robbins BW, Caiola E, et al. Prescribing of Controlled Medications to Adolescents and Young Adults in the United States. Pediatrics. 2010 Nov 29.
Friday JH, Kanegaye JT, McCaslin I, Zheng A, Harley JR. Ibuprofen provides analgesia equivalent to acetaminophen-codeine in the treatment of acute pain in children with extremity injuries: a randomized clinical trial. Acad Emerg Med. 2009 Aug;16(8):711-6. Epub 2009 Jul 14. Acute pain relief from ibuprofen is equivalent to that of acetaminophen-codeine for children presenting to the emergency department with extremity injury. More than half the children in this study were consequently found to have fractures. (LOE = 1b)
Fulda GJ, Giberson F, Fagraeus L. A prospective randomized trial of nebulized morphine compared with patient-controlled analgesia morphine in the management of acute thoracic pain. J Trauma. 2005 Aug;59(2):383-8; discussion 389-90.
Furlan AD, Reardon R, Weppler C; National Opioid Use Guideline Group. Opioids for chronic noncancer pain: a new Canadian practice guideline. (NOUGG) CMAJ. 2010 Jun 15;182(9):923-30.
Part A Executive summary & background: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_a_v4_5.pdf
Part B Recommendations for practice: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf
Gallagher R. The use of opioids for dyspnea in advanced disease. CMAJ. 2011 Jul 12;183(10):1170.
Gana TJ, et al. The 023 Study Group. Extended-release tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. Curr Med Res Opin. 2006 Jul;22(7):1391-401.
Glatstein MM, Garcia-Bournissen F, Finkelstein Y, Koren G. Methadone exposure during lactation. Can Fam Physician. 2008 Dec;54(12):1689-90.
Gomes T, Juurlink DN, Dhalla IA, et al. Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Medicine 2011;5(1). www.openmedicine.ca/article/viewArticle/421/373 (Jan 24, 2011).
Gomes Tara; Mamdani Muhammad M.; Dhalla IA.; et al. Opioid Dose and Drug-Related Mortality in Patients With Nonmalignant Pain. *Arch Intern Med*. 2011;171(7):686-691.
Gowing L, et al. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD002022. Heavy sedation compared to light sedation does not confer additional benefits in terms of less severe withdrawal or increased rates of commencement on naltrexone maintenance treatment. Given that the adverse events are potentially life-threatening, the value of antagonist-induced withdrawal under heavy sedation or anaesthesia is not supported. The high cost of anaesthesia-based approaches, both in monetary terms and use of scarce intensive care resources, suggest that this form of treatment should not be pursued.
Gowing L, Farrell M, Ali R, et al. Alpha(2)-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD002024. Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone. No significant difference in efficacy was detected for treatment regimes based on clonidine or lofexidine, and those based on reducing doses of methadone over a period but methadone is associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.

TOP

Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD002025.
Grady Deborah; Berkowitz Seth; Katz Mitchell H.. Opioids for Chronic Pain. Arch Intern Med. 2011;0(2011):archinternmed.2011.213.
Green R, Bulloch B, Kabani A, Hancock BJ, Tenenbein M. Early analgesia for children with acute abdominal pain. Pediatrics. 2005 Oct;116(4):978-83. (InfoPOEMs: The immediate administration of morphine in children aged 5 years to 16 years with acute abdominal pain does not obscure the diagnosis of appendicitis and does not affect the surgeon's confidence in his or her diagnosis. It also causes a small decrease in pain. As with adults, pain relief should not be withheld in children until the cause of the pain is determined. (LOE = 2b))
Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008 Dec 10;300(22):2613-20. The majority of overdose deaths in West Virginia in 2006 were associated with nonmedical use and diversion of pharmaceuticals, primarily opioid analgesics.
Hawkins, Joy L. Epidural Analgesia for Labor and Delivery. N Engl J Med 2010 362: 1503-1510.
Hawton Keith, Bergen Helen, Simkin Sue, et al. Effect of withdrawal of co-proxamol (dextropropoxyphene & acetaminophen) on prescribing and deaths from drug poisoning in England and Wales: time series analysis. BMJ 2009;338:b2270, doi: 10.1136/bmj.b2270 (Published 18 June 2009)
Health Canada July/10 RELISTOR (methylnaltrexone bromide) Subcutaneous Injection - Association with gastrointestinal perforation - Wyeth Canada Patients with advanced illness being treated with RELISTOR may be at increased risk of gastrointestinal perforation.
Health Canada Nov/10 Darvon-N (dextropropoxyphene) - Recall and Withdrawal in Canada - Paladin Labs Inc. Paladin Labs Inc. in collaboration with Health Canada would like to inform healthcare professionals of the voluntary recall and withdrawal of the opioid analgesic Darvon-N (dextropropoxyphene) in Canada. (widen the QRS complex, prolong the QT interval and therefore increase the risk of serious abnormal heart rhythms.)
Hodgins David C, Stea Jonathan N, Grant Jon E. Gambling disorders. www.thelancet.com Published online May 19, 2011 DOI:10.1016/S0140-6736(10)62185-X
Holbrook TL et al. Morphine use after combat injury in Iraq and post-traumatic stress disorder. *N Engl J Med* 2010 Jan 14; 362:110.
Hudak ML, Tan RC et al. Neonatal Drug Withdrawal. Pediatrics. 2012 Jan 30.
Induru RR, Laman RL. Cancer Diagnosis and Management: Managing cancer pain: Frequently asked questions. Cleveland Clinic Journal of Medicine 2011; 78(7):449-464.
Jansson LM, Choo R, Velez ML, et al. et al. Methadone maintenance and breastfeeding in the neonatal period. Pediatrics. 2008 Jan;121(1):106-14. (n=8) Results contribute to the recommendation of breastfeeding for methadone-maintained women.
Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010 Dec 9;363(24):2320-31.
Kahan Meldon, Mailis-Gagnon Angela, Wilson Lynn, et al. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: Clinical summary for family physicians. Part 1: general population. Can Fam Physician November 2011 57: 1257-1266.
Kahan Meldon, Wilson Lynn, Mailis-Gagnon Angela, et al. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: Clinical summary for family physicians. Part 2: special populations. Can Fam Physician November 2011 57: 1269-1276.
Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran. BMJ 2012;344:e2502.
Kimber J, Copeland L, Hickman M, et al. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. BMJ. 2010 Jul 1;341:c3172. doi: 10.1136/bmj.c3172.
Kokki H, Lintula H, Vanamo K, et al. Oxycodone vs placebo in children with undifferentiated abdominal pain: a randomized, double-blind clinical trial of the effect of analgesia on diagnostic accuracy. Arch Pediatr Adolesc Med 2005;159:320-25. (InfoPOEMs: Giving analgesics to children with abdominal pain does not obscure the surgical diagnosis. We don't need to make kids suffer while waiting for a surgeon to evaluate their abdominal pain. (LOE = 2b))
Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet. 2006 Aug 19;368(9536):704.
Krantz MJ, Martin J, et al. QTc Interval Screening in Methadone Treatment. Ann Intern Med. 2009 Jan 19. [Epub ahead of print]
Krupitsky E, Nunes EV, Ling W, Illeperuma A, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet 2011; published online April 28. DOI:10.1016/S0140-6736(11)60358-9.
Lakha, S. Fatima, Yegneswaran, Balaji, Furlan JC, et al. Referring patients with chronic noncancer pain to pain clinics: Survey of Ontario family physicians. Can Fam Physician 2011 57: e106-112.
Lam J, Kelly L, Ciszkowski C, et al. Central Nervous System Depression of Neonates Breastfed by Mothers Receiving Oxycodone for Postpartum Analgesia. J Pediatr. 2011 Aug 31.
Ling Walter; Casadonte P; Bigelow G, et al. Buprenorphine Implants for Treatment of Opioid Dependence: A Randomized Controlled Trial. JAMA. 2010;304(14):1576-1583.
Lukasewycz S, Holman M, Kozlowski P, et al. Does a perioperative belladonna and opium suppository improve postoperative pain following robotic assisted laparoscopic radical prostatectomy? Results of a single institution randomized study. Can J Urol. 2010 Oct;17(5):5377-82.
Lynch M. A review of the use of methadone for the treatment of noncancer pain. Pain Res Manage 2005;10(3):133-44.
Madadi P, Moretti M, Djokanovic N, Bozzo P, et al. Guidelines for maternal codeine use during breastfeeding. Can Fam Physician. 2009 Nov;55(11):1077-8.
Madadi P, Koren G, et al. Safety of codeine during breastfeeding. Canadian Family Physician. Vol 53 Jan 2007 p33-35..
Mailis-Gagnon, Angela, Lakha, S. Fatima, Ou, Ting, et al. Chronic noncancer pain: Characteristics of patients prescribed opioids by community physicians and referred to a tertiary pain clinic. Can Fam Physician 2011 57: e97-105.
Manterola C, Astudillo P, Losada H, Pineda V, Sanhueza A, Vial M. Analgesia in patients with acute abdominal pain. In: Cochrane database of systematic reviews [database online]. Malden (MA): Wiley Interscience; 2009. Issue 2. Avail: http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005660/pdf_fs.html
Marsch LA, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. Arch Gen Psychiatry. 2005 Oct;62(10):1157-64.
Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD002207. Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is less effective than methadone delivered at adequate dosages.

TOP

McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. BMJ 2009;338:b2225, doi: 10.1136/bmj.b2225 (Published 17 June 2009)
MacDonald N, MacLeod SM. Has the time come to phase out codeine? CMAJ. 2010 Nov 23;182(17):1825.
Medical Letter: Treatment guidelines. Drugs for Pain April 2007.
Medical Letter. A Morphine/Naltrexone Combination (Embeda) for pain. Mar 22, 2010.
Methadone: a focus on safety. Pharmacist's Letter Sept 2006. (FDA Nov/06 warning http://www.fda.gov/cder/drug/InfoSheets/HCP/methadoneHCP.htm)
Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. J Pain. 2011 May;12(5):554-62.
Miller M, Sturmer T, Azrael D, et al. Opioid analgesics and the risk of fractures in older adults with arthritis. J Am Geriatr Soc. 2011 Mar;59(3):430-8.
Mora B, et al. Transcutaneous electrical nerve stimulation: an effective treatment for pain caused by renal colic in emergency care. J Urol. 2006 May;175(5):1737-41; discussion 1741. (InfoPOEMs: Local transcutaneous electrical nerve stimulation (TENS) is a rapid and effective nondrug treatment for pain caused by renal colic. TENS may be most useful in the difficult circumstance of out-of-hospital rescue. (LOE = 1b))
Nüesch E, Rutjes AW, Husni E, Welch V, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD003115. The small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. Non-tramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe.
Nicholson B. Morphine sulfate extended-release capsules (Kadian) for the treatment of chronic, moderate-to-severe pain. Expert Opin Pharmacother. 2008 Jun;9(9):1585-94.
Nicholson AB. Methadone for cancer pain. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003971.
Okie, Susan. A Flood of Opioids, a Rising Tide of Deaths. N Engl J Med 2010; 363:1981-1985
Oviedo-Joekes, Eugenia, Brissette, Suzanne, Marsh, David C., et al. Diacetylmorphine versus Methadone for the Treatment of Opioid Addiction. N Engl J Med 2009 361: 777-786
Papaleontiou M, Henderson CR Jr, Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2010 Jul;58(7):1353-69.
Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. Ann Pharmacother. 2007 Feb;41(2):255-66. Epub 2007 Feb 13. Review. Erratum in: Ann Pharmacother. 2007 Mar;41(3):531. Access online at: http://www.theannals.com/cgi/content/abstract/41/2/255
Patrick SW, Schumacher RE, Benneyworth BD, et al. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009 [published online April 30, 2012]. JAMA.
Pharmacist's Letter Oct 2006. Alternative or Off-label Routes of Drug Administration. (Rectal administration of: Ms Contin, OxyContin; Sublingual administration of: methadone, fentanyl & buprenorphine; Inhalational use of morphine, hydromorphone & fentanyl)
Pharmacist's Letter Suboxone (buprenorphine / naloxone 2/0.5mg & 8/2mg sl tabs) Dec 2007.
Pharmacist's Letter. Onsolis (Fentanyl Buccal Film) and BuTrans (Buprenorphine Patch). Aug 2010.
Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. Drugs. 2010 Sep 10;70(13):1657-75. doi: 10.2165/11537940-000000000-00000.
Rakhman Evgeny, Shmain Dmitri, White Ian, et al. Repeated and Escalating Preoperative Subanesthetic Doses of Ketamine for Postoperative Pain Control in Patients Undergoing Tumor Resection: A Randomized, Placebo-Controlled, Double-Blind Trial, Clinical Therapeutics, In Press, Corrected Proof, Available online 1 July 2011
Ranji SR, Goldman LE, Simel DL, Shojania KG. Do opiates affect the clinical evaluation of patients with acute abdominal pain? JAMA. 2006 Oct 11;296(14):1764-74. (InfoPOEMs: Opiate analgesia for adults and children presenting with acute abdominal pain may alter the physical examination, but does not increase the risk of management errors. Since most patients prefer pain control, it makes sense to abandon the outdated and incorrect practice of withholding opiate analgesia from patients with acute abdominal pain. (LOE = 1a))
Reddy RG, Aung T, Karavitaki N, Wass JA. Opioid induced hypogonadism. BMJ. 2010 Aug 31;341:c4462. doi: 10.1136/bmj.c4462.
Reid CM, et al. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Apr 24;166(8):837-43.
Ringdahl E, Pandit S. Treatment of Knee Osteoarthritis. Am Fam Physician. 2011;83(11):1287-1292.
Safdar B, et al. Intravenous morphine plus ketorolac is superior to either drug alone for treatment of acute renal colic. Ann Emerg Med. 2006 Aug;48(2):173-81, 181.e1. (InfoPOEMs: Intravenous morphine 5 mg combined with ketorolac (Toradol) 15 mg provided greater pain relief than either drug alone. The combination did not increase the likelihood of nausea or vomiting. (LOE = 1b))
Schneider JP, Matthews M, Jamison RN. Abuse-deterrent and tamper-resistant opioid formulations: what is their role in addressing prescription opioid abuse? CNS Drugs. 2010 Oct 1;24(10):805-10. doi: 10.2165/11584260-000000000-00000.
Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim methadone maintenance. Arch Gen Psychiatry. 2006 Jan;63(1):102-9.
Seal KH, Shi Y, Cohen G et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA. 2012 Mar 7;307(9):940-7.
See also RxFiles Newsletter – Fall, 2005 - Opioids in Chronic Non-Malignant Pain Troubleshooting Drug Therapy Issues www.RxFiles.ca
Sharek PJ, McClead RE Jr, Taketomo C, et al. An intervention to decrease narcotic-related adverse drug events in children's hospitals. Pediatrics. 2008 Oct;122(4):e861-6.
Shiran MR, Lennard MS, Iqbal MZ, et al.et al. Contribution of the activities of CYP3A, CYP2D6, CYP1A2 and other potential covariates to the disposition of methadone in patients undergoing methadone maintenance treatment. Br J Clin Pharmacol. 2009 Jan;67(1):29-37. CYP3A activity has a modest influence on methadone disposition. Inhibitors and inducers of this enzyme should be monitored in patients taking methadone.
Shirk MB, Donahue KR, Shirvani J. Unlabeled uses of nebulized medications. Am J Health Syst Pharm. 2006 Sep 15;63(18):1704-16.
Sinha M, et al. Evaluation of nonpharmacologic methods of pain and anxiety management for laceration repair in the pediatric emergency department. Pediatrics. 2006 Apr;117(4):1162-8.
Smith J, Owen E, Earis J, Woodcock A. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006 Apr;117(4):831-5. Epub 2006 Feb 7.
Solomon Daniel H.; Rassen Jeremy A.; Glynn Robert J.; et al. The Comparative Safety of Analgesics in Older Adults With Arthritis. Arch Intern Med. 2010;170(22):1968-1978. The comparative safety of analgesics varies depending on the safety event studied. Opioid use exhibits an increased relative risk of many safety events compared with nsNSAIDs.

TOP

Solomon Daniel H.; Rassen Jeremy A.; Glynn RJ.; et al. The Comparative Safety of Opioids for Nonmalignant Pain in Older Adults. Arch Intern Med. 2010;170(22):1979-1986.
Sproule B, Brands B, Li S, Catz-Biro L. Changing patterns in opioid addiction: characterizing users of oxycodone and other opioids. Can Fam Physician. 2009 Jan;55(1):68-9, 69.e1-5.
Srivastava A, Kahan M. Buprenorphine: a potential new treatment option for opioid dependence. CMAJ;2006;174(13). http://www.cmaj.ca/cgi/content/full/174/13/1835
Standridge JB, Adams SM, Zotos AP. Urine drug screening: a valuable office procedure. Am Fam Physician. 2010 Mar 1;81(5):635-40.
Starrels JL., Becker WC., Alford DP., et al. Systematic Review: Treatment Agreements and Urine Drug Testing to Reduce Opioid Misuse in Patients With Chronic Pain. *Ann Intern Med* June 1, 2010 152:712-720; doi:10.1059/0003-4819-152-11-201006010-00004
Strang John, Hall Wayne, Hickman Matt, et al Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland. BMJ 341:doi:10.1136/bmj.c4851 (Published 16 September 2010)
Taddio A, et al. Intravenous morphine and topical tetracaine for treatment of pain in preterm neonates undergoing central line placement.JAMA. 2006 Feb 15;295(7):793-800.
Tapentadol-Nucynta-A New Analgesic. Medical Letter Aug 10, 2009.
Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. 2008 May 29;358(22):2332-43. Subcutaneous methylnaltrexone rapidly induced laxation in patients with advanced illness and opioid-induced constipation. Treatment did not appear to affect central analgesia or precipitate opioid withdrawal. {InfoPOEMs Aug2008: Methylnaltrexone (Relistor) is effective for the treatment of opioid-induced constipation in hospice patients. However, long-term safety is not known, so it should not be widely used for nonterminally ill patients until longer studies have been performed. (LOE = 1b)}
Treatment Guidelines from the Medical Letter. Pharmaceutical Drug Overdose. Sept 2006. (Opiates: naloxone treatment)
Van den Brink W, Haasen C. Evidenced-based treatment of opioid-dependent patients. Can J Psychiatry. 2006 Sep;51(10):635-46.
Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. Ann Intern Med. 2011 Sep 6;155(5):325-8.
Wahawisan Joy, Kolluru Srikanth, Nguyen Tu, et al. Methadone Toxicity Due to Smoking Cessation—A Case Report on the Drug-Drug Interaction Involving Cytochrome P450 Isoenzyme 1A2. Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1P759. Ann Pharmacother ;45:e34.
Wenghofer, Elizabeth Francis, Wilson, Lynn, Kahan, Meldon, et al. Survey of Ontario primary care physicians' experiences with opioid prescribing. Can Fam Physician 2011 57: 324-332.
Whitley H, Lindsey W. Sex-based differences in drug activity. Am Fam Physician. 2009 Dec 1;80(11):1254-8.
Whittle SL, Richards BL, Husni E, et al. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev. 2011 Nov 9;11:CD003113. There is limited evidence that weak oral opioids may be effective analgesics for some patients with RA, but adverse effects are common and may offset the benefits of this class of medications.
Wilson JF. Strategies to stop abuse of prescribed opioid drugs. Ann Intern Med. 2007 Jun 19;146(12):897-900.
Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA. 2008 Nov 5;300(17):2003-11. Continuing treatment with buprenorphine-naloxone improved outcome compared with short-term detoxification. Further research is necessary to assess the efficacy and safety of longer-term treatment with buprenorphine for young individuals with opioid dependence.

TOP

Additional references:

Adams Denise, Cheng Florence, Jou Hsing, et al. The Safety of Pediatric Acupuncture: A Systematic Review. Pediatrics 2011; peds.2011-1091; November 21, 2011

Atkinson Paul, Chesters Adam,Heinz Peter. Pain management and sedation for children in the emergency department. BMJ 2009;339:b4234, doi: 10.1136/bmj.b4234

Axelin A, Salantera S, Kirjavainen J, et al. Oral glucose and parental holding preferable to opioid in pain management in preterm infants. Clin J Pain. 2009 Feb;25:138-45. Our study demonstrated that "facilitated tucking by parents" is not just equal, but preferable to other pain management methods when both efficacy and safety are considered.

Babl FE, Goldfinch C, et al. Does nebulized lidocaine reduce the pain and distress of nasogastric tube insertion in young children? A randomized, double-blind, placebo-controlled trial. Pediatrics. 2009 Jun;123(6):1548-55. Nasogastric tube insertion results in very high FLACC scores irrespective of lidocaine use. Nebulized lidocaine cannot be recommended as pain relief for nasogastric tube insertion in children. The delay and distress of nebulization likely outweigh a possible benefit in the postinsertion period.

Biran V, Gourrier E, et al. Analgesic Effects of EMLA Cream and Oral Sucrose During Venipuncture in Preterm Infants. Pediatrics. 2011 Jul;128(1):e63-70.

Brummelte S, Grunau RE, Chau V, et al Procedural pain and brain development in premature newborns. Ann Neurol. 2012 Feb 28.

Bueno M, Stevens B, et al. Breast Milk and Glucose 25% for Pain Relief in Preterm Infants: A Noninferiority Randomized Controlled Trial. Pediatrics. 2012 Mar 5.

Bulloch B et al. Reliability of the color analog scale: Repeatability of scores in traumatic and nontraumatic injuries. Acad Emerg Med 2009 May; 16:465.

Carbajal R, Rousset A, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA. 2008 Jul 2;300(1):60-70. During neonatal intensive care in the Paris region, large numbers of painful and stressful procedures were performed, the majority of which were not accompanied by analgesia.

Chermont, Aurimery Gomes, Falcao, Luis Fabio Magno, et al. Skin-to-Skin Contact and/or Oral 25% Dextrose for Procedural Pain Relief for Term Newborn Infants. Pediatrics 2009 124: e1101-e1107.

Cignacco EL, Sellam G, et al. Oral Sucrose and "Facilitated Tucking" for Repeated Pain Relief in Preterms: A Randomized Controlled Trial. Pediatrics. 2012 Jan 9.

Cobb JE, Cohen LL. A randomized controlled trial of the ShotBlocker for children`s immunization distress. Clin J Pain. 2009 Nov-Dec;25(9):790-6. (Data not support effectiveness)

Codipietro L, et al. Breastfeeding or oral sucrose solution in term neonates receiving heel lance: a randomized, controlled trial. Pediatrics. 2008 Sep;122(3):e716-21. This study suggests that breastfeeding provides superior analgesia for heel lance compared with oral sucrose in term neonates.

de Sousa Freire NB, et al. Evaluation of analgesic effect of skin-to-skin contact compared to oral glucose in preterm neonates. Pain. 2008 Sep 30;139(1):28-33.

Dilli D, Küçük IZ, Dallar Y. Interventions to Reduce Pain during Vaccination in Infancy. J Pediatr. 2008 Oct 10.

Drendel AL, Lyon R, Bergholte J, et al. Outpatient pediatric pain management practices for fractures. Pediatr Emerg Care. 2006 Feb;22(2):94-9. Most children with fractures have the "worst" pain in the first 48 hours after injury and used analgesia for 3 days after injury. There are noteworthy functional limitations for both children and their caregivers. Ibuprofen and acetaminophen with codeine are the analgesics most commonly used, with no clear superiority.

Drendel AL, Gorelick MH, Weisman SJ, et al. A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. Ann Emerg Med. 2009 Oct;54(4):553-60.

Ekbom K, Kalman S, Jakobsson J, Marcus C. Efficient Intravenous Access Without Distress: A Double-blind Randomized Study of Midazolam and Nitrous Oxide in Children and Adolescents. Arch Pediatr Adolesc Med. 2011 Sep;165(9):785-91.

Eidelman A, Weiss JM, Baldwin CL, et al. Topical anaesthetics for repair of dermal laceration. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD005364. DOI: 10.1002/14651858.CD005364.pub2. Based on mostly descriptive analysis, topical anaesthetics are possibly an efficacious, non-invasive means of providing analgesia prior to suturing of dermal lacerations.

Falagas ME, Vouloumanou EK, Plessa E, et al. Inaccuracies in dosing drugs with teaspoons and tablespoons. Int J Clin Pract. 2010 Aug;64(9):1185-9.

FDA Jan/09 An public health advisory reminds patients and physicians of potentially serious side effects from the improper use of topical anesthetics, including lidocaine, tetracaine, benzocaine, and prilocaine. The latest advisory was prompted by a small study that tested whether lidocaine reduced discomfort during breast mammography. No serious adverse events were noted. However, the FDA remains concerned about the potential for seizures, irregular heartbeat, and breathing problems when topical anesthetics are applied over a large area or are covered by plastic wrap or a heating pad. Two deaths were previously reported in women using the anesthetics before laser hair removal.

Fortier, Michelle A., MacLaren, Jill E., Martin, Sarah R., et al. Pediatric Pain After Ambulatory Surgery: Where's the Medication? Pediatrics 2009 124: e588-e595.

Franck LS, Oulton K, Nderitu S, et al. Parent Involvement in Pain Management for NICU Infants: A Randomized Controlled Trial. Pediatrics. 2011 Aug 22.

Harrington JW, Logan S, Harwell C, et al. Effective Analgesia Using Physical Interventions for Infant Immunizations. Pediatrics. 2012 Apr 16.

Hay AD, Redmond NM, Costelloe C, et al. Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial. Health Technol Assess. 2009 May;13(27):iii-iv, ix-x, 1-163. Young children who are unwell with fever should be treated with ibuprofen first, but the relative risks (inadvertently exceeding the maximum recommended dose) and benefits (extra 2.5 hours without fever) of using paracetamol plus ibuprofen over 24 hours should be considered.

Harrison D, Stevens B, et al. Efficacy of sweet solutions for analgesia in infants between 1 and 12 months of age: a systematic review. Arch Dis Child. 2010 May 12.

Health Canada Apr/12 is informing Canadians that it has requested companies to add new risk statements to the packaging and labelling of licensed benzocaine products. In April 2011, Health Canada reminded Canadians of certain health risks associated with benzocaine products, including a very rare but serious blood condition known as methemoglobinemia that can affect sensitive individuals.

Hogan ME et al. Systematic review and meta-analysis of the effect of warming local anesthetics on injection pain. Ann Emerg Med 2011 Jul; 58:86.

Holsti, Liisa, Grunau, Ruth E. Considerations for Using Sucrose to Reduce Procedural Pain in Preterm Infants. Pediatrics 2010 125: 1042-1047.

Jalota Leena, Kalira Vicki, George Elizabeth, et a. l on behalf of the Perioperative Clinical Research Core. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ 342:doi:10.1136/bmj.d1110 (15 Mar 2011)

Klein EJ, Brown JC, Kobayashi A, et al. A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. Ann Emerg Med. 2011 Oct;58(4):323-9.

Nabulsi M. Is combining or alternating antipyretic therapy more beneficial than monotherapy for febrile children? BMJ. 2009Oct 1;339:b3540. doi: 10.1136/bmj.b3540.

Pillai Riddell RR, Racine NM, Turcotte K, et al. Non-pharmacological management of infant and young child procedural pain.Cochrane Database Syst Rev. 2011 Oct 5;10:CD006275. There is evidence that different non-pharmacological interventions can be used with preterms, neonates, and older infants to significantly manage pain behaviors associated with acutely painful procedures.

Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic paracetamol/acetaminophen administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet. 2009 Oct 17;374(9698):1339-50.

Reinoso-Barbero F, Pascual-Pascual SI, de Lucas R, et al. Equimolar Nitrous Oxide/Oxygen Versus Placebo for Procedural Pain in Children: A Randomized Trial. Pediatrics 2011;127:e1464-70.

Savino, Francesco, Lupica, Maria Maddalena, Tarasco, Valentina, et al. Fulminant Hepatitis After 10 Days of Acetaminophen Treatment at Recommended Dosage in an Infant. Pediatrics 2011 127: e494-e497.

Schechter NL, Bernstein BA, Zempsky WT, Bright NS, Willard AK. Educational Outreach to Reduce Immunization Pain in Office Settings. Pediatrics. 2010 Nov 15.

Simonse E, Mulder PG, et al. Analgesic Effect of Breast Milk Versus Sucrose for Analgesia During Heel Lance in Late Preterm Infants. Pediatrics. 2012 Mar 5.

Slater R, Cornelissen L, Fabrizi L, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. Lancet. 2010 Sep 1.

Stevens, Bonnie J., Abbott, Laura K., Yamada, Janet, et al. Epidemiology and management of painful procedures in children in Canadian hospitals. CMAJ 2011 0: cmaj.101341

Taddio A, Shah V, Katz J. Reduced infant response to a routine care procedure after sucrose analgesia. Pediatrics. 2009 Mar;123(3):e425-9.

Taddio A, Shah V, Hancock R, et al. Effectiveness of sucrose analgesia in newborns undergoing painful medical procedures. CMAJ. 2008 Jul 1;179(1):37-43.

Taddio, A, Appleton, M, et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline (summary). CMAJ 2010 0: cmaj.092048.

Taddio, A, Appleton, M, Bortolussi, R, et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline. CMAJ 2010 0: cmaj.101720

Taddio, Anna, Shah, Vibhuti, Stephens, Derek, et al. Effect of Liposomal Lidocaine and Sucrose Alone and in Combination for Venipuncture Pain in Newborns. Pediatrics 2011 0: peds.2010-2914

Thyr M, Sundholm A, Teeland L, et al. Oral glucose as an analgesic to reduce infant distress following immunization at the age of 3, 5 and 12 months. Acta Paediatr 2007;96(2):233-6.

Tomlinson D, von Baeyer CL, Stinson JN, Sung L. A Systematic Review of Faces Scales for the Self-report of Pain Intensity in Children. Pediatrics. 2010 Oct 4.

van Tilburg MA, et al. Audio-Recorded Guided Imagery Treatment Reduces Functional Abdominal Pain in Children: A Pilot Study. Pediatrics. 2009 Oct 12.

Weissman, Amir, Aranovitch, Michal, Blazer, Shraga, Zimmer, Etan Z. Heel-Lancing in Newborns: Behavioral and Spectral Analysis Assessment of Pain Control Methods. Pediatrics 2009 124: e921-e926.

Zempsky WT, et al. Needle-free powder lidocaine delivery system provides rapid effective analgesia for venipuncture or cannulation pain in children: randomized, double-blind Comparison of Venipuncture and Venous Cannulation Pain After Fast-Onset Needle-Free Powder Lidocaine or Placebo Treatment trial. Pediatrics. 2008 May;121(5):979-87. The needle-free powder lidocaine delivery system was well tolerated and produced significant analgesia within 1 to 3 minutes.

TOP

References: Osteoporosis Treatment Chart

[1] E-cps, accessed online Jan 11, 2011

[2] Reid RL, Blake J, Abramson B, et al. **SOGC** (Society of Obstetricians and Gynaecologists of **Canada**)-Menopause and Osteoporosis Update 2009. JOGC. 2009;222:S34-S45. http://www.sogc.org/guidelines/documents/Menopause_JOGC-Jan_09.pdf

Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of **glucocorticoid-induced Osteoporosis** (GIO). Arthritis Care Res (Hoboken). 2010 Jul 26.

Papaioannou, Alexandra, Morin, Suzanne, Cheung, Angela M., et al. **2010 clinical practice guidelines** for the diagnosis and management of osteoporosis in **Canada**: summary CMAJ 2010 0: cmaj.100771.

Leslie WD, Berger C, Langsetmo L, et al. Construction and validation of a simplified fracture risk assessment tool for Canadian women and men: results from the CaMos and Manitoba BMD cohorts. Osteoporos Int. (**CAROC** 2010) In press.

Treatment Guidelines-Medical Letter: **Drugs for Postmenopausal Osteoporosis**. Nov 2011.

[3] Sweet MG, Sweet JM, Jeremiah MP, et al. **Diagnosis and Treatment of Osteoporosis**. Am Fam Physician. **2009**;79(3):193-202.

[4] Simonelli C, Clarke B, Cohan D, et al. Diagnosis and Treatment of Osteoporosis. Institute for Clinical systems improvement. 2006(5):1-64 (**ICSI**: http://www.icsi.org/)

[5] **NAMS**: Management of **osteoporosis in postmenopausal women**: 2010 position statement of The North American Menopause Society. Menopause. **2010** Jan-Feb;17(1):25-54. http://www.menopause.org/PSosteo10.pdf

[6] Bell KJ, Hayen A, Macaskill P, et al. Value of routine monitoring of **bone mineral density** after starting bisphosphonate treatment: secondary analysis of trial data. BMJ. 2009 Jun 23;338:b2266. doi: 10.1136/bmj.b2266. Monitoring bone mineral density in postmenopausal women in the first three years after starting treatment with a potent bisphosphonate is unnecessary and may be misleading. Routine monitoring should be avoided in this early period after bisphosphonate treatment is commenced.

Korownyk, Christina, Allan, G. Michael, Kolber, Michael R. **Bone mineral density testing**: Too much of a good thing? Can Fam Physician 2010 56: 1299.

[7] Siminoski K, Leslie WD, Frame H, et al. Canadian Association of Radiologists. Recommendations for **bone mineral density** reporting in **Canada**. Can Assoc Radiol J. 2005 Jun;56(3):178-88.

[8] Lim LS, Hoeksema LJ, Sherin K; **ACPM** Prevention Practice Committee. **Screening** for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. Am J Prev Med. 2009 Apr;36(4):366-75.

Trombetti Andrea; Hars Melany; Herrmann Francois R.; et al. Effect of Music-Based Multitask Training on Gait, Balance, and **Fall Risk** in Elderly People: A Randomized Controlled Trial. Arch Intern Med. 2010;0(2010):archinternmed.2010.446.

Haines Terry P.; Hill Anne-Marie; Hill Keith D.; et al. Patient Education to **Prevent Falls** Among Older Hospital Inpatients: A Randomized Controlled Trial. Arch Intern Med. 2010;0(2010):archinternmed.2010.444.

Papaioannou, Alexandra, Morin, Suzanne, Cheung, Angela M., et al. **2010 clinical practice guidelines** for the diagnosis and management of osteoporosis in **Canada**: summary CMAJ 2010 0: cmaj.100771.

Michael Yvonne L., Whitlock Evelyn P., Lin Jennifer S., et al. Primary Care–Relevant Interventions to **Prevent Falling** in Older Adults: A Systematic Evidence Review for the U.S. Preventive Services Task Force (USPSTF). Ann Intern Med Dec 21, 2010 153:815-825.

Thomas S, Mackintosh S, Halbert J. Does the `**Otago exercise programme**` reduce mortality and falls in older adults?: a systematic review and meta-analysis. Age Ageing. 2010 Nov;39(6):681-7.

Panel on Prevention of Falls in Older Persons, **American Geriatrics Society (AGS)** and British Geriatrics Society. Summary of Updated American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for **Prevention of Falls in Older Persons**. Article first published online: 13 JAN 2011 DOI: 10.1111/j.1532-5415.2010.03234.x http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2010.03234.x/pdf

National Institute for Clinical Excellence. Falls: the assessment and prevention of falls in older people. (Clinical guideline 21.) 2004. http://guidance.nice.org.uk/CG21 .

Haines Terry P.; Hill Anne-Marie; Hill Keith D.; et al. Patient Education to Prevent Falls Among Older Hospital Inpatients: A Randomized Controlled Trial. Arch Intern Med. 2011;171(6):516-524.

Spink MJ, Menz HB, Fotoohabadi MR, Wee E, Landorf KB, Hill KD, et al. Effectiveness of a multifaceted **podiatry intervention** to prevent falls in community dwelling older people with disabling foot pain: randomised controlled trial. BMJ 2011;342:d3411.

[9] Black DM, Schwartz AV, Ensrud KE, et al. FLEX Research Group. Effects of continuing or **stopping alendronate** after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (**FLEX**): a randomized trial. JAMA. 2006 Dec 27;296(24):2927-38.

Schwartz AV, Bauer DC, Cummings SR, et al. FLEX Research Group. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. J Bone Miner Res. 2010 May;25(5):976-82.

Ott SM. What is the optimal duration of bisphosphonate therapy? Cleve Clin J Med. 2011 Sep;78(9):619-30. (If bone density stable or improved and no fractures after 5yrs of bisphosphonate tx, consider checking urinary N-telopeptide cross-linked type 1 collagen–NTx, if NTx < 40 nmol bone collagen equivalent per mmol creatinine, stop bisphosphonate & monitor NTx yearly)

(FLEX: Only significant fracture rate difference was in the group with T scores below -2.5 who did not have a vertebral fracture at the outset of the trial.)

TOP

[10] Bone HG, Hosking D, Devogelaer JP, et al. Alendronate Phase III Osteoporosis Treatment Study Group. **Ten years' experience** with **alendronate** for osteoporosis in postmenopausal women. N Engl J Med. 2004 Mar 18;350(12):1189-99.
[11] Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X, Grauer A. Fracture risk remains reduced **one year after discontinuation** of risedronate. Osteoporos Int. 2008 Mar;19(3):365-72. Epub 2007 Oct 16.
[12] Khan AA, Sándor GK, Dore E, et al. **Canadian** Taskforce on Osteonecrosis of the Jaw. Bisphosphonate associated **osteonecrosis** of the **jaw**. J Rheumatol.2009Mar;36(3):478-90.
[13] Khan AA, Sándor GK, Dore E, et al. **Canadian** Association of Oral and Maxillofacial Surgeons. Canadian consensus practice guidelines for bisphosphonate associated **osteonecrosis of the jaw**. J Rheumatol. 2008 Jul;35(7):1391-7.
Fellows JL, Rindal DB, Barasch A, et al. **ONJ in Two Dental Practice-Based** Research Network Regions. J Dent Res. 2011 Feb 11.
Barasch A, Cunha-Cruz J, Curro FA, et al. Risk factors for osteonecrosis of the jaws: a case-control study from the CONDOR dental PBRN. J Dent Res. 2011 Apr;90(4):439-44.
[14] Ruggiero SL, Dodson TB, Assael LA, et al.; **American** Association of Oral and Maxillofacial Surgeons. (**AAOMS**-American Association of Oral and Maxillofacial Surgeons position paper on **bisphosphonate-related osteonecrosis of the jaws--2009** update. J Oral Maxillofac Surg. 2009 May;67(5 Suppl):2-12.
http://www.aaoms.org/docs/position_papers/bronj_update.pdf
Canadian Adverse Reaction Newsletter. **Fluticasone propionate and osteonecrosis**. April 2011.
Baillargeon J, Kuo YF, Lin YL, Wilkinson GS, Goodwin JS. Osteonecrosis of the Jaw in Older Osteoporosis Patients Treated with Intravenous Bisphosphonates (October). Ann Pharmacother. 2011 Sep 27.
Hellstein JW, Adler RA, Edwards B, et al, the American Dental Association (**ADA**) Council on Scientific Affairs Expert Panel on Antiresorptive Agents, "Managing the Care of Patients Receiving Antiresorptive Therapy for Prevention and Treatment of Osteoporosis: Recommendations from the American Dental Association Council on Scientific Affairs."http://www.ada.org/sections/professionalResources/pdfs/topics_ARONJ_report.pdf Accessed Nov 25, 2011.
Hellstein JW, Adler RA, Edwards B, et al, "Managing the Care of Patients Receiving Antiresorptive Therapy for Prevention and Treatment of Osteoporosis," Executive Summary of Recommendations from the American Dental Association (**ADA**) Council on Scientific Affairs, J Am Dent Assoc, 2011, 142(11):1243-51.
[15] Lenart BA et al. Association of **low-energy femoral fractures** with prolonged bisphosphonate use: A case control study. Osteoporos Int 2009 Aug; 20:1353.
Capeci CM, Tejwani NC. Bilateral **low-energy** simultaneous or sequential **femoral fractures** in patients on long-term alendronate therapy. *J Bone Joint Surg Am* 2009Nov; 91:2556.
Ing-Lorenzini K, Desmeules J, Plachta O, et al. **Low-energy femoral fractures** associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital. Drug Saf. 2009;32(9):775-85.
Vasikaran SD. Association of **low-energy femoral fractures** with prolonged bisphosphonate use: a case--control study. Osteoporos Int. 2009 Aug;20(8):1457-8.
Abrahamsen B, Eiken P, Eastell R. **Subtrochanteric and diaphyseal femur fractures** in patients treated with **alendronate**: a register-based national cohort study. J Bone Miner Res 2009; 24:1095-102.
Nieves JW, Bilezikian JP, Lane JM, et al. Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int 2009;21:399-408.
Black, Dennis M., Kelly, Michael P., Genant, Harry K., et al. the Fracture Intervention Trial (**FIT, FLEX**) and **HORIZON** Pivotal Fracture Trial Steering Committees, Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur. N Engl J Med 2010 0: NEJMoa1001086. (N=12 fractures were subtrochanteric or diaphyseal femur in 14,195 women; a rate of 2.3 per 10,000 pt-yrs).
Giusti A, Hamdy NA, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy. A systematic review of case/case series studies. Bone. 2010 May 19.
Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. N Engl J Med. 2010 May 13;362(19):1848-9.
Shane E, Burr D, Ebeling PR, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research. (ASBMR) J Bone Miner Res. 2010 Sep 14. . http://www.jbmr.org/details/journalArticle/843323/Atypical_subtrochanteric_and_diaphyseal_femoral_fractures_Report_of_a_task_force.html
Sellmeyer Deborah E. **Atypical Fractures** as a Potential Complication of Long-term Bisphosphonate Therapy. *JAMA*. 2010;304(13):1480-1484.
Park-Wyllie LY, Mamdani MM, Juurlink DN, et al. Bisphosphonate use and the risk of **subtrochanteric or femoral shaft fractures** in older women. JAMA. 2011 Feb 23;305(8):783-9.
Schilcher J et al. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 2011 May 5; 364:1728.
Meier RP, Perneger TV, Stern R, et al. Increasing Occurrence of Atypical Femoral Fractures Associated With Bisphosphonate UseAtypical Femoral Fractures and Bisphosphonate Use. Arch Intern Med. 2012 Jun 25;172(12):930-6.
[16] Black DM, Delmas PD, Eastell R, et al., for the **HORIZON** Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22.
Bhuriya R, Singh M, Molnar J, Arora R, et al. Bisphosphonate use in women and the risk of atrial **fibrillation**: A systematic review and meta-analysis. Int J Cardiol. 2010 Jan 3.
Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident **atrial fibrillation** in women. Arch Intern Med. 2008 Apr 28;168(8):826-31.
Loke YK, Jeevanantham V, Singh S. Bisphosphonates and **atrial fibrillation**: systematic review and meta-analysis. Drug Saf. 2009;32(3):219-28.
Wilkinson GS, Baillargeon J, Kuo YF, et al. **Atrial fibrillation** and stroke associated with intravenous bisphosphonate therapy in older patients with cancer. J Clin Oncol. 2010 Nov 20;28(33):4898-905.

TOP

[17] Wysowski DK. Reports of **esophageal cancer** with oral bisphosphonate use. N Engl J Med. 2009 Jan 1;360(1):89-90.
Cardwell CR.; Abnet CC.; Cantwell MM.; et al. Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer. JAMA. 2010;304(6):657-663.
Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010 Sep 1;341:c4444. doi:10.1136/bmj.c4444. The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe and North America, the incidence of oesophageal cancer at age 60-79 is **typically 1 per 1000** population **over five years, and this is estimated to increase to about 2 per 1000 with five years' use** of oral bisphosphonates.
FDA July/11 notified healthcare professionals and patients about its ongoing review of data from published studies to evaluate whether use of oral bisphosphonate drugs is associated with an increased risk of cancer of the esophagus. FDA has not concluded that taking an oral bisphosphonate drug increases the risk of esophageal cancer. There are insufficient data to recommend endoscopic screening of asymptomatic patients.
[18] Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fractures Intervention Trial Research Group. Lancet. 1996;348(9041):1535-41. (**FIT**)
[19] Wells GA, Cranney A, Peterson J et al. **Alendronate** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001155.
[20] Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fractures Intervention Trial Research Group. Lancet. 1996;348(9041):1535-41. (**FIT**)
Cummings SR, Black DM, Thompson DE, et al. Effect of **alendronate** on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. (**FIT**)JAMA 1998; 280(24):2077-82.
[21] McClung MR, Geusens P, Miller PD, et al., for the Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med. 2001;344(5):333-340. (**HIP**)
[22] Wells G, Cranney A, Peterson J, et al. **Risedronate** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004523.
[23] Heaney RP, Zizec tM, Fogelman I, et al. Risedronate reduces the fisk of first vertebral fracture in osteoporotic women. Osteoporos Int. 2002;13(6):501-5.
[24] Harris, ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. JAMA. 1999;282:1344-52. (**VERT**)
[25] Black DM, Delmas PD, Eastell R, et al., for the **HORIZON** Pivotal Fracture Trial (PFT). Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22.
[26] Black DM, Delmas PD, Eastell R, et al., for the **HORIZON** Pivotal Fracture Trial (PFT). Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22.
Lyles KW, Colón-Emeric CS, Magaziner JS, et al. **HORIZON** Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality **after hip fracture**. N Engl J Med. 2007 Nov 1;357(18):1799-809. Epub 2007 Sep 17.
[27] Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women.[update of Cochrane Database Syst Rev. 2001;(4):CD003376; PMID: 11687195]. [Review] [85 refs]
[28] Barrett-Connor E, Mosca L, Collins P, et al.; Raloxifene Use for The Heart (**RUTH**) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006 Jul 13;355(2):125-37.
[29] Ettinger B, black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical tiral. Multiple Outcomes of Raloxifene Evaluation (**MORE**) Investigators. JAMA. 1999;282(7):637-45.
[30] Vogel VG, Constantino JP, Wickerham DI, et al. National Surgical Adjuvant Breast and Bowel Project. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (**STAR**) P-2 trial. JAMA 2006;295:2727-41. Epub 2006 Jun 5.
[31] Chestnut CH III, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. **PROOF** Study Group. Am J Med. 2000;109(4):267-76.
[32] Neer RM, arnaud Cd, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434-41.
[33] Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669-83. (**WHI**)
Manson JE, Allison MA, Carr JJ, et al. for the Women's Health Initiative and Women's Health Initiative-Coronary Artery Calcium Study Investigators. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause. 2010 Jun 14.
Warensjö Eva, Byberg Liisa, Melhus Håkan, et al. **Dietary calcium intake** and risk of fracture and osteoporosis: prospective longitudinal cohort study. BMJ 2011;342:doi:10.1136/bmj.d1473 (Published 24 May 2011)
[34] Avenell a, Gillespie WJ, Gillespie LD et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database of Systematic Reviews. (2):CD000227, 2009

TOP

[35] Bischoff-Ferrari HA, willett WC, Wong JB, et a. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293(18):2257-64.
Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009 Mar 23;169(6):551-61.
Bischoff-Ferrari HA, Willett WC, Oray EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012;367:40-9. {highest actual-intake quartile (792 to 2000 IU daily), there was a 30% reduction in hip fracture incidence}

[36] Brown JP, Joss RG. **2002 clinical practice guidelines** for the diagnosis and management of osteoporosis in **Canada**. CMAJ 2002;167(10 suppl):S1-34.
Brown JP, Fortier M, Frame H, et al. **Canadian** consensus conference on osteoporosis, **2006 update**. J Obstet Gynaecol Can. 2006 Feb;28(2 Suppl 1):S95-S112.
Hanley DA, Cranney A, Jones G, et al. **Vitamin D** in adult health & disease: a review and guideline statement from **Osteoporosis Canada**–summary.CMAJ 2010 0: cmaj.091062.
Kalyani RR, Stein B, Valiyil R, et al. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. J Am Geriatr Soc. 2010 Jul;58(7):1299-310. Epub 2010 Jun 23. Vitamin D treatment effectively reduces the risk of falls in older adults. Future studies should investigate whether particular populations or treatment regimens may have greater benefit.
Manson JE. Vitamin D and the heart: Why we need large-scale clinical trials (**VITAL**). Cleveland Clinic Journal of Medicine 2010; 77(12):903-910.

[37] Avenell a, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database of Systematic Reviews. (2):CD000227, 2009.
Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral **vitamin D** and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009 Mar 23;169(6):551-61.

[38] Canadian Cancer Society http://www.cancer.ca/Canada-wide/About%20us/Media%20centre/CW-Media%20releases/CW-2006/Canadian%20Cancer%20Society%20comments%20on%20key%20findings%20from%20UV%20%20Vitamin%20D%20and%20Health%20Conference.aspx?sc_lang=en
Hanley DA, Cranney A, Jones G, et al. **Vitamin D** in adult health & disease: a review and guideline statement from **Osteoporosis Canada**–summary.CMAJ 2010 0: cmaj.091062.
Vitamin D supplementation: Recommendations for Canadian mothers and infants. Paediatr Child Health 2007;12(7):583-9. Reference No. FNIM07-01. http://www.cps.ca/english/statements/ii/fnim07-01.htm
IOM (Institute of Medicine): Dietary Reference Intakes for **Calcium and Vitamin D** Nov,2010. http://www.iom.edu/~/media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf
Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the u.s. Preventive services task force (USPSTF). Ann Intern Med. 2010 Dec 21;153(12):815-25.
Zhu K, Austin N, Devine A, et al. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. J Am Geriatr Soc. 2010 Nov;58(11):2063-8. doi: 10.1111/j.1532-5415.2010.03142.x.
Manson JE. Vitamin D and the heart: Why we need large-scale clinical trials (**VITAL**). Cleveland Clinic Journal of Medicine 2010; 77(12):903-910.
Rosen Clifford J. **Vitamin D Insufficiency**. N Engl J Med 2011; 364:248-254.
Bosomworth, N.J. Mitigating epidemic vitamin D deficiency: The agony of evidence. Can Fam Physician 2011 57: 16-20.
Winzenberg Tania, Powell Sandi, Shaw Kelly Anne, et al. Effects of vitamin D supplementation on bone density in healthy **children**: systematic review and meta-analysis. BMJ 2011;342:doi:10.1136/bmj.c7254 (Published 25 January 2011).
Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D3 and/or calcium (**RECORD** trial). J Clin Endocrinol Metab 2011; DOI:10.1210jc.2011-1309.

[39] Cauley JA, Robbins J, Chen Z, et al. for the Women's Health Initiative Investigators. Effects of **estrogen plus progestin** on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290(13):1729-38. (**WHI**)
Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine **estrogen** in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291(14):1701-1712.
Toh Sengwee, Hernández-Díaz Sonia, Logan Roger, Et al. Coronary Heart Disease in Postmenopausal Recipients of Estrogen Plus Progestin Therapy: Does the Increased Risk Ever Disappear?: A Randomized Trial. (**WHI**) Ann Intern Med February 16, 2010.

Additional articles:

AAOS- Guideline on the Treatment of Symptomatic Osteoporotic Spinal Compression Fractures- **Vertebroplasty** 2010 Recommendations (Calcitonin for 4 weeks post acute injury) http://www.aaos.org/Research/guidelines/SCFsummary.pdf

Abrahamsen B, Eiken P, Eastell R. **Subtrochanteric and diaphyseal femur fractures** in patients treated with **alendronate**: a register-based national cohort study. J Bone Miner Res 2009; 24:1095-102.

TOP

Abrahamsen B. **Bisphosphonate adverse effects**, lessons from large databases. Curr Opin Rheumatol. 2010 Jul;22(4):404-9.
Abrahamsen B. **Adverse effects of bisphosphonates**. Calcif Tissue Int. 2010 Jun;86(6):421-35. Epub 2010 Apr 21.
Abrahamsen Bo; Eiken Pia; Eastell Richard. **Proton Pump Inhibitor Use** and the Antifracture Efficacy of Alendronate. Arch Intern Med. 2011;0(2011):archinternmed.2011.20.
Abou-Setta AM, Beaupre LA, Rashiq S, et al. Comparative effectiveness of pain management interventions for **hip fracture:** a systematic review. Ann Intern Med. 2011 Aug 16;155(4):234-45.
ACCORD Schwartz AV, Margolis KL, Sellmeyer DE, et al. Intensive Glycemic Control Is Not Associated With **Fractures or Falls** in the ACCORD Randomized Trial. Diabetes Care. 2012 Jul;35(7):1525-31.
Adachi JD, Bensen WG, Brown J., et al. Intermittent **etidronate** therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 1997; 337:382-8.
Alibhai SM, Duong-Hua M, et al. Impact of **androgen deprivation therapy** on cardiovascular disease and diabetes. J Clin Oncol. 2009 Jul 20;27(21):3452-8. Epub 2009 Jun 8.
Alonso-Coello P, García-Franco AL, Guyatt G, Moynihan R. Drugs for **pre-osteoporosis**: prevention or disease mongering? BMJ. 2008 Jan 19;336(7636):126-9.
American Association of Oral and Maxillofacial Surgeons-**AAOMS** Position Paper on **Bisphosphonate-Related Osteonecrosis of the Jaw**—2009 Update http://www.aaoms.org/docs/position_papers/bronj_update.pdf
Anastassios G. Pittas, Mei Chung, Thomas Trikalinos, Et al. Systematic Review: **Vitamin D and Cardiometabolic Outcomes**. Ann Intern Med March 2, 2010 152:307-314; doi:10.1059/0003-4819-152-5-201003020-00009.
Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine **estrogen** in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291(14):1701-1712.
Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. **Vitamin D** and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD000227.
Bacon CJ, Gamble GD, Horne AM, Scott MA, Reid IR. **High-dose oral vitamin D(3) supplementation** in the elderly. Osteoporos Int. 2008 Dec 20.
Banks E, Beral V, Reeves G, et al., for the **Million Women Study** Collaborators. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. JAMA 2004;291:2212-2220.
Barrett-Connor E, Grady D, Sashegyi A, et al. **Raloxifene** and cardiovascular events in osteoporotic postmenopausal women: four-year results from the **MORE** (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 2002; 287(7):847- 857.
Barrett-Connor E, Mosca L, Collins P, et al. Effects of **raloxifene** on cardiovascular events and breast cancer in postmenopausal women. (**RUTH**)N Engl J Med 2006; 355(2):125-137.
Barrett-Connor Elizabeth, Nielson Carrie M, Orwoll Eric, et al., for the Osteoporotic Fractures in Men (MrOS) Study Group. Epidemiology of **rib fractures in older men**: Osteoporotic Fractures in Men (MrOS) prospective cohort study. BMJ 2010;340:c1069, doi: 10.1136/bmj.c1069 (Published 15 March 2010).
Bashutski JD, Eber RM, Kinney JS, et al. **Teriparatide and Osseous Regeneration** in the Oral Cavity. N Engl J Med. 2010 Oct 16. (n=40, 6 weeks, 1yr follow up)
Bazelier MT, van Staa T-P, Uitdehaag BMJ, et al. Risk of **fractures** in patients with **multiple sclerosis**: a population based cohort study. Neurology 2012;78:1967–1973.
BC Guideline: Medical Services Commission. **Vitamin D testing protocol**. British Columbia Medical Services Commission; 2010 Oct 1. http://www.bcguidelines.ca/pdf/vitamind.pdf
Bell KJ, Hayen A, Macaskill P, et al. Value of routine monitoring of **bone mineral density** after starting bisphosphonate treatment: secondary analysis of trial data. BMJ. 2009 Jun 23;338:b2266. doi: 10.1136/bmj.b2266.
Berger C, Langsetmo L, Joseph L, et al.; Canadian Multicentre Osteoporosis Study Research Group. Change in **bone mineral density** as a function of age in women and men and association with the use of antiresorptive agents. CMAJ. 2008 Jun 17;178(13):1660-8. The extent of bone loss that we observed in both sexes indicates that, in the absence of additional risk factors or therapy, repeat testing of bone mineral density to diagnose osteoporosis could be delayed to every 5 years.
Bhasin S, et al. **Testosterone therapy** in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006 Jun;91(6):1995-2010. Epub 2006 May 23. Erratum in: J Clin Endocrinol Metab. 2006 Jul;91(7):2688.
Bhuriya R, Singh M, Molnar J, Arora R, et al. Bisphosphonate use in women and the risk of atrial **fibrillation**: A systematic review and meta-analysis. Int J Cardiol. 2010 Jan 3.
Bingham CO 3rd, Buckland-Wright JC, Garnero P, et al. **Risedronate** decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment **osteoarthritis** of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum 2006; 54: 3494–507.
Binkley N et al. Evaluation of **ergocalciferol or cholecalciferol** dosing, 1600 IU daily or 50,000 IU monthly in older adults. *J Clin Endocrinol Metab* 2011 Apr; 96:981.
Bischoff-Ferrari H A, Dawson-Hughes B, Staehelin H B, et al. **Fall prevention** with supplemental and active forms of **vitamin D**: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692, doi: 10.1136/bmj.b3692 (Published 1 October 2009)
Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral **vitamin D** and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009 Mar 23;169(6):551-61.
Bischoff-Ferrari Heike A.; Dawson-Hughes Bess; Platz Andreas; et al. Effect of **High-Dosage Cholecalciferol** (2000 vs 800 IU/day) and Extended Physiotherapy on Complications After Hip Fracture: A Randomized Controlled Trial. Arch Intern Med. 2010;170(9):813-820.
Bischoff-Ferrari HA, Willett WC, Oray EJ, et al. A pooled analysis of **vitamin D dose** requirements for fracture prevention. N Engl J Med 2012;367:40-9. {highest actu

TOP

quartile (792 to 2000 IU daily), there was a 30% reduction in hip fracture incidence}

Bjelakovic G, Gluud LL, Nikolova D, et al. **Vitamin D** supplementation for **prevention of mortality in adults**. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD007470. DOI: 10.1002/14651858.CD007470.pub2. Vitamin D in the form of vitamin D3 seems to decrease mortality in predominantly elderly women who are mainly in institutions and dependent care. Vitamin D2, alfacalcidol, and calcitriol had no statistically significant effect on mortality. Vitamin D3 combined with calcium significantly increased nephrolithiasis. Both alfacalcidol and calcitriol significantly increased hypercalcaemia.

Black DM, Schwartz AV, Ensrud KE, et al. FLEX Research Group. Effects of continuing or **stopping alendronate** after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (**FLEX**): a randomized trial. JAMA. 2006 Dec 27;296(24):2927-38.

Black DM, Reid IR, Boonen S, et al. The effect of **3 versus 6 years of zoledronic acid** treatment in osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2012;27:243-54.

Black DM, Bauer DC, Schwartz AV, et al. **Continuing Bisphosphonate Treatment for Osteoporosis** - For Whom and for How Long? N Engl J Med. 2012 May 9.

Blau LA, Hoehns JD. Analgesic efficacy of **calcitonin** for vertebral fracture pain. Ann Pharmacother 2003; 37(4):564-570.

Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of Osteoporosis Treatment on **Mortality**: A Meta-Analysis. J Clin Endocrinol Metab. 2010 Jan 15.

Bolland MJ, Avenell A, Baron JA, et al, Effect of **calcium** supplements on risk of **myocardial infarction** and cardiovascular events: meta-analysis. BMJ 2010;341:c3691

Bone HG, Hosking D, Devogelaer JP, et al. Alendronate Phase III Osteoporosis Treatment Study Group. **Ten years' experience** with **alendronate** for osteoporosis in postmenopausal women. N Engl J Med. 2004 Mar 18;350(12):1189-99.

Boonen S, Sellmeyer DE, Lippuner K, et al. **Renal safety of annual zoledronic** acid infusions in osteoporotic postmenopausal women. Kidney Int 2008; 74(5):641-648.

Bordelon P, Ghetu MV, Langan RC. Recognition and management of **vitamin D deficiency**. Am Fam Physician. 2009 Oct 15;80(8):841-6.

Boucher M, Murphy G, Coyle D, et al. **Bisphosphonates and teriparatide** for the prevention of osteoporotic fractures in postmenopausal women [Technology overview no 22]. 22. 2006. Ottawa, Canadian Agency for Drugs and Technologies in Health.

Bridgeman MB, Pathak R. **Denosumab** for the reduction of bone loss in postmenopausal osteoporosis: a review. Clin Ther. 2011 Nov;33(11):1547-59.

Briggs GE, Freeman RK, Yaffe SJ, editors. **Drugs in Pregnancy and Lactation**. 9th ed. Williams and Wilkins; Philadelphia, PA: 2011

Briot Karine, Legrand Erik, Pouchain Denis, et al. Accuracy of patient-reported **height loss** and risk factors for height loss among postmenopausal women. CMAJ 2010 0: cmaj.090710.

Brufsky AM, Harker WG, Beck JT, et al. Final 5-year results of **Z-FAST** trial: **Adjuvant Zoledronic** Acid Maintains Bone Mass in Postmenopausal **Breast Cancer** Patients Receiving Letrozole. Cancer. 2011 Oct 10.

Buchbinder R, Osborne RH, Ebeling, PR., et al. A Randomized Trial of **Vertebroplasty** for Painful Osteoporotic Vertebral Fractures. N Engl J Med 2009 361: 557-568.

Buppasiri P, Lumbiganon P, Thinkhamrop J, et al. **Calcium supplementation** (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD007079. DOI: 10.1002/14651858.CD007079.pub2. Calcium supplementation is associated with a significant protective benefit in the prevention of **pre-eclampsia**, and should be used for this indication according to a previous review. This review indicates that there are no additional benefits for calcium supplementation in prevention of preterm birth or low infant birth weight.

Cadarette SM, Katz JN, Brookhart MA, Sturmer T, Stedman MR, Solomon DH. **Relative effectiveness** of osteoporosis drugs for preventing nonvertebral fracture. Ann Intern Med 2008; 148(9):637-646.

Cameron ID, Murray GR, Gillespie LD, et al. Interventions for **preventing falls** in older people in nursing care facilities and hospitals. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD005465. There is evidence that multifactorial interventions reduce falls and risk of falling in hospitals and may do so in nursing care facilities. Vitamin D supplementation is effective in reducing the rate of falls in nursing care facilities. Exercise in subacute hospital settings appears effective but its effectiveness in nursing care facilities remains uncertain.

Capeci CM and Tejwani NC. Bilateral **low-energy** simultaneous or sequential **femoral fractures** in patients on long-term alendronate therapy. *J Bone Joint Surg Am* 2009 Nov; 91:2556.

Cauley JA, Lacroix AZ, Wu L, et al. Serum **25-hydroxyvitamin D** concentrations and risk for hip fractures. Ann Intern Med. 2008 Aug 19;149(4):242-50.

Cazanave C, Dupon M, Lavignolle-Aurillac V, et al. Groupe d'Epidémiologie Clinique du SIDA en Aquitaine. Reduced bone mineral density in **HIV**-infected patients: prevalence and associated factors. AIDS. 2008 Jan 30;22(3):395-402.

Chen CH et al. Alendronate in the **prevention of collapse of the femoral head in non-traumatic osteonecrosis** (a randomized, multicenter, double-blind study). Arthritis Rheum. 2011 Nov 29. (no effect)

Cheung AM, Tile l, Cardew S, et al. **Bone density and structure** in healthy postmenopausal women treated with **exemestane** for the primary prevention of breast cancer: a nested substudy of the MAP.3 randomised controlled trial. Lancet Oncol 2012; online February 7.

Chilibeck PD, Vatanparast H, Cornish SM, Abeysekara S, Charlesworth S. Evidencebased risk assessment and recommendations for **physical activity**: arthritis, osteoporosis, and low back pain. *Appl Physiol Nutr Metab* 2011;36(Suppl 1):S49-S79.

Chlebowski RT, Chen Z, Cauley JA, et al. Oral **Bisphosphonate Use and Breast Cancer Incidence** in Postmenopausal Women. J Clin Oncol. 2010 Jun 21.

Christmas C. Hip fracture. Ann Intern Med. 2011 Dec 6;155(11):ITC61.

Chung M, Lee J, Terasawa T, et al. **Vitamin D With or Without Calcium** Supplementation for Prevention of Cancer and **Fractures**: An Updated Meta-analysis for the U.S. Preventive Services Task Force (USPSTF). Ann Intern Med. 2011 Dec 20;155(12):827-38.

Coco M. Treating the **renal patient** who has a fracture: opinion vs evidence. Cleve Clin J Med. 2009 Dec;76(12):684-8.

Coleman RE, Marshall H, Cameron D, et al. **AZURE** Investigators. **Breast-cancer adjuvant therapy** with **zoledronic acid**. N Engl J Med. 2011 Oct 13;365(15):1396-4

TOP

Collier J. Bone disorders in **chronic liver disease**. HEPATOLOGY 2007;46: 1271-1278.
Collins Gary S, Mallett Susan, Altman Douglas G. Predicting risk of osteoporotic and hip fracture in the United Kingdom: prospective independent and external validation of **QfractureScores**. BMJ 2011;342:doi:10.1136/bmj.d3651 (Published 22 June 2011)
Cosman F, Nieves JW, Zion M, et al. Retreatment with **teriparatide** one year after the first teriparatide course in patients on continued long-term alendronate. J Bone Miner Res. 2009 Jun;24(6):1110-5.
Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, et al.. Daily and cyclic **parathyroid hormone** in women receiving alendronate. N Engl J Med. 2005 Aug 11;353(6):566-75.
Cummings SR, Black DM, Thompson DE, et al. Effect of **alendronate** on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. (**FIT**) JAMA 1998; 280(24):2077-82.
Cummings SR, Eckert S, Krueger KA, et al. The effect of **raloxifene** on risk of breast cancer in postmenopausal women: results from the **MORE** randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281(23):2189-2197.
Cummings SR, San Martin J, McClung MR, et al.; **FREEDOM** Trial. **Denosumab** for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009 Aug 20;361(8):756-65.
Cummings SR, Ettinger B, Delmas PD, et al. **LIFT** Trial Investigators. The effects of **tibolone** in older postmenopausal women. N Engl J Med. 2008 Aug 14;359(7):697-708.
Cummings SR. A 55-year-old woman with **osteopenia**. JAMA. 2006 Dec 6;296(21):2601-10.
Cummings SR, Eastell R, Ensrud K, et al. The effects of **lasofoxifene** on fractures and breast cancer: 3-year results from the PEARL trial. J Bone Miner Res 2008;23 (Suppl 1):S81.
Cummings SR et al. **Lasofoxifene** in postmenopausal women with osteoporosis. (**PEARL**) N Engl J Med 2010 Feb 25; 362:686.
Curtis JR, Carbone L, Cheng H, et al. **Longitudinal trends in use of bone mass measurement** among older Americans, 1999-2005. J Bone Miner Res. 2008;23:1061-7.
Dalhousie CME Academic Detailing Service. **Osteoporosis in 2009**. Dalhousie CME Academic Detailing Service. http://cme.medicine.dal.ca/files/AD_Osteo_2009.pdf
de Villiers TJ, Chines AA, Palacios S, et al. Safety and tolerability of **bazedoxifene** in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. Osteoporos Int. 2010 Jun 10.
Digiovanna JJ. Fracturing support for the role of systemic **retinoid therapy** as a cause of bone demineralization. Arch Dermatol. 2010 May;146(5):551-3.
DIPART (**Vitamin D** Individual Patient Analysis of Randomized Trials) Group.Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010 Jan 12;340:b5463. doi:10.1136/bmj.b5463. This individual patient data analysis indicates that vitamin D given alone in doses of 10-20 microg is not effective in preventing fractures. By contrast, calcium and vitamin D given together reduce hip fractures and total fractures, and probably vertebral fractures, irrespective of age, sex, or previous fractures.
Dore RK. How to prevent glucocorticoid-induced osteoporosis (GIO). Cleve Clin J Med. 2010 Aug;77(8):529-36.
Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. **Thiazolidinediones** and fractures in men and women. Arch Intern Med. 2009 Aug 10;169(15):1395-402.
Durie BG, Katz M, Crowley J. **Osteonecrosis of the jaws** and bisphosphonates. N Engl J Med 2005;353:99-102.
Dykes Patricia C.; Carroll Diane L.; Hurley Ann; et al. **Fall Prevention** in Acute Care Hospitals: A Randomized Trial. *JAMA*. 2010;304(17):1912-1918. (**Tool kit**)
Ebeling PR. Clinical practice. **Osteoporosis in men**. N Engl J Med. 2008 Apr 3;358(14):1474-82.
Edwards BJ, Song J, Dunlop DD, et al. Functional decline after incident **wrist fractures**--Study of Osteoporotic Fractures: prospective cohort study. BMJ. 2010 Jul 8.
Ensrud Kristine E.; Lui Li-Yung; Taylor Brent C.; et al. for the Study of Osteoporotic Fractures Research Group A Comparison of Prediction Models for Fractures in Older Women: Is More Better? (**FRAX**) Arch Intern Med. 2009;169(22):2087-2094. Simple models based on age and BMD alone or age and fracture history alone predicted 10-year risk of hip, major osteoporotic, and clinical fracture as well as more complex FRAX models.
Ensrud K, Lacroix A, Thompson JR, et al. **Lasofoxifene** and Cardiovascular Events in Postmenopausal Women With Osteoporosis: Five-Year Results From the Postmenopausal Evaluation and Risk Reduction With Lasofoxifene (**PEARL**) Trial. Circulation. 2010 Oct 26;122(17):1716-24. Epub 2010 Oct 11.
Ensrud KE, Schousboe JT. Clinical practice. **Vertebral fractures**. N Engl J Med. 2011 Apr 28;364(17):1634-42.
Etminan M, Forooghian F, Maberley D. Inflammatory **ocular adverse events with the use of oral bisphosphonates**: a retrospective cohort study. CMAJ. 2012 Apr 2.
Favus Murray J., **Bisphosphonates for Osteoporosis**. N Engl J Med 2010; 363:2027-2035.
FDA Oct/10 **Atypical subtrochanteric femur fractures** are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% of all hip and femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.
FDA Nov/10 has approved **denosumab** (marketed as **Xgeva**) for the prevention of fracture and bone pain in patients with cancer that has metastasized to the bone. FDA news release (Free) Xgeva prescribing information (Free PDF)
FDA July/11 notified healthcare professionals and patients about its ongoing review of data from published studies to evaluate whether use of **oral bisphosphonate** drugs is associated with an **increased risk of cancer of the esophagus**. FDA has not concluded that taking an oral bisphosphonate drug increases the risk of esophageal cancer. There are insufficient data to recommend endoscopic screening of asymptomatic patients.
FDA Sep/11 notified healthcare professionals and patients of an update to the drug label for **Reclast (zoledronic acid)** regarding the risk of kidney failure. Cases of acute renal failure requiring dialysis or having a fatal outcome following Reclast use have been reported to FDA. The revised label states that Reclast is contraindicated in

TOP

with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment.
FDA. Bisphosphonate Treatment for Osteoporosis- Background document for meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. Sept 2011 http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM270958.pdf
Ferrari S, Bianchi ML, Eisman JA, et al. For the **IOF** Committee of Scientific Advisors Working Group on Osteoporosis Pathophysiology. **Osteoporosis in young adults**: pathophysiology, diagnosis, and management. Osteoporos Int. 2012 Jun 9.
Feskanich D, Willett W, Colditz G. **Walking** and leisure-time activity and risk of hip fracture in postmenopausal women. JAMA 2002; 288(18):2300-2306.
Finkelstein JS, Wyland JJ, Lee H, et al. Effects of **Teriparatide, Alendronate, or Both** in Women with Postmenopausal Osteoporosis. J Clin Endocrinol Metab. 2010 Feb 17.
Fizazi K, Carducci M, Smith M, et al. **Denosumab versus zoledronic** acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011 Feb 24.
Fraunfelder, Frederick W., Fraunfelder, Frederick T. **Bisphosphonates and Ocular Inflammation**. N Engl J Med 2003 348: 1187-1188.
Frick KD, Kung JY, Parrish JM, et al. Evaluating the cost-effectiveness of **fall prevention programs** that reduce fall-related hip fractures in older adults. J Am Geriatr Soc. 2010 Jan;58(1):136-41. Of single interventions studied, management of psychotropics and tai chi reduces costs the most.
Ftouh Saoussen, Morga Antonia, Swift Cameron. Guidelines: Management of **hip fracture** in adults: summary of **NICE** guidance. BMJ 2011;342:doi:10.1136/bmj.d3304 June/11
Fung V, Kendler D. **Preventing fractures** in postmenopausal women: how to **assess risk**. CMAJ. 2011 Dec 13;183(18):2129-31.
Gallagher JC, Levine JP. Preventing osteoporosis in **symptomatic postmenopausal women**. Menopause. 2010 Aug 5.
Gerber Y, Melton LJ, Weston SA, et al. Association between **myocardial infarction and fractures**. An emerging phenomenon. Circulation 2011;
Gillespie WJ, Gillespie LD, Parker MJ. **Hip protectors for preventing hip fractures** in older people. Cochrane Database Syst Rev. 2010 Oct 6;10:CD001255. The effectiveness of the provision of hip protectors in reducing the incidence of hip fracture in older people is still not clearly established, although they may reduce the rate of hip fractures if made available to frail older people in nursing care.
Gimsing P, Carlson K, Turesson I, et al. Effect of **pamidronate 30 mg** versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. Lancet Oncol. 2010 Oct;11(10):973-82.
Goldstein SR, Neven P, Cummings S, et al. Postmenopausal Evaluation and Risk Reduction With Lasofoxifene (Pearl): 5-yr gynecological outcomes. Menopause. 2010 Aug 3.
Gnant M, Mlineritsch B, Schippinger W, et al. **ABCSG-12** Trial Investigators, Marth C. Endocrine therapy plus **zoledronic** acid in premenopausal breast cancer. N Engl J Med. 2009 Feb 12;360(7):679-91.
Gnant M, Mlineritsch B, Stoeger H, et al. on behalf of the Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the **ABCSG-12** randomised trial. Lancet Oncol. 2011 Jun 3.
Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Austrian Breast and Colorectal Cancer Study Group (ABCSG). Adjuvant endocrine therapy plus **zoledronic** acid in premenopausal women with early-stage **breast cancer**: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol. 2008 Sep;9(9):840-9.
Goldhahn J, Little D, Mitchell P, et al.; ISFR working group drugs and fracture repair. Evidence for anti-osteoporosis therapy in **acute fracture situations**--recommendations of a multidisciplinary workshop of the International Society for Fracture Repair. Bone. 2010 Feb;46(2):267-71.
Gordon PL, Frassetto LA. Management of **osteoporosis in CKD Stages 3 to 5**. Am J Kidney Dis. 2010 May;55(5):941-56.
Grey A, Bolland MJ, Wattie D, Horne A, Gamble G, Reid IR. The antiresorptive effects of a single dose of **zoledronate persist** for **two years**: a randomized, placebo-controlled trial in osteopenic postmenopausal women. J Clin Endocrinol Metab. 2009 Feb;94(2):538-44.
Green JO, Nagaraja S, Diab T, et al. **Age-related changes in human trabecular bone**: Relationship between microstructural stress and strain and damage morphology. J Biomech. 2011 Aug 11;44(12):2279-85.
Greenspan SL, Coates P, Sereika SM, et al. Bone loss after initiation of **androgen deprivation therapy** in patients with prostate cancer. J Clin Endocrinol Metab 2005;90:6410-7.
Greenspan SL, Bone HG, Ettinger MP, et al.; Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (**1-84**) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med. 2007 Mar 6;146(5):326-39.
Greenspan SL, Schneider DL, McClung MR, et al. **Alendronate** improves bone mineral density in **elderly women** with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002 May 21;136(10):742-6.
Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral **alendronate** on bone loss in men receiving **androgen deprivation therapy** for prostate cancer: a randomized trial. Ann Intern Med 2007;146:416-24.
Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology (ACR) 2010 recommendations for the prevention and treatment of **glucocorticoid-induced Osteoporosis** (GIO). Arthritis Care Res (Hoboken). 2010 Jul 26.
Haentjens Patrick, Magaziner Jay, Colón-Emeric Cathleen S., Et al. Meta-analysis: Excess **Mortality After Hip Fracture** Among Older Women and Men. *Ann Intern Med* March 16, 2010 152:380-390; doi:10.1059/0003-4819-152-6-201003160-00008.
Hanley DA, Cranney A, Jones G, et al. **Vitamin D** in adult health & disease: a review and guideline statement from **Osteoporosis Canada**–summary.CMAJ 2010 0: cmaj.091062.
Health Canada Oct/10 & Novartis, is notifying healthcare professionals and the public of reports of renal impairment and renal failure requiring dialysis or with fatal outcome that occurred in patients with history of renal impairment or other risk factors receiving ACLASTA (zoledronic acid).
Health Canada Dec/11 is updating Canadians with respect to its review of bisphosphonate drugs, used to treat osteoporosis, and the risk of a rare but serious type of thigh

TOP

fracture known as an "**atypical femur fracture** <1% ."
Health Canada May/12: Cases of severe, sometimes **fatal, symptomatic hypocalcemia associated with XGEVA (denosumab)** treatment have been reported in cancer patients with bone metastases
Heaney RP et al. **Vitamin D3 is more potent than vitamin D2** in humans. *J Clin Endocrinol Metab* 2011 Mar; 96:E447.
Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident **atrial fibrillation** in women. Arch Intern Med. 2008 Apr 28;168(8):826-31.
Hippisley-Cox Julia, Coupland Carol, Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of **QFractureScores.** BMJ 2009;339:b4229, doi: 10.1136/bmj.b4229 (Published 19 November 2009)
Hippisley-Cox J, Coupland C. Derivation and validation of **updated QFracture algorithm** to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ. 2012 May 22;344:e3427.
Hodsman A, Papaioannou A, Ann C. Clinical practice guidelines for the use of **parathyroid hormone** in the treatment of osteoporosis. CMAJ 2006; 175(1):48.
Holick MF. **Vitamin D deficiency**. N Engl J Med. 2007 Jul 19;357(3):266-81.
Hopkins RB, Goeree R, Pullenayegum E, et al. The **relative efficacy of nine osteoporosis medications** for reducing the rate of fractures in post-menopausal women. BMC Musculoskelet Disord. 2011 Sep 26;12(1):209. Teriparatide, zoledronic acid & denosumab have the highest probabilities of being most efficacious for non-vertebral & vertebral fractures, & having the greatest effect sizes.
Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with **alendronate** in postmenopausal women under 60 years of age. N Engl J Med 1998; 338:485-92.
Howe TE, Shea B, Dawson LJ, et al. **Exercise for preventing and treating osteoporosis** in postmenopausal women. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD000333. DOI: 10.1002/14651858.CD000333.pub2. Our results suggest a relatively small statistically significant, but possibly important, effect of exercise on bone density compared with control groups. Exercise has the potential to be a safe and effective way to avert bone loss in postmenopausal women.
Huang J, Meixner L, Fernandez S, McCutchan JA. A double-blinded, randomized controlled trial of zoledronate therapy for **HIV**-associated osteopenia and osteoporosis. AIDS. 2009 Jan 2;23(1):51-7.
Hung WW, Egol KA, Zuckerman JD, Siu AL. **Hip fracture management**: tailoring care for the older patient. JAMA. 2012 May 23;307(20):2185-94.
ICSI: Institute for Clinical Systems Improvement. Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Jul.
International Society for Clinical Densitometry http://www.iscd.org/
Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between **fractures and mortality**: results from the Canadian Multicentre Osteoporosis Study. CMAJ. 2009 Sep 1;181(5):265-71. Epub 2009 Aug 4.
Ito K, Elkin EB, Girotra M, Morris MJ. Cost-effectiveness of fracture prevention in men who receive **androgen deprivation therapy** for localized prostate cancer. Ann Intern Med. 2010 May 18;152(10):621-9.
Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006; 354(7):669-683.
Jamal SA, Hamilton CJ, Eastell R, et al. Effect of **nitroglycerin** ointment (15mg-1 inch of nitroglycerin 2% ointment) on bone density and strength in postmenopausal women: a randomized trial. JAMA. 2011 Feb 23;305(8):800-7.
Järvinen TL, Sievänen H, Khan KM, Heinonen A, Kannus P. Shifting the focus in fracture prevention from osteoporosis to **falls**. BMJ. 2008 Jan 19;336(7636):124-6.
Jette Nathalie; Lix Lisa M; Metge CJ; et al. Association of **Antiepileptic Drugs** With **Nontraumatic Fractures**: Population-Based Analysis. Arch Neurol. 2011;68(1):107-112.
Jones S, Restrepo D, Kasowitz A, et al. Risk factors for decreased bone density and effects of **HIV** on bone in the elderly. Osteoporos Int. 2008 Jul;19(7):913-8.
Kallmes, David F., Comstock, Bryan A., Heagerty, Patrick J., et al. A Randomized Trial of **Vertebroplasty** for Osteoporotic Spinal Fractures. N Engl J Med 2009 361: 569-579.
Kaemmerer D, Lehmann G, Wolf G, et al. Treatment of osteoporosis after **liver transplantation** with **ibandronate**. Transpl Int. 2010 Feb 15.
Kanis JA, Johnell O, Black DM, et al. Effect of **raloxifene** on the risk of new vertebral fracture in postmenopausal women with **osteopenia** or osteoporosis: a reanalysis of the multiple outcomes of raloxifene evaluation trial. (**More**) Bone 2003;33:293-300.
Kaulfers, Anne-Marie D., Bean, Judy A., Inge, Thomas H., Dolan, et al. Bone Loss in Adolescents **After Bariatric Surgery**. Pediatrics 2011 0: peds.2010-0785.
Karaplis AC, Chouha F, Djandji M, Sampalis JS, Hanley DA. **Vitamin D Status and Response to Daily 400 IU Vitamin D3 and Weekly Alendronate 70 mg** in Men and Women with Osteoporosis. Ann Pharmacother. 2011 May;45(5):561-8.
Karim R, Dell RM, Greene DF, et al. Hip fracture in postmenopausal women **after cessation of hormone therapy**: results from a prospective study in a large health management organization. Menopause. 2011 Nov;18(11):1172-7.
Kavanagh KL, Guo K, Dunford JE, et al. The molecular **mechanism** of nitrogen-containing **bisphosphonates** as antiosteoporosis drugs. Proc Natl Acad Sci U S A. 2006 May 16;103(20):7829-34. Epub 2006 May 9.
Kemmler Wolfgang; von Stengel Simon; Engelke Klaus; et al. **Exercise** Effects on Bone Mineral Density, Falls, Coronary Risk Factors, and Health Care Costs in Older Women: The Randomized Controlled Senior Fitness and Prevention (**SEFIP**) Study. Arch Intern Med. 2010;170(2):179-185.
Khan AA, Sándor GK, Dore E, et al. **Canadian** Taskforce on Osteonecrosis of the Jaw. Bisphosphonate associated **osteonecrosis** of the **jaw**. J Rheumatol.2009Mar;36(3):478-90.
Khan AA, Sándor GK, Dore E, et al. **Canadian** Association of Oral and Maxillofacial Surgeons. Canadian consensus practice guidelines for bisphosphonate associated **osteonecrosis of the jaw**. J Rheumatol. 2008 Jul;35(7):1391-7. Epub 2008 Jun 1. Erratum in: J Rheumatol. 2008 Oct;35(10):2084. J Rheumatol. 2008 Aug;35(8):1688.
Khan AA, Sandor GK, Dore E, Morrison AD, Alshali M, Amin F, et al. **Bisphosphonate-associated osteonecrosis** of the jaw—literature review. J Rheumatol 2009;36:

TOP

Khosla S. Update in **male osteoporosis**. J Clin Endocrinol Metab. 2010 Jan;95(1):3-10.
Khosla S, Melton LJ 3rd. Clinical practice. **Osteopenia**. N Engl J Med. 2007 May 31;356(22):2293-300.
Kirby MW and Spritzer C. **Radiographic detection of hip and pelvic fractures** in the emergency department. *AJR Am J Roentgenol* 2010 Apr; 194:1054.
Klazen CA, Lohle PN, de Vries J, et al. **Vertebroplasty** versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet. 2010 Aug 9.
Knopp JA, Diner BM, Blitz M, Lyritis GP, Rowe BH. **Calcitonin** for treating **acute pain** of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. Osteoporos Int. 2005 Oct;16(10):1281-90. Epub 2004 Dec 22.
Korpelainen Raija; Keinanen-Kiukaanniemi Sirkka; Nieminen Pentti; et al. Long-term Outcomes of **Exercise**: Follow-up of a Randomized Trial in Older Women With Osteopenia. Arch Intern Med. 2010;170(17):1548-1556.
Kurmis AP, et al. Effect of **nonsteroidal anti-inflammatory drug administration on acute phase fracture-healing**: a review. J Bone Joint Surg Am. 2012 May 2;94(9):815-23.
Kyle RA, Yee GC, Somerfield MR, et al. Society of Clinical Oncology. **American** Society of Clinical Oncology 2007 clinical practice guideline update on the role of **bisphosphonates in multiple myeloma**. J Clin Oncol. 2007 Jun 10;25(17):2464-72.
Lamberg AL, Horvath-Puho E, et al. Use of oral bisphosphonates and risk of venous **thromboembolism**: a population-based case-control study. Osteoporos Int. 2009 Dec 9.
Lansang MC, Hustak LK. **Glucocorticoid-induced diabetes and adrenal suppression**: How to detect and manage them. Cleve Clin J Med. 2011 Nov;78(11):748-56.
Langsetmo L, Nguyen TV, Nguyen D, et al. Independent external validation of **nomograms (Dubbo & FRAX) for predicting risk of low-trauma fracture and hip fracture** CMAJ 2010 0: cmaj.100458. Dec 20/10. (BMD not required for Dubbo or Frax. Dubbo: less variables to calculate, formula published & classifies Canadian men better).
Leblanc ES, Hillier TA, Pedula KL, et al. **Hip Fracture and Increased Short-term** but Not Long-term **Mortality** in Healthy Older Women. Arch Intern Med. 2011 Sep 26.
Lenart BA et al. Association of **low-energy femoral fractures** with prolonged bisphosphonate use: A case control study. Osteoporos Int 2009 Aug; 20:1353.
Leslie WD, Tsang JF, Lix LM. Validation of ten-year fracture **risk prediction**: a clinical cohort study from the Manitoba Bone Density Program. Bone 2008; 43(4):667-671.
Leslie WD, Berger C, Langsetmo L, et al. Construction and validation of a simplified fracture risk assessment tool for Canadian women and men: results from the CaMos and Manitoba BMD cohorts. Osteoporos Int. (**CAROC** 2010) In press. http://osteoporosis.bluerush.ca/www/pdf/caroc_oct_2010.pdf
Leslie WD., Morin S, Lix LM. A Before-and-After Study of **Fracture Risk Reporting** and Osteoporosis treatment Initiation. *Ann Intern Med* November 2, 2010 153:580-586.
Leslie WD, LaBine L, Klassen P, et al. Closing the **gap in postfracture care** at the population level: a randomized controlled trial. CMAJ 2012;184:290-6.
Levis S, Strickman-Stein N, Ganjei-Azar P, et al. **Soy isoflavones** in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial. (SPARE) Arch Intern Med. 2011;171 (15):1363-1369. (200mg for 2yrs did not prevent bone loss or menopausal symptoms)
Lewiecki EM. **Managing osteoporosis**: challenges and strategies. Cleve Clin J Med. 2009 Aug;76(8):457-66.
Lewiecki E. Michael. **In the Clinic: Osteoporosis**. Ann Intern Med July 5, 2011 155:ITC1-1; doi:10.1059/0003-4819-155-1-201107050-01001.
Li Kuanrong, Kaaks R, Linseisen J, et al. Associations of **dietary calcium intake and calcium supplementation** with **myocardial infarction** and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart 2012. (In press)
Lim LS, Hoeksema LJ, Sherin K; **ACPM** Prevention Practice Committee. **Screening** for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. Am J Prev Med. 2009 Apr;36(4):366-75. All adult patients aged >or=50 years should be evaluated for risk factors for osteoporosis. Screening with BMD testing for osteoporosis is recommended in women aged >or=65 years and in men aged >or=70 years. Younger postmenopausal women and men aged 50-69 years should undergo screening if they have at least one major or two minor risk factors for osteoporosis. It is also recommended that clinicians consider using an osteoporosis risk-assessment tool to evaluate absolute fracture risk to determine appropriate osteoporosis therapies.
Lim SH, Benseler SM, Tyrrell PN, et al. Low bone mineral density is present in newly diagnosed **paediatric systemic lupus erythematosus** patients. Ann Rheum Dis. 2011 Nov;70(11):1991-4.
Lips P, Bouillon R, van Schoor NM, et al. Reducing fracture risk with **calcium and vitamin D**. Clin Endocrinol (Oxf). 2009 Sep 10. [Epub ahead of print]
Liu JM, Wai-Chee Kung A, et al. Efficacy and safety of 2 g/day of **strontium ranelate** in Asian women with postmenopausal osteoporosis. Bone. 2009 Sep;45(3):460-5.
Logan PA, Coupland CA, Gladman JR, et al. Community **falls prevention** for people who call an emergency ambulance after a fall:randomised controlled trial. BMJ. 2010May11
Loke YK, Singh S, Furberg CD. Long-term use of **thiazolidinediones** and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009 Jan 6;180(1):32-9. Epub 2008 Dec 10.
Loke YK, Jeevanantham V, Singh S. Bisphosphonates and **atrial fibrillation**: systematic review and meta-analysis. Drug Saf. 2009;32(3):219-28. doi: 10.2165/00002018-200932030-00004.
Lu PY, Hsieh CF, Tsai YW, Huang WF. **Alendronate and raloxifene** use related to **cardiovascular diseases**: differentiation by different dosing regimens of alendronate. Clin Ther. 2011 Sep;33(9):1173-9.
Maalouf Naim M.; Sato Alicia H.; Welch Brian J.; et al. **Postmenopausal Hormone Use** and the Risk of **Nephrolithiasis**: Results From the Women's Health Initiative Hormone Therapy Trials. Arch Intern Med. 2010;170(18):1678-1685.
Majumdar SR, Lix LM, Yogendran M, et al. Population-Based Trends in Osteoporosis Management after **New Initiations of Long-Term Systemic Glucocorticoids** (1998-2008). J Clin Endocrinol Metab. 2012 Feb 1.
Martino S, Cauley JA, Barrett-Connor E, et al. **CORE** Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a Randomized trial of raloxifene. J Natl Cancer Inst. 2004 Dec 1;96(23):1751-61.

TOP

Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of **bisphosphonate-associated osteonecrosis** of the jaws in Australia. J Oral MaxillofacSurg 2007;65:415-23.
Mazziotti G, Canalis E, Giustina A. **Drug-induced osteoporosis**: mechanisms and clinical implications. Am J Med. 2010 Oct;123(10):877-84.
McClung MR, Siris E, Cummings S, et al. Prevention of bone loss in postmenopausal women treated with **lasofoxifene** compared with raloxifene. Menopause 2006;13:377-386.
McClung MR, Lewiecki EM, Cohen SB, et al. **Denosumab** in postmenopausal women with low bone mineral density. N Engl J Med 2006;354:821-831.
McClung M, et al. **Zoledronic** acid for the prevention of bone loss in postmenopausal women with **low bone mass**: a randomized controlled trial. Obstet Gynecol. November 2009;114(5):999–1007.
McComsey GA, Kendall MA, Tebas P, et al. Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in **HIV**. AIDS. 2007 Nov 30;21(18):2473-82.
McComsey GA, Tebas P, Shane E, et al. Bone disease in **HIV** infection: a practical review and recommendations for HIV care providers.Clin Infect Dis.2010Oct 15;51(8):937-46.
McKague M, Jorgenson D, Buxton KA. **Ocular side effects of bisphosphonates**: A case report and literature review. Can Fam Physician. 2010 Oct;56(10):1015-7.
Merriman NA, Putt ME, Metz DC, Yang YX. Hip Fracture Risk in Patients with a Diagnosis of **Pernicious Anemia**. Gastroenterology. 2009 Dec 16.
Meunier PJ, Roux C, Seeman E, et al. The effects of **strontium ranelate** on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med. 2004 Jan 29;350(5):459-68.
Meunier PJ, Roux C, Ortolani S, et al. Effects of long-term **strontium ranelate** treatment on vertebral fracture risk in postmenopausal women with osteoporosis. Osteoporos Int. 2009 Oct;20(10):1663-73. Epub 2009 Jan 20.
Mhaskar R, Redzepovic J, Wheatley K, Clark OAC, Miladinovic B, Glasmacher A, Kumar A, Djulbegovic B. **Bisphosphonates** in **multiple myeloma**: a network meta-analysis. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD003188. DOI: 10.1002/14651858.CD003188.pub3. Use of bisphosphonates in patients with MM reduces pathological vertebral fractures, SREs and pain. Assuming a baseline risk of 20% to 50% for vertebral fracture without treatment, between 8 and 20 MM patients should be treated to prevent vertebral fracture(s) in one patient. Assuming a baseline risk of 31% to 76% for pain amelioration without treatment, between 5 and 13 MM patients should be treated to reduce pain in one patient. With a baseline risk of 35% to 86% for SREs without treatment, between 6 and 15 MM patients should be treated to prevent SRE(s) in one patient. Overall, there were no significant adverse effects associated with the administration of bisphosphonates identified in the included RCTs. We found no evidence of superiority of any specific aminobisphosphonate (zoledronate, pamidronate or ibandronate) or nonaminobisphosphonate (etidronate or clodronate) for any outcome. However, zoledronate appears to be superior to placebo and etidronate in improving overall survival.
Miller PD. Fragility fractures in **chronic kidney disease**: an opinion-based approach. Cleve Clin J Med. 2009 Dec;76(12):715-23.
Miller PD, Chines AA, Christiansen C, et al. Effects of **bazedoxifene** on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 2008;23:525-535.
Mittan D, Lee S, Miller E, et al. Bone loss following hypogonadism in men with **prostate cancer treated with GnRH analogs**. J Clin Endocrinol Metab 2002;87:3656-61.
Mok Chi Chiu, Ying King Yee, To Chi Hung, et al. **Raloxifene for prevention of glucocorticoid-induced bone loss**: a 12-month randomised double-blinded placebo-controlled trial. Ann Rheum Dis 2011;70:778-784 Published Online First: 27 December 2010 doi:10.1136/ard.2010.143453.
Morgan GJ, Child JA, Gregory WM, et al. National Cancer Research Institute Haematological Oncology Clinical Studies Group. Effects of **zoledronic acid versus clodronic** acid on skeletal morbidity in patients with newly diagnosed **multiple myeloma** (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. Lancet Oncol. 2011 Aug;12(8):743-52.
Mosca L, Grady D, Barrett-Connor E, et al. Effect of **raloxifene** on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. Stroke 2009; 40(1):147-155.
Mueller NJ, Fux CA, Ledergerber B, et al. the Swiss **HIV** Cohort Study. High prevalence of severe vitamin D deficiency in combined antiretroviral therapy-naive and successfully treated Swiss HIV patients. AIDS. 2010 Feb 15.
NAMS: North American Menopause Society. Management of osteoporosis in postmenopausal women: **2006** position statement of The North American Menopause Society. Menopause. 2006 May-Jun;13(3):340-67
NAMS: Management of **osteoporosis in postmenopausal women**: **2010** position statement of The North American Menopause Society. Menopause. **2010** Jan-Feb;17(1):25-54.
Mazziotti G, Canalis E, Giustina A. **Drug-induced osteoporosis**: mechanisms and clinical implications. Am J Med. 2010 Oct;123(10):877-84.
Moen SM, Celius EG, Sandvik L, et al. **Low bone mass** in newly diagnosed **multiple sclerosis** and clinically isolated syndrome. Neurology. 2011 Jul 12;77(2):151-7.
Morgan Gareth J, Davies Faith E, Gregory Walter M et al.,on behalf of the National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with **zoledronic** acid as compared with clodronic acid in **multiple myeloma** (MRC Myeloma IX): a randomised controlled trial. The Lancet - 4 Dec 2010.
Murad MH, Drake MT, Mullan RJ, et al. **Comparative Effectiveness** of Drug Treatments to Prevent Fragility Fractures: A Systematic Review and Network Meta-Analysis. J Clin Endocrinol Metab. 2012 Mar 30. Teriparatide, bisphosphonates, and denosumab are most effective in reducing the risk of fragility fractures.
Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into **actions of bisphosphonates** on bone: differences in interactions with hydroxyapatite. Bone. 2006 May;38(5):617-27.
National Osteoporosis Foundation (**NOF**) http://www.nof.org/
Nayak S, Roberts MS, Greenspan SL. **Cost-effectiveness of different screening** strategies for osteoporosis in postmenopausal women. Ann Intern Med. 2011; 155:751-61. Screening strategies composed of alternative tests (central dual-energy x-ray absorptiometry [DXA], calcaneal quantitative ultrasonography [QUS], and the Simple Calculated Osteoporosis Risk Estimation [SCORE] tool) initiation ages, treatment thresholds, and rescreening intervals. No strategy substantially outperforms another.
Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of **parathyroid hormone** (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.

TOP

N Engl J Med 2001; 344(19):1434-1441.
Nelson HD, Helfand M, Woolf SH, et al. **Screening** for postmenopausal osteoporosis: a review of the evidence for the U.S. Preventive Services Task Force. (**USPSTF**) Ann Intern Med. 2002 Sep 17;137(6):529-41.
Nelson Heidi D., Haney Elizabeth M., Dana Tracy, et al. **Screening** for Osteoporosis: An Update for the U.S. Preventive Services Task Force (**USPSTF**). Ann Intern Med published ahead of print July 5, **2010**, doi:10.1059/0003-4819-153-2-201007200-00262.
Newcomb PA, Trentham-Dietz A, Hampton JM. Bisphosphonates for osteoporosis treatment are associated with reduced **breast cancer risk**. Br J Cancer. 2010 Mar 2;102(5):799-802.
NICE: National Institute for Clinical Excellence. Falls: the assessment and prevention of **falls** in older people. (Clinical guideline 21.) 2004. http://guidance.nice.org.uk/CG21 .
NICE: National Institute for Health and Clinical Excellence. **Denosumab** for the prevention of osteoporotic fractures in postmenopausal women. London (UK): 2010 Oct.
NICE:National Institute for Health and Clinical Excellence. **Osteoporosis—secondary prevention** including strontium ranelate. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended). (Technology appraisal 161.) 2011 (originally published 2008, amended 2010 and 2011). http://guidance.nice.org.uk/TA161.
NICE: Management of **hip fracture** in adults: summary of NICE guidance June 2011. http://www.nice.org.uk/nicemedia/live/13489/54921/54921.pdf
NIH Osteoporosis and Related Bone Diseases ~ National Resource Center http://www.niams.nih.gov/Health_info/bone/Osteoporosis/default.asp
O'Donnell S, Cranney A, Wells GA, et al. **Strontium ranelate** for preventing and treating postmenopausal osteoporosis. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005326.
Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. **Severely suppressed bone turnover**: a potential complication of **alendronate** therapy. J Clin Endocrinol Metab 2005; 90:1294-301.
Orwig Denise L.; Hochberg Marc; Yu-Yahiro Janet; et al. Delivery and Outcomes of a Yearlong Home **Exercise Program** After Hip Fracture: A Randomized Controlled Trial. Arch Intern Med. 2011;171(4):323-331.
Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J et al. **Alendronate** for the treatment of osteoporosis in **men**. N Engl J Med 2000; 343(9):604-610.
Ott SM. What is the optimal **duration of bisphosphonate therapy**? Cleve Clin J Med. 2011 Sep;78(9):619-30.
Pallan S, Khan A. **Primary hyperparathyroidism**: Update on presentation, diagnosis, and management in primary care. Can Fam Physician. 2011 Feb;57(2):184-9.
Pallan S, Rahman MO, Khan AA. Diagnosis and management of **primary hyperparathyroidism**. BMJ. 2012 Mar 19;344:e1013.
Palmer SC, McGregor DO, Macaskill P, et al. Meta-analysis: **vitamin D** compounds in chronic kidney disease. Ann Intern Med. 2007;147(12):840–853.
Park-Wyllie LY, Mamdani MM, Juurlink DN, et al. Bisphosphonate use and the risk of **subtrochanteric or femoral shaft fractures** in older women. JAMA. 2011 Feb 23;305(8):783-9.
Paterson AHG, Anderson SJ, Lembersky BC, et al. Oral **clodronate** for adjuvant treatment of operable **breast cancer** (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. Lancet Oncol 2012
Pearce Simon HS, Cheetham Tim D. Diagnosis and management of **vitamin D** deficiency. BMJ 2010;340:b5664, doi: 10.1136/bmj.b5664 (Published 11 January 2010)
Peppone LJ, Hebl S, Purnell JQ, et al. The efficacy of **calcitriol** therapy in the management of bone loss and fractures: a qualitative review. Osteoporos Int. 2009 Dec 4.
Peris P, Martínez-Ferrer A, et al. **25 hydroxyvitamin D serum levels** influence adequate response to bisphosphonate treatment in postmenopausal osteoporosis. Bone. 2012Apr 1.
Pham AN, Datta SK, Weber TJ, et al. **Cost-Effectiveness** of Oral **Bisphosphonates** for Osteoporosis at Different **Ages** and Levels of **Life Expectancy**. J Am Geriatr Soc. 2011 Aug 30. doi: 10.1111/j.1532-5415.2011.03571.x.
Pollock NK, Bernard PJ, Gutin B, et al. **Adolescent** obesity, bone mass, and cardiometabolic risk factors. J Pediatr. 2011 May;158(5):727-34.
Poole KE, Compston JE. **Bisphosphonates in the treatment of osteoporosis**. BMJ. 2012 May 22;344:e3211.
Premaor MO, Compston JE. **Testing for secondary causes of osteoporosis**. BMJ. 2010 Dec 16;341:c6959. doi: 10.1136/bmj.c6959.
Prieto-Alhambra D, Javaid MK, Judge A, et al. Association between **bisphosphonate use and implant survival** after primary total arthroplasty of the knee or hip: population based retrospective cohort study. BMJ. 2011 Dec 6;343:d7222. doi: 10.1136/bmj.d7222.
Pun KK, Chan LW. **Analgesic** effect of intranasal salmon **calcitonin** in the treatment of osteoporotic vertebral fractures. Clin Ther. 1989 Mar-Apr;11(2):205-9.
Qaseem A, Snow V, Shekelle P, et al.; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. **ACP Pharmacologic treatment** of low bone density or osteoporosis to prevent fractures:a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008 Sep 16;149(6):404-15.
Qaseem A, Snow V, Shekelle P, et al.; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. **ACP Screening for osteoporosis in men**: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008 May 6;148(9):680-4. Erratum in: Ann Intern Med. 2008 Jun 3;148(11):888.
QFractureScore http://www.qfracture.org/
Quandt SA, Thompson DE, Schneider DL, et al. Effect of **alendronate** on vertebral fracture risk in women with bone mineral density T score of −1.6 to −2.5 at the femoral neck: the fracture intervention trial. Mayo Clin Proc 2005;80:343-9.
Rachner Tilman D. **Osteoporosis: now and the future**. www.thelancet.com Published online March 29, 2011 DOI:10.1016/S0140-6736(10)62349-5
Rahmani, Poupak, Morin, Suzanne. **Prevention of osteoporosis**-related fractures among postmenopausal women and older men. CMAJ 2009 0: cmaj.080709
Rao SS, Budhwar N, Ashfaque A. **Osteoporosis in men**. Am Fam Physician. 2010 Sep 1;82(5):503-8.

TOP

Reginster JY, Seeman E, De Vernejoul MC, et al. **Strontium ranelate** reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (**TROPOS**) study. J Clin Endocrinol Metab. 2005 May;90(5):2816-22.

Reginster JY, Bruyère O, Sawicki A, et al. Long-term treatment of postmenopausal osteoporosis with **strontium ranelate**: results at 8 years. Bone. 2009 Dec;45(6):1059-64.

Reginster JY, Felsenberg D, Boonen S, et al. Effects of long-term **strontium ranelate** treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum. 2008 Jun;58(6):1687-95.

Reid DM, Devogelaer JP, Saag K, et al. **Zoledronic** acid and risedronate in the prevention and treatment of **glucocorticoid-induced** osteoporosis (**HORIZON**): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2009; 373(9671):1253-1263.

Rejnmark L, Avenell A, Masud T, et al. **Vitamin D with Calcium Reduces Mortality**: Patient Level Pooled Analysis of 70,528 Patients from Eight Major Vitamin D Trials. J Clin Endocrinol Metab. 2012 May 17.

Richards JB, Papaioannou A, Adachi JD,et al.; Canadian Multicentre Osteoporosis Study Research Group. Effect of selective **serotonin reuptake inhibitors** on the risk of fracture. Arch Intern Med. 2007 Jan 22;167(2):188-94.

Ringe JD, Farahmand P, Faber H, Dorst A. Sustained efficacy of **risedronate in men** with primary and secondary osteoporosis: results of a 2-year study. Rheumatol Int 2009; 29(3):311-315.

Robertson MC, Campbell AJ, Gardner MM, Devlin N. Preventing injuries in older people by **preventing falls**: a meta-analysis of individual-level data. J Am Geriatr Soc 2002; 50(5):905-911

Rousing R, Hansen KL, Andersen MO, et al. Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with **percutaneous vertebroplasty**: a clinical randomized study. Spine (Phila Pa 1976). 2010 Mar 1;35(5):478-82.

Roux C, Fechtenbaum J, Kolta S, et al. **Strontium ranelate** reduces the risk of vertebral fracture in young postmenopausal women with severe osteoporosis. Ann Rheum Dis. 2008 Dec;67(12):1736-8.

Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B; **American** Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on **bisphosphonate-related osteonecrosis** of the jaws--2009 update. J Oral Maxillofac Surg. 2009 May;67(5 Suppl):2-12.

Russell RG, Watts NB, Ebetino FH, Rogers MJ. **Mechanisms of action of bisphosphonates**: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 2008;19:733-59.

Saad F, Gleason DM, Murray R, et al, for the **Zoledronic Acid Prostate Cancer Study Group**. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002; 94: 1458–68.

Saad F, Abrahamsson PA, Miller K. Preserving bone health in patients with hormone-sensitive **prostate cancer**: the role of **bisphosphonates**. BJU Int. 2009 Dec;104(11):1573-9.

Saag KG, Emkey R., Schnitzer TJ, et al. **Alendronate** for the prevention and treatment of **glucocorticoid-induced** osteoporosis. N Engl J Med 1998; 339:292-9.

Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of **teriparatide versus alendronate** for treating **glucocorticoid**-induced osteoporosis: Thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009 Oct 29;60(11):3346-3355.

Saag KG, Shane E, Boonen S, et al. **Teriparatide or alendronate** in glucocorticoid-induced osteoporosis. N Engl J Med 2007; 357(20):2028-2039.

Sanders Kerrie M.; Stuart Amanda L.; Williamson Elizabeth J.; et al. Annual **High-Dose Oral Vitamin D** (500,000IU x1/yr for 3-5yrs: increased falls & fractures) and Falls and Fractures in Older Women: A Randomized Controlled Trial. JAMA. 2010;303(18):1815-1822.

Sarnes E, Crofford L, Watson M, et al. Incidence and US Costs of **Corticosteroid-Associated Adverse Events**: A Systematic Literature Review. Clin Ther. 2011 Oct 12.

Sawka AM, Ismaila N, Raina P, et al. **Hip fracture prevention strategies in long-term care**: a survey of Canadian physicians' opinions. Can Fam Physician. 2010 Nov;56(11):e392-7.

Schlingmann Karl P., Weber Stefanie, Goos Caroline, et al. **Mutations in CYP24A1 and Idiopathic Infantile Hypercalcemia**. June 15, 2011 (10.1056/NEJMoa1103864).

Schwartz AV, Bauer DC, Cummings SR, et al. for the **FLEX** Research Group. Efficacy of continued **alendronate** for fractures in women **with and without prevalent vertebral fracture**: The FLEX trial. J Bone Miner Res. 2010 Jan 8.

Schwartz AV, Vittinghoff E, Bauer DC, et al. Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging, and Body Composition (Health ABC) Research Group. Association of **BMD and FRAX score with risk of fracture in older adults with type 2 diabetes**. JAMA. 2011 Jun 1;305(21):2184-92.

Scott LJ, Muir VJ. **Denosumab**: in the prevention of skeletal-related events in patients with **bone metastases** from solid tumours. Drugs 2011;71:1059-69.

Seeman E, Boonen S, Borgström F, et al. Five years treatment with **strontium ranelate** reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life-years in women over 80 years of age. Bone. 2009 Dec 21. [Epub ahead of print]

Seeman E, Devogelaer J, Lorenc R, et al. **Strontium** ranelate reduces the risk of vertebral fractures in patients with **osteopenia**. J Bone Miner Res 2007 Nov 12.

Seeman E, Vellas B, Benhamou C, et al. **Strontium** ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. J Bone Miner Res. 2006 Jul;21(7):1113-20.

Seton M, **How soon after hip fracture surgery** should a patient **start bisphosphonates**? *Cleveland Clinic Journal of Medicine* 2010; 77(11):751-755; doi:10.3949/ccjm.77a.10045

Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after **androgen deprivation for prostate cancer**. N Engl J Med 2005;352:154-64.

TOP

Shiek Ahmad B, Hill KD, O'Brien TJ, et al. **Falls and fractures** in patients chronically treated with antiepileptic drugs. Neurology. 2012 Jun 13.
Shumaker SA, Legault C, Rapp SR, et al, for the **WHIMS** Investigators. **Estrogen plus progestin** and the incidence of **dementia** and mild cognitive impairment in postmenopausal women: the Women_s Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2651-2662.
Silverman SL, Cummings SR, Watts NB; Consensus Panel of the ASBMR, ISCD, and NOF. Recommendations for the **clinical evaluation** of agents for treatment of osteoporosis: consensus of an expert panel representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation (NOF). J Bone Miner Res. 2008 Jan;23(1):159-65.
Silverman SL, Christiansen C, Genant HK, et al. Efficacy of **bazedoxifene** in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res 2008;23:1923-1934.
Silverman S, Christiansen C. Individualizing osteoporosis therapy. Osteoporos Int. 2012 Jan 5.
Siminoski K, Leslie WD, Frame H, et al. Canadian Association of Radiologists. Recommendations for **bone mineral density** reporting in **Canada**. Can Assoc Radiol J. 2005 Jun;56(3):178-88.
Simunovic N, Devereaux PJ, et al. Effect of **early surgery after hip fracture** on mortality and complications: systematic review and meta-analysis. CMAJ 2010 0: cmaj.092220.
Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment (**NORA**). JAMA 2001;286:2815-2822.
Siris ES, Simon JA, Barton IP, et al. Effects of **risedronate** on fracture risk in postmenopausal women with **osteopenia**. Osteoporos Int 2007 Oct 30.
Skversky AL, Kumar J, Abramowitz MK, et al. Association of **Glucocorticoid Use and Low 25-Hydroxyvitamin D Levels**: Results from the National Health and Nutrition Examination Survey (NHANES): 2001-2006. J Clin Endocrinol Metab. 2011 Sep 28.
Slatkovska Lubomira, Alibhai Shabbir M.H., Beyene Joseph, et al. Effect of 12 Months of **Whole-Body Vibration Therapy** on Bone Density and Structure in Postmenopausal Women: A Randomized Trial. Ann Intern Med November 15, 2011 155:668-679.
Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of **zoledronic acid** to prevent bone loss in men receiving **androgen deprivation therapy** for nonmetastatic prostate cancer. J Urol 2003; 169:2008-12.
Smith MR, McGovern FJ, Zietman AL, et al. **Pamidronate** to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 2001;345:948-55.
Smith MR, Lee WC, Brandman J, et al. **Gonadotropin-releasing hormone agonists** and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol 2005;23:7897-903.
Smith H, Anderson F, Raphael H, et al. Effect of annual intramuscular **vitamin D** on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007 Dec;46(12):1852-7. An **annual i.m. injection of 300 000 IU vitamin D(2)** is not effective in preventing non-vertebral fractures among elderly men and women resident in the general population.
Smith MR, Egerdie B, Hernández Toriz N, et al. **Denosumab HALT** Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009 Aug 20;361(8):745-55. Epub 2009 Aug 11.
Smith MR, Fallon MA, Lee H, Finkelstein JS. **Raloxifene** to **prevent gonadotropin-releasing hormone agonist**-induced bone loss in men with prostate cancer: a randomized controlled trial. J Clin Endocrinol Metab 2004;89:3841-6.
Smith MR, Morton RA, Barnette KG, et al. **Toremifene** to reduce fracture risk in men receiving **androgen deprivation therapy** for prostate cancer. J Urol 2010;184:1316-21.
Smith Matthew R.,. Zietman Anthony L, Finkelstein Joel S., et al. Case 16-2011 — A 67-Year-Old Man with Recurrent **Prostate Cancer**. N Engl J Med 2011; 364:2044-2051.
Smith MR, Saad F, Coleman R, et al. **Denosumab and bone-metastasis**-free survival in men with castration-resistant **prostate** cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2011; published online Nov 16. DOI:10.1016/S0140-6736(11)61226-9.
Solomon DH, Iversen MD, Avorn J et al. Osteoporosis **Telephonic Intervention** to Improve Medication Regimen Adherence: A Large, Pragmatic, Randomized Controlled Trial. Arch Intern Med. 2012 Feb 27.
Sonneville KR, Gordon CM, Kocher MS, et al. **Vitamin D**, Calcium, & Dairy Intakes and **Stress Fractures** Among Female Adolescents. Arch Pediatr Adolesc Med. 2012 Mar 5.
Sontag A, Krege JH. **First fractures** among postmenopausal women with osteoporosis. (**MORE**) J Bone Miner Metab. 2010 Jan 7. (Spine & radius fractures)
Staples MP, Kallmes DF, Comstock BA, Jarvik JG, Osborne RH, Heagerty PJ, et al. Effectiveness of **vertebroplasty** using individual patient data from two randomised placebo controlled trials: meta-analysis. BMJ 2011;343:d3952.
Stopeck AT, Lipton A, Body JJ, et al. **Denosumab Compared With Zoledronic** Acid for the Treatment of **Bone Metastases** in Patients With Advanced **Breast Cancer**: A Randomized, Double-Blind Study. J Clin Oncol. 2010 Nov 8.
Stoch SA, Saag KG, Greenwald M, et al. Once-weekly oral alendronate 70 mg in patients with **glucocorticoid-induced** bone loss: a 12-month randomized, placebo-controlled clinical trial. J Rheumatol. 2009 Aug;36(8):1705-14.
Straube S, Derry S, Moore RA, et al. **Vitamin D** for the treatment of **chronic painful conditions** in adults. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007771.
Strom T., Thamsborg G., Steiniche T., et al. Effect of intermittent cyclical **etidronate** therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322:1265-71.
Svejme O, Ahlborg H, et al. **Early menopause** and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. BJOG. 2012 A

TOP

Targownik LE, Lix LM, Leung S, Leslie WD. **Proton Pump Inhibitor** Use Is Not Associated With Osteoporosis or Accelerated Bone Mineral Density Loss. Gastroenterology. 2009 Nov 18.

Targownik LE, Lix LM, Metge CJ, et al. Use of **proton pump inhibitors** and risk of osteoporosis-related fractures. CMAJ. 2008 Aug 12;179(4):319-26.

Taxel P, Dowsett R, Richter L, Fall P, Klepinger A, Albertsen P. Risedronate prevents early bone loss and increased bone turnover in the first 6 months of **luteinizing hormone-releasing hormone-agonist therapy** for prostate cancer. BJU Int. 2010 Apr 30.

Tee Shang-Ian; Yosipovitch Gil; Chan Yuin Chew; et al. **Prevention of Glucocorticoid-Induced Osteoporosis in Immunobullous Diseases** With **Alendronate**: A Randomized, Double-blind, Placebo-Controlled Study. Arch Dermatol. 2011;0(2011):archdermatol.2011.354.

Teng K. Premenopausal osteoporosis, an overlooked **consequence of anorexia nervosa**. Cleve Clin J Med. 2011 Jan;78(1):50-8.

Tejero García S, Giráldez Sánchez MA, et al. Bone health, **daily physical activity**, and exercise tolerance in patients with **cystic fibrosis**. Chest. 2011 Aug;140(2):475-81.

Terpos E, Sezer O, Croucher PI, et al. **European** Myeloma Network. The use of **bisphosphonates in multiple myeloma**: recommendations of an expert panel on behalf of the European Myeloma Network. Ann Oncol. 2009 Aug;20(8):1303-17. Epub 2009 May 22.

Toh Sengwee, Hernández-Díaz Sonia, Logan Roger, Et al. Coronary Heart Disease in Postmenopausal Recipients of Estrogen Plus Progestin Therapy: Does the Increased Risk Ever Disappear?: A Randomized Trial. (**WHI**) Ann Intern Med February 16, 2010.

Thomas D, Henshaw R, Skubitz K, et al. **Denosumab** in patients with **giant-cell tumour** of bone: an open-label, phase 2 study. Lancet Oncol. 2010 Mar;11(3):275-80.

Tsourdi E, Rachner TD, Gruber M, Hamann C, Ziemssen T, Hofbauer LC. **Seizures Associated with Zoledronic** Acid for Osteoporosis. J Clin Endocrinol Metab. 2011 Apr 20.

USPSTF- U.S. Preventive Services Task Force. **Hormone therapy** for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. Ann Intern Med. 2005 May 17;142(10):855-60.

USPSTF- U.S. Preventive Services Task Force. **Postmenopausal hormone replacement therapy** for primary prevention of chronic conditions: recommendations and rationale. Ann Intern Med. 2002 Nov 19;137(10):834-9.

USPSTF- U.S. Preventive Services Task Force. **Screening** for osteoporosis in postmenopausal women: recommendations & rationale. Ann Intern Med.2002 Sep 17;137(6):526-8.

USPSTF- U.S. Preventive Services Task Force. **Screening** for Osteoporosis: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* E-307 Jan 17, 11.
Screen all women aged 65 and older; screen women younger than 65 if their 10-year fracture risk is similar to or greater than that of a 65-year-old white woman without additional risk factors — roughly 9%. (The article recommends using the WHO's FRAX tool to estimate fracture risk.) The USPSTF expanded its review to include men, and concludes that there is not enough evidence to determine whether screening is beneficial or harmful

USPSTF- U.S. Preventive Services Task Force (USPSTF). **Screening** for osteoporosis: U.S. preventive services task force **recommendation statement**. Ann Intern Med. 2011 Mar 1;154(5):356-64.

Van Poznak CH, Temin S, Yee GC, et al. American Society of Clinical Oncology (**ASCO**) Executive Summary of the Clinical Practice Guideline Update on the Role of **Bone-Modifying Agents in Metastatic Breast Cancer**. J Clin Oncol. 2011 Feb 22.

Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of **oral corticosteroids** and risk of fractures. J Bone Miner Res. 2000 Jun;15(6):993-1000.

Vatanparast H, Dolega-Cieszkowski JH, Whiting SJ. Many adult Canadians are not meeting current **calcium recommendations from food and supplement** intake. Appl Physiol Nutr Metab. 2009 Apr;34(2):191-6.

Vestergaard P, Rejnmark L, Mosekilde L. High-dose treatment with **vitamin A analogues** and risk of fractures. Arch Dermatol. 2010 May;146(5):478-82. Risk not ↑.

Wang, Lu, Manson, JoAnn E. Song, Yiqing et al. Systematic Review: **Vitamin D and Calcium** Supplementation in Prevention of **Cardiovascular Events**. Ann Intern Med March 2, 2010 152:315-323; doi:10.1059/0003-4819-152-5-201003020-00010.

Ward L. M., Rauch F., Whyteet M. P. al. Alendronate for the Treatment of **Pediatric Osteogenesis Imperfecta**: A Randomized Placebo-Controlled Study. J. Clin. Endocrinol. Metab. published November 24, 2010, doi:10.1210/jc.2010-0636. (not reduce fractures)

Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X, Grauer A. Fracture risk remains reduced **one year after discontinuation** of risedronate. Osteoporos Int. 2008 Mar;19(3):365-72. Epub 2007 Oct 16.

Watts NB, Harris ST, Genant H, et al. Intermittent cyclical **etidronate** treatment of postmenopausal osteoporosis. N Engl J Med 1990; 323:73-79.

Watts NB, Diab DL. **Long-term use** of bisphosphosphonates in osteoporosis. J Clin Endocrinol Metab 2010 February 19 (Epub ahead of print).
Bisphosphonates have demonstrated antifracture efficacy in randomized, placebo-controlled trials of 3 and 4 yr duration and have been widely used since the initial release of alendronate in 1995. For zoledronic acid and risedronate, an early effect (fractures reduced within 6-12 months of starting therapy) has been shown. A sustained effect for risedronate has been shown through 5 yr and suggested through 7 yr. Ten-year data with alendronate and 8 yr data with risedronate indicated good tolerability and safety; it is unlikely that longer-term studies will be done.

Watts NB, Bilezikian JP, Camacho PM, et al. **AACE** Osteoporosis Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the **diagnosis and treatment of postmenopausal osteoporosis**. Endocr Pract 2010 Nov-Dec;16(Suppl 3):1-37.

Watts NB, Adler RA, Bilezikian JP, et al. **Osteoporosis in men**: an **Endocrine Society** clinical practice guideline. J Clin Endocrinol Metab. 2012 Jun;97(6):1802-22.

Weinstein Robert S. **Glucocorticoid-Induced Bone Disease**. N Engl J Med 2011; 365:62-70.

Wells G, Cranney A, Peterson J, et al. **Risedronate** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004523.

Wells GA, Cranney A, Peterson J, et al. **Etidronate** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003376.

Wells GA, Cranney A, Peterson J et al. **Alendronate** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database

TOP

RA - EXTRAS

Approach & Considerations for Drug Tx in RA

- Initial: DMARD + NSAID +/- Corticosteroid for symptoms. MTX often the DMARD of choice, however, HCQ is safer but suitable only for mild cases.
  -NSAIDs now used primarily for bridging and pain management.
  -Oral corticosteroids associated with complications, so use controversial. Short courses &/or low doses for ≤2yrs sometimes used (↓ joint pain & systemic symptoms). Intra-articular injections useful & few AEs.
  -Earlier combo DMARD or biologic tx warranted for those with high disease activity & poor prognositic factors.
  {Features of poor prognosis include: functional limitation, extraarticular disease rheumatoid nodules, RA vasculitis, Felty's syndrome, +'ve rheumatoid factor, anti-cyclic citrullinated peptide antibodies, bony erosions radiographic.}
- TNF inhibitors - 1st line biologics after an inadequate response to a DMARD. They are given +/- MTX (synergistic). Note, infliximab given with MTX (not recommended for monotherapy).
  - Initial TNF inhibitor choice: varies with clinician (often etanercept rapid onset, short t ½ or infliximab)
  - Relative to other agents, TNF-inhibitors may be more effective in relieving symptoms & limiting joint destruction. They often also act more rapidly.
  - AEs: 1) Injection site reactions (back pain, fever, urticaria, dyspnea, ↓BP): common with etanercept, golimumab, certolizumab, & adalimumab.
    2) Cytopenia: uncommon, but can occur with any anti-TNF tx. Monitor CBC.
    3) The potential for Serious Infections: (eg. bacterial sepsis, TB reactivated & disseminated, fungal, viral & opportunistic unusual eg. *p. jiroveci*) are important; screen for active infection, latent TB, etc.
    4) Malignancies (esp. lymphomas): reported but causality not established. The condition of RA ↑ lymphoma risk on its own. Avoid anti-TNF tx in patients with recent ca.
    5) Other AEs: (rare) – CHF, reversible lupus-like syndrome, demyelinating conditions eg. M.S. (avoid if hx), hepatoxicity (caution with infliximab).
  - If 1st TNF inhibitor is not effective, switching to a 2nd TNF inhibitor may be effective; however, many specialists will opt for a non-TNF biologic for a different mechanism of action.
- Non-TNF Biologics – include rituximab co-admin with a DMARD; pre-treat to prevent infusion reaction, abatacept +/- a DMARD, tocilizumab may work in ≥2wks, AEs (many; severe complications reported), anakinra less effective.
- Aggressive early therapy with MTX &/or a biologic ⇨ longer remissions, less joint destruction & improved quality of life.
- Combination Tx with 2-3 DMARDs (or a DMARD + biologic): often more effective than monotherapy without more toxicity.
  - Triple DMARD Tx: MTX +SSZ + HCQ (+/- prednisone low-dose ≤7.5-10mg/day) effective. ◆MTX + Biologic more efficatious than either alone. ◆Combination of 2+ Biologics NOT recommended as ↑ toxicity!
- Comorbidity & biologics ACR RA 2012:
  - 1) Hepatitis: a) Hep C ⇨ potentially recommend etanercept;
    b) Hep B: untreated chronic or treated chronic with Child-Pugh class B or higher: avoid any biologic!
  - 2) Malignancy: a) treated solid malignancy >5yrs or non-melanoma skin ca >5ys ago – recommend any biologic;
    b) treated solid malignancy <5yr or treated non-melanoma skin ca within 5yr – recommend rituximab;
    c) treated skin melanoma, & treated lymphoproliferative malignancy – recommend rituximab;
  - 3) CHF: a) NYHA class III-IV with ejection fraction ≤50%: avoid anti-TNF biologics!

Vaccinations: before DMARD or biologic, immunize for influenza, pneumococcal, hep-B & HZV. Live vaccines should not be given to patients on biologics (should be given ≥1 month prior to starting tx).

Pain Management in RA:

- Neuromodulators: Cochrane Review RCT, placebo controlled - few trials, all short term (~2-5 weeks) with high risk of bias (ie. Weak evidence)
  1) Nefopam (ACUPAN): not in Canada; 5HT, NE & DA receptor blocking; NNT=2 for pain relief, offset by significant SE's
  2) Topical capsaicin: reasonable add-onn option; NNT=2-3 for pain relief, offset by some burning at application site
  3) Oromucosal cannabis: small reduction in pain, highly offset by SE's leading to withdrawal (NNH=3) including dizziness 26%, dry mouth 13% & lightheadedness (10%)
  4) Lack of data for other agents included: anticonvulsants, ketamine, bupropion, methylphenidate

RHEUMATOID ARTHRITIS: DMARD Comparison Chart References (www.RxFiles.ca):

1. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46. http://www.rheumatology.org/publications/guidelines/raguidelines02.asp?aud=mem
   Guidelines for the management of rheumatoid arthritis: 2008 Update. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008 Jun 15;59(6):762-84. http://www.rheumatology.org/publications/guidelines/recommendations.asp?aud=mem
   Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39.
2. Treatment Guidelines: Drugs for Rheumatoid Arthritis. The Medical Letter: January, 2003; (5) pp. 25-32. Updated Vol 3 (Issue 40) Dec 2005. Updated Vol 7 (Issue 81) May 2009. May 2012.
3. Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. 1996 May;39(5):713-22.
4. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. 1996 May;39(5):723-31.
5. Drugs for Rheumatoid Arthritis. The Medical Letter July 10, 2000; (1082) pp. 57-64.
6. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001 Sep 15;358(9285):903-11.
7. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med. 2000 Mar 13;160(5):610-9.
8. Anakinra (Kineret) for Rheumatoid Arthritis. The Medical Letter: February 18, 2002; (1124) pp. 18-19.
9. Aletaha D, Kapral T, Smolen JS. Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. Ann Rheum Dis. 2003 May;62(5):482-6.
10. Adalimumab (Humira) for Rheumatoid Arthritis. The Medical Letter: March 31, 2003; (1153) pp. 25-27.
11. Micromedex 2011
12. Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2008.
13. Drug Information Handbook 10th edition, 2002-2003
14. Drugs in Pregnancy & Lactation 9th edition, 2011.
15. Geriatric Dosage Handbook 7th Edition, 2002

TOP

16. Handbook of Clinical Drug Data 10th edition, 2002
17. Therapeutic Choices 4rd edition, 2003
18. Moreland LW, O'Dell JR. Glucocorticoids and rheumatoid arthritis: back to the future? Arthritis Rheum. 2002 Oct;46(10):2553-63.
19. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.
20. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med. 2004 May 20;350(21):2167-79.
21 . USA Food & Drug Administration: Safety update meeting on TNF blocking agents Mar 4 & 5, 2003 http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t1.htm , http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t2.htm
22. O'Dell, James R., Therapeutic Strategies for Rheumatoid Arthritis. N Engl J Med 2004 350: 2591-2602.
Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580-8. In the new criteria set, classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in four domains: number and site of involved joints (range 0-5), serological abnormality (range 0-3), elevated acute-phase response (range 0-1) and symptom duration (two levels; range 0-1).
23. Fleischmann RM, Cohen SB, Moreland LW, et al.; iRAMT Study Group. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin. 2005 Aug;21(8):1181-90.
24. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1414-20.
25. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2005 Sep 15;72(6):1037-47.
26. Health Canada Jan/06 Hepatitis B Reactivation assoc. with the anti-TNFα products ENBREL (etanercept), HUMIRA (adalimumab), and REMICADE (infliximab)http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/anti-tnf_therap_hpc-cps_e.pdf
27. New drug: Orencia (abatacept). Pharmacist's Letter/Prescriber's Letter 2006;22(2):220207. (& also Medical Letter Feb 27,2006.)
28. Emery P. Treatment of rheumatoid arthritis. BMJ. 2006 Jan 21;332(7534):152-5.
29. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, et al. Canadian Rheumatology Association (CRA) Recommendations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs. J Rheumatol. 2011 Sep 15.

Additional references:

Agarwal SK, et al. Pattern of **infliximab utilization** in rheumatoid arthritis patients at an academic medical center. Arthritis Rheum. 2005 Dec;53(6):872-8.
Alarcon GS, McGwin G, Bertoli AM, et al. Effect of **hydroxychloroquine** on the survival of patients with systemic **lupus** erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). Ann Rheum Dis 2007;66:1168-72.
Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of **pemphigus vulgaris** with **rituximab** and intravenous immune globulin. N Engl J Med. 2006 Oct 26;355(17):1772-9.
Aletaha D, Neogi T, Silman AJ, et al. **2010 rheumatoid arthritis classification criteria**: an American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580-8. In the new criteria set, classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in four domains: number and site of involved joints (range 0-5), serological abnormality (range 0-3), elevated acute-phase response (range 0-1) and symptom duration (two levels; range 0-1).
Aletaha Daniel, Funovits Julia, Smolen Josef S. **Physical disability** in rheumatoid arthritis is associated with cartilage damage rather than bone destruction. Ann Rheum Dis 2011;70:733-739 Published Online First: 14 February 2011.
Aletaha D, Alasti F, Smolen JS. **Rheumatoid arthritis near remission**: clinical rather than laboratory inflammation is associated with radiographic progression. Ann Rheum Dis. 2011 Nov;70(11):1975-80.
Aksentijevich I, Masters SL, Ferguson PJ,et al. An Autoinflammatory Disease with Deficiency of the Interleukin-1-Receptor Antagonist. (**DIRA**) N Engl J Med. 2009 Jun 4;360(23):2426-2437.
Arabelovic S, et al. Preliminary evidence shows that folic acid fortification of the food supply is associated with higher methotrexate dosing in patients with rheumatoid arthritis. J Am Coll Nutr. 2007 Oct;26(5):453-5.This preliminary study suggests that folic acid supplementation may contribute to higher MTX dosing in patients with RA.
Arkema EV, Neovius M, Joelsson JK, et al. Is there a **sex bias in prescribing anti-tumour necrosis factor** medications to patients with rheumatoid arthritis? A nation-wide cross-sectional study. Ann Rheum Dis. 2012 Apr 13.
Arts E E A, Jansen T L, Broeder A Den, et al. **Statins inhibit the antirheumatic effects of rituximab** in rheumatoid arthritis: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Ann Rheum Dis 2011;70:877-878 Published Online First: 18 October 2010 doi:10.1136/ard.2010.136093.
Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the **EULAR** recommendations for the management of **psoriatic arthritis**. Ann Rheum Dis. 2011 Jul 28.
Askling J, van Vollenhoven RF, Granath F, et al. **Cancer risk** in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: Does the risk change with the time since start of treatment? Arthritis Rheum. 2009 Oct 29;60(11):3180-3189. During the first 6 years after the start of anti-TNF therapy in routine care, no overall elevation of cancer risk and no increase with followup time were observed.
Au WY, Ma ES, Choy C, Chung LP, Fung TK, Liang R, Kwong YL. Therapy-related **lymphomas** in patients with autoimmune diseases after treatment with disease-modifying anti-rheumatic drugs. Am J Hematol. 2006 Jan;81(1):5-11.
Bacani AK, Gabriel SE, Crowson CS, et al. Noncardiac vascular disease in rheumatoid arthritis: increase in **venous thromboembolic** events?. Arthritis Rheum. 2012 Jan;64(1):53-61.
Bakker MF, Jacobs JW, Welsing PM, et al. the Utrecht Arthritis Cohort Study Group. **Early clinical response to treatment predicts 5-year outcome** in RA patients: follow-up results from the CAMERA study. Ann Rheum Dis. 2011 Mar 15.
Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, et al. **Low-dose prednisone** inclusion into a **methotrexate-based**, tight control strategy for early rheumatoid arthritis. A randomized trial. Ann Intern Med. 2012;156:329-39.
Baranauskaite A, Raffayová H, Kungurov N, et al. **Infliximab plus methotrexate** is superior to methotrexate alone in the treatment of **psoriatic arthritis** in methotrexate-naive patients: the **RESPOND** study. Ann Rheum Dis. 2012 Apr;71(4):541-8.
Barnes PJ, Adcock IM. **Glucocorticoid resistance** in inflammatory diseases. Lancet. 2009 May 30;373(9678):1905-17.
Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. **Anti-infliximab and anti-adalimumab antibodies** in relation to response to adalimumab in infliximab switchers and anti-TNF naive patients: a cohort study. Ann Rheum Dis. 2009 Jul 5.
Bartelds Geertje M., Krieckaert Charlotte L. M., Nurmohamed Michael T., et al. Development of **Antidrug Antibodies Against Adalimumab** and Association With Disease Activity and Treatment Failure During Long-term Follow-up. *JAMA*. 2011;305(14):1460-1468.doi:10.1001/jama.2011.406
Baszis K, Garbutt J, Toib D, et al. Clinical outcomes after **withdrawal of anti-tumor necrosis factor-alpha therapy in juvenile idiopathic arthritis**: A twelve-year experience. Arthritis Rheum. 2011 Jun 23. doi: 10.1002/art.30502.
Bathon JM, Martin RW, et al A comparison of **etanercept** and **methotrexate** in patients with **early** rheumatoid arthritis. (**ERA trial**) N Engl J Med. 2000 Nov 30;343(22):1586-93.
Bathon J, Robles M, et al. Sustained disease remission and inhibition of radiographic progression in methotrexate-naïve patients with rheumatoid arthritis and poor prognostic factors treated with **abatacept**: 2-year outcomes. (**AGREE**) Ann Rheum Dis. 2011 Nov;70(11):1949-56.
Bernatsky S, Clarke AE, Suissa S. Hematologic **malignant neoplasms** after drug exposure in rheumatoid arthritis. Arch Intern Med. 2008 Feb 25;168(4):378-81. In this large cohort of patients with rheumatoid arthritis, the greatest relative risk for hematologic malignant neoplasms was noted after use of cyclophosphamide.
Beukelman T, Patkar NM, Saag KG, et al. **2011 American College of Rheumatology** recommendations for the treatment of **juvenile idiopathic arthritis**: Initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res(Hoboken). 2011 Apr;63(4):465-82. doi: 10.1002/acr.20460. http://www.rheumatology.org/practice/clinical/guidelines/ACR_2011_jia_full_manuscript.pdf
Beukelman T, Haynes K, Curtis JR, et al. Rates of **malignancy associated with juvenile idiopathic arthritis** and its treatment. Arthritis Rheum. 2012 Feb 10.
Beukelman T, Xie F, Chen L, et al; On behalf of the Safety Assessment of Biological ThERapeutics (SABER) Collaboration. Rates of **hospitalized bacterial infection** associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012 May 8.
Bingham CO 3rd, et al. **Immunization** responses in rheumatoid arthritis patients treated with **rituximab**: Results from a controlled clinical trial. Arthritis Rheum. 2009 Dec 28;62(1):64-74.
Bisset L, et al. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for **tennis elbow**: randomised trial. BMJ. 2006 Nov 4;333(7575):939. Epub 2006 Sep 29.
Bliddal H, et al. A randomized, controlled study of a single **intra-articular** injection of **etanercept** or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Sep-Oct;35(5):341-5.
Bodar EJ, Kuijk LM, Drenth JP, et al. On-demand **anakinra** treatment is effective in **mevalonate kinase deficiency**. Ann Rheum Dis. 2011 Dec;70(12):2155-8.
Boers M, Verhoeven AC, et al. Randomised comparison of combined step-down **prednisolone**, **methotrexate and sulphasalazine** with **sulphasalazine alone** in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18.
Bongartz T, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of **serious infections & malignancies**: systematic review & meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. (see also Pharmacist's Letter July 2006) Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI, 39-125) within a treatment period of 3 to 12 months. (Health Canada July/06 Possible Association of REMICADE® with hepatosplenic T-cell lymphoma in pediatric and young adult patients with Crohn's disease http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/remicade_3_hpc-cps_e.html) (Setoguchi S, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rh Arthritis Rheum. 2006 Aug 31;54(9):2757-2764 [Epub ahead of print] Our results indicate that users of biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with MTX users. Despite the use of large combined data

TOP

effect of an infrequent exposure (biologic DMARDs) on rare diseases (hematologic malignancies) remains a challenge.) (Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007 May;56(5):1433-9. In a study of lymphoma in 19,591 RA patients over 89,710 person-years of followup, which included exposure to anti-TNF therapy in 10,815 patients, we did not observe evidence for an increase in the incidence of lymphoma among patients who received anti-TNF therapy.)

Bose N, Calabrese LH. Q: Should I **order an anti-CCP antibody test** to diagnose rheumatoid arthritis? Cleve Clin J Med. 2012 Apr;79(4):249-52.

Bourre-Tessier J, Haraoui B. **Methotrexate drug interactions** in the treatment of rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jul;37(7):1416-21. Epub 2010 May 1.

Brandt J, Khariouzov A, et al. Six-month results of a double-blind, placebo-controlled trial of **etanercept** treatment in patients with active **ankylosing spondylitis**. Arthritis Rheum. 2003 Jun;48(6):1667-75.

Braun J, Brandt J, et al. Treatment of active **ankylosing spondylitis** with **infliximab**: a randomised controlled multicentre trial. Lancet. 2002 Apr 6;359(9313):1187-93.

Braun J, et al. Long-term efficacy & safety of **infliximab** in **ankylosing spondylitis**: an open, observational, extension study of a 3month, randomized, placebo-controlled trial. Arthritis Rheum. 2003 Aug;48(8):2224-33.

Braun J, Kästner P, Flaxenberg P, et al; MC-MTX.6/RH Study Group. Comparison of the clinical efficacy and safety of **subcutaneous (15-20mg) versus oral administration of methotrexate** (15mg) in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008 Jan;58(1):73-81. This 6-month prospective, randomized, controlled trial is the first to examine oral versus SC administration of MTX. We found that SC administration was significantly more effective than oral administration of the same MTX dosage. There was no difference in tolerability.

Braun J, Davis J, Dougados M, et al. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with **ankylosing spondylitis**. Ann Rheum Dis 2006; 65: 316–20.

Braun J, van den Berg R, Baraliakos X, et al. **2010 update of the ASAS/EULAR recommendations** for the management of **ankylosing spondylitis**. Ann Rheum Dis 2011;70:896-904 doi:10.1136/ard.2011.151027.

Braun J, Deodhar A, Inman RD, van et al. **Golimumab** administered subcutaneously every 4 weeks in **ankylosing spondylitis**: 104-week results of the GO-RAISE study. Ann Rheum Dis. 2011 Nov 11.

Braun J, Baraliakos X, Hermann KG, et al. **Golimumab** reduces spinal inflammation in **ankylosing spondylitis**: MRI results of the randomised, placebo- controlled GO-RAISE study. Ann Rheum Dis. 2012 Jun;71(6):878-84.

Breedveld FC, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2005 Dec 29;54(1):26-37 [Epub ahead of print]

Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of **anakinra** monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol. 2004 Jun;31(6):1103-11.

Buch MH, Smolen JS, Betteridge N, et al. for the **Rituximab Consensus** Expert Committee. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Mar 6.

Buchbinder R, Barber M, Heuzenroeder L, et al. Incidence of **melanoma** and other malignancies among rheumatoid arthritis patients treated with **methotrexate**. Arthritis Rheum. 2008 May 30;59(6):794-799.[Epub ahead of print]Compared with the general population, methotrexate-treated RA patients have an increased incidence of melanoma, non-Hodgkin's lymphoma, and lung cancer.

Bulatović M, Heijstek MW, Verkaaik M, et al. High prevalence of **methotrexate intolerance in juvenile** idiopathic arthritis: Development and validation of a methotrexate intolerance severity score. Arthritis Rheum. 2011 Mar 24. doi: 10.1002/art.30367.

Burmester Gerd R, Feist E, Kellner H, et al. Effectiveness and safety of the interleukin 6-receptor antagonist **tocilizumab** after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). Ann Rheum Dis 2011;70:755-759 Published Online First: 27 December 2010 doi:10.1136/ard.2010.139725.

Burmester Gerd, Lanas Angel, Biasucci Luigi, et al. The appropriate use of **non-steroidal anti-inflammatory drugs** (NSAIDS) in rheumatic disease: opinions of a multidisciplinary **European expert panel**. Ann Rheum Dis 2011;70:818-822 Published Online First: 10 September 2010 doi:10.1136/ard.2010.128660.

Burmester GR, Panaccione R, Gordon KB, et al. **Adalimumab: long-term safety (up to 12yrs)** in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2012 Jun 26.

Buszewicz M, et al. **Self management** of arthritis in primary care: randomised controlled trial. BMJ. 2006 Oct 13; [Epub ahead of print]

Buttgereit F. Do the treatment with **glucocorticoids** and/or the disease itself drive the impairment in glucose metabolism in patients with rheumatoid arthritis? Ann Rheum Dis. 2011 Nov;70(11):1881-3.

Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, et al. **Canadian Rheumatology Association** Recommendations for Pharmacological Management of **Rheumatoid Arthritis with Traditional and Biologic** Disease-modifying Antirheumatic Drugs. J Rheumatol. **2011** Sep 15.

Calguneri M, Pay S, et al. **Combination therapy** versus **monotherapy** for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1999 Nov-Dec;17(6):699-704.

Cameron M, Gagnier JJ, Chrubasik S. **Herbal therapy** for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD002948. Several herbal interventions are inadequately justified by single studies or non-comparable studies in the treatment of rheumatoid arthritis. There is moderate evidence that oils containing GLA (evening primrose, borage, or blackcurrant seed oil) afford some benefit in relieving symptoms for RA, while evidence for Phytodolor® N is less convincing.Tripterygium wilfordii products may reduce some RA symptoms, however, oral use may be associated with several side effects.

Campbell L, Chen C, Bhagat SS, et al. Risk of adverse events including **serious infections** in rheumatoid arthritis patients treated with **tocilizumab**: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2011 Mar;50(3):552-62.

Cassina M, Johnson D, Robinson L, et al. **Pregnancy outcome in women exposed to leflunomide** before or during pregnancy. Arthritis Rheum. 2012 Feb 3. n=45

Chakravarty EF, Michaud K, Wolfe F. **Skin cancer**, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005 Nov;32(11):2130-5. CONCLUSION: In this large, national cohort, RA was associated with an increased risk for development of NMSC. Among patients with RA, use of TNF inhibitors and prednisone were associated with an increased risk of NMSC.

Chambers CD, Johnson DL, Robinson LK, et al.. Birth outcomes in **pregnant women taking leflunomide**. Arthritis Rheum. 2010 Jan 28.

Chatzidionysiou K, Lie E, Nasonov E, et al. Effectiveness of disease-modifying antirheumatic drug **co-therapy with methotrexate and leflunomide in rituximab**-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. Ann Rheum Dis. 2012 Mar;71(3):374-7.

Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of **infliximab** monotherapy for plaque-type **psoriasis**: a randomised trial. Lancet. 2001 Jun 9;357(9271):1842-7.

Chen YF, et al. A systematic review of the effectiveness of **adalimumab**, **etanercept** and **infliximab** for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov;10(42):1-248.

Chen YJ et al. Association between systemic **anti-psoriatic drugs and cardiovascular risk** in patients with psoriasis and psoriatic arthritis: A nationwide cohort study. Arthritis Rheum. 2011 Dec 12.

Chilibeck PD, Vatanparast H, Cornish SM, Abeysekara S, Charlesworth S. Evidencebased risk assessment and recommendations for **physical activity**: arthritis, osteoporosis, and low back pain. Appl Physiol Nutr Metab 2011;36(Suppl 1):S49-S79.

Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. **Methotrexate and mortality** in patients with rheumatoid arthritis: a prospective study. Lancet. 2002 Apr 6;359(9313):1173-7.

Chung ES, Packer M, et al. Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of **infliximab**, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive **Heart Failure** (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40.

Chung HY, Machado P, van der Heijde D, et al. **Smokers in early axial spondyloarthritis** have earlier disease onset, more disease activity, inflammation and damage, and poorer function and healthrelated quality of life: results from the DESIR cohort. Ann Rheum Dis. Published Online First: 11 Oct 2011.

Clifford DB, Ances B, Costello C,et al. **Rituximab-Associated Progressive Multifocal Leukoencephalopathy** (PML) in Rheumatoid Arthritis. Arch Neurol. 2011 May 9.

Cochrane Musculoskeletal Group- **Patient Decision Aids** http://musculoskeletal.cochrane.org/decision-aids

Cohen S, Cannon GW, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with **leflunomide** compared with **methotrexate**. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group.(**ULTRA**) Arthritis Rheum. 2001 Sep;44(9):1984-92.

Cohen S, Hurd E, et al. Treatment of rheumatoid arthritis with **anakinra**, a recombinant human interleukin-1 receptor antagonist, in combination **with methotrexate**: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.

Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, Hanrahan PS, Kraishi MM, Patel A, Sun G, Bear MB; 990145 Study Group. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8. Epub 2004 Apr 13.

Cohen SB, Emery P, Greenwald MW, Dougados M, et al. **REFLEX** Trial Group. **Rituximab** for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006 Sep;54(9):2793-806.

Cohen SB, et al. **Rituximab** for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006 Aug 31;54(9):2793-2806 [Epub ahead of print]

Combe B, et al. Etanercept European Investigators Network (Etanercept Study 309 Investigators). **Etanercept and sulfasalazine**, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a do comparison. Ann Rheum Dis. 2006 Oct;65(10):1357-62. Epub 2006 Apr 10.

TOP

Conaghan PG, Emery P, et al. Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving **golimumab**: results of the **GO-FORWARD** trial. Ann Rheum Dis. 2011 Nov;70(11):1968-74.

Coulson E, Saravanan V, Hamilton J, et al. **Pneumococcal antibody levels after pneumovax** in patients with rheumatoid arthritis on methotrexate. Ann Rheum Dis. 2011 Jul;70(7):1289-91.

Crowson CS, et al. How much of the increased incidence of **heart failure** in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? Arthritis Rheum. 2005 Oct;52(10):3039-44.

Crowson Cynthia S, Gabriel Sherine E. Towards improving **cardiovascular risk management** in patients with rheumatoid arthritis: the need for accurate risk assessment. Ann Rheum Dis 2011;70:719-721 Published Online First: 22 February 2011 doi:10.1136/ard.2010.145482.

Coulson E, Saravanan V, Hamilton J, et al. **Pneumococcal antibody levels after pneumovax** in patients with rheumatoid arthritis on methotrexate. Ann Rheum Dis. 2011 Apr 22.

Curtis JR, Beukelman T, Onofrei A, Cassell S, et al. **Elevated liver enzyme tests** among patients with rheumatoid arthritis or psoriatic arthritis treated with **methotrexate and/or leflunomide**. Ann Rheum Dis [Internet]. 2010 Jan;69(1):43-7.

Curtis JR, Chen L, Luijtens K, et al. **No additional efficacy with dose escalation of certolizumab** pegol from 200 mg to 400 mg every other week: An analysis of individual patient-level data from RAPID 1. Arthritis Rheum. 2011 Apr 11.

Curtis JR, Xie F, Chen L, et al. The comparative risk of **serious infections** among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis. 2011 Aug;70(8):1401-6.

Dagfi nrud H, Kvien TK, Hagen KB. Physiotherapy interventions for **ankylosing spondylitis**. Cochrane Database Syst Rev 2008; 1: CD002822.

Daïen CI, Duny Y, Barnetche T, et al. Effect of **TNF inhibitors on lipid profile** in rheumatoid arthritis: a systematic review with meta-analysis. Ann Rheum Dis. 2012 Jun;71(6):862-8.

Dalrymple JM, Stamp LK, O'Donnell JL, Chapman PT, Zhang M, Barclay ML. **Pharmacokinetics of oral methotrexate** in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Nov;58(11):3299-308.

Da Silva JA, et al. Safety of **low dose glucocorticoid** treatment in rheumatoid arthritis: published evidence and prospective trial data.Ann Rheum Dis. 2006 Mar;65(3):285-93. Epub 2005 Aug 17. (InfoPOEMs: Available data are scant, but seem to provide evidence that low-dose glucocorticoids (10 mg or less of prednisolone/equivalent) in the treatment of rheumatoid arthritis do not increase osteoporotic fractures, blood pressure, cardiovascular diseases, or peptic ulcer incidence. Weight gain is common when taking these drugs, as are skin changes. (LOE = 2b))

Davies R, Galloway JB, Watson KD, Lunt M, Symmons DP, Hyrich KL; ; BSRBR Control Centre Consortium, British Society for Rheumatology Biologics Register. **Venous thrombotic events** are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Jul 22.

De Benedetti F, Brunner H, Ruperto N, et al. Effi cacy and safety of **tocilizumab** in patients with systemic juvenile idiopathic arthritis (sJIA): 12-week data from the phase 3 tender trial. Ann Rheum Dis 2010; 69 (suppl 146): 146.

den Uyl D, van Raalte DH, Nurmohamed MT, et al. Metabolic effects of **high-dose prednisolone** treatment in early rheumatoid arthritis: Diabetogenic effects and inflammation reduction on the balance. Arthritis Rheum. 2011 Sep 27.

Diak P, Siegel J, La Grenade L, Choi L, Lemery S, McMahon A. **Tumor necrosis factor alpha blockers and malignancy in children**: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum. 2010 Aug;62(8):2517-24.

Dixon WG, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving **anti-tumor necrosis factor** therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Jul 25;54(8):2368-2376 [Epub ahead of print]

Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2009 Oct 22. [Epub ahead of print] The rate of TB in patients with RA treated with anti-TNF therapy was 3-4 fold higher in patients receiving infliximab and adalimumab compared to etanercept.

Dixon WG, Kezouh A, Bernatsky S, et al. The influence of **systemic glucocorticoid** therapy upon the risk of **non-serious infection** in older patients with rheumatoid arthritis: a nested case-control study. Ann Rheum Dis. 2011 Feb1.

Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of **oral glucocorticoid** therapy on risk of **serious infection** in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012 Jan 12.

Donahue KE, Gartlehner G, Jonas DE, et al. Systematic Review: Comparative Effectiveness and Harms of Disease-Modifying Medications for Rheumatoid Arthritis. Ann Intern Med. 2007 Nov 19; [Epub ahead of print] Limited available comparative evidence does not support one monotherapy over another for adults with rheumatoid arthritis. Although combination therapy is more effective for patients whose monotherapy fails, the evidence is insufficient to draw firm conclusions about whether one combination or treatment strategy is better than another or is the best treatment for early rheumatoid arthritis.

Dougados M, Braun J, Szanto S, et al. Efficacy of **etanercept** on rheumatic signs and pulmonary function tests in advanced **ankylosing spondylitis**: results of a randomised double-blind placebo-controlled study (SPINE). Ann Rheum Dis 2011;70:799-804 Published Online First: 13 February 2011 doi:10.1136/ard.2010.139261.

Dougados M, Baeten D. **Spondyloarthritis**. Lancet. (psoriatic arthritis, reactive arthritis, arthritis related to IBD, subgroup of JIA & ankylosing spondylitis) 2011 Jun 18;377(9783):2127-37.

Ducharme J, Pelletier C, Zacharias R. The safety of **infliximab infusions** in the community setting. Can J Gastroenterol. 2010 May;24(5):307-11.

Edwards JC, et al. Efficacy of B-cell-targeted therapy with **rituximab** in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81.

Emery P, et al. DANCER Study Group. The efficacy and safety of **rituximab** in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006 May;54(5):1390-400.

Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of **methotrexate and etanercept** in active, early, moderate to severe rheumatoid arthritis (**COMET**): a randomised, double-blind, parallel treatment trial. Lancet. 2008 Aug 2;372(9636):375-82. Epub 2008 Jul 16.

Emery P, Breedveld F, van der Heijde D, et al. Combination of **Methotrexate and Etanercept** in Early Rheumatoid Arthritis Trial Group. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: A two-year, double-blind, randomized study. Arthritis Rheum. 2010 Feb 25;62(3):674-682.

Emery P, Fleischmann R, van der Heijde D, et al. The effect of **golimumab** on radiographic progression in rheumatoid arthritis: Results of the GO-BEFORE and GO-FORWARD randomized, controlled studies. Arthritis Rheum. 2011 Jan 28.

Emery P, Kvien TK, Combe B, et al. Combination **etanercept and methotrexate provides better disease control in very early (≤4 months)** versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the COMET study. *Ann Rheum Dis* 2012; published online March 8. DOI:10.1136/annrheumdis-2011-201066.

Emery P, Smolen JS, Kavanaugh A, et al. **Maintenance of biologic-free disease control** in early rheumatoid arthritis patient after induction of low disease activity with adalimumab plus methotrexate. *Ann Rheum Dis* 2011; **70** (suppl 3)**:** 262–63.

Emery P, Kvien TK, Combe B, et al. Combination **etanercept and methotrexate** provides better disease control in very early (<=4 months) versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the **COMET** study. Ann Rheum Dis. 2012 Jun;71(6):989-92.

Ersoy A, Baran B, Ersoy C, Kahvecioglu S, Akdag I. Calcineurin inhibitors and post-transplant weight gain. Nephrology (Carlton). 2008 Mar 5; [Epub ahead of print] Only pretransplant BMI, creatinine clearance, **cyclosporine A** usage, being hypertensive and dysplipidemic were independent predictors of weight gain at the 12th month. Our results suggested that the type of immunosuppression may affect post-transplant weight gain.

Estellat C, Ravaud P. **Lack of head-to-head trials and fair control arms**: randomized controlled trials of biologic treatment for rheumatoid arthritis. Arch Intern Med. 2012;172(3):237-244.

Faber WR, et al. Treatment of recurrent **erythema nodosum leprosum** with **infliximab**. N Engl J Med. 2006 Aug 17;355(7):739.

FDA July/10 will require that the label for the rheumatoid arthritis drug **leflunomide (Arava)** carry an added warning for severe liver injury. The label already warns against the drug's use in pregnant women and those of childbearing potential. The new warning comes after the FDA received **49 reports of severe liver injury**, including 14 instances of fatal liver failure, from 2002 to 2009. Risk for liver injury was higher among patients using other drugs associated with liver injury and patients with liver disease. Clinicians should monitor liver enzymes at least monthly for 3 months after beginning the drug. After that, enzymes should be monitored every quarter. Treatment should be halted if liver enzymes rise to two times the upper limit of normal. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm218912.htm

FDA Sep/11 notified healthcare professionals that the Boxed Warning for the entire class of **Tumor Necrosis Factor-alpha (TNFα) blockers** has been updated to include the risk of infection from two bacterial pathogens, **Legionella and Listeria**. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNFα blockers have been revised so that they contain consistent information about the risk for serious infections and the associated disease-causing pathogens.

Felson David T, Smolen Josef S, Wells George, et al. American College of Rheumatology/European League Against Rheumatism Provisional **Definition of Remission** in Rheumatoid Arthritis for Clinical Trials. Ann Rheum Dis 2011;70:404-413.

Finckh A, Simard JF, Gabay C, Guerne PA; SCQM physicians. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):746-52.

Finckh A Finckh A, Bansback N, et al. Treatment of very early rheumatoid arthritis with symptomatic therapy, **disease-modifying antirheumatic drugs**, or biologic agents: a cost-effectiveness analysis. Ann Intern Med. 2009 Nov 3;151(9):612-21.

Fleischmann RM, et al. **Anakinra**, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra),in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003 Apr;48(4):927-34.

Fleischmann RM, et al. Safety of extended treatment with **anakinra** in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Aug;65(8):1006-12. Epub 2006 Jan 5.

Fleischmann R, Cutolo M, Genovese MC, et al. Phase 2B dose-ranging study of the oral JAK inhibitor **tofacitinib** (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to DMARDs. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33383.

Foell Dirk; Wulffraat Nico; Wedderburn Lucy R.; et al. for the Paediatric Rheumatology International Trials Organization (PRINTO) **Methotrexate Withdrawal at 6 vs 12 Months in Juvenile** Idiopathic Arthritis in Remission: A Randomized Clinical Trial. JAMA. 2010;303(13):1266-1273.

Fournier MR, Klein J, Minuk GY, Bernstein CN. Changes in **Liver Biochemistry** During **Methotrexate** Use for Inflammatory Bowel Disease. Am J Gastroenterol. 2010 Feb 16. Methotrexate is commonly associated with LET abnormalities, but these frequently normalize while still on therapy, and in only 5% will drug discontinuation be necessary. Liver biopsies rarely have substantive abnormalities

TOP

Furst DE, et al. Updated consensus statement on **biological agents**, specifically tumour necrosis factor {alpha} (TNF{alpha}) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2005. Ann Rheum Dis. 2005 Nov;64 Suppl 4:iv2-14.

Gabay C, Bel M, Combescure C, et al; for the **H1N1** study group. Impact of synthetic and biological disease modifying antirheumatic drugs on antibody responses to the ASO3-adjuvanted pandemic influenza vaccine. Arthritis Rheum. 2011 Mar 7. doi: 10.1002/art.30325.

Galloway JB, Hyrich KL, Mercer LK, et al. BSRBR Control Centre Consortium, Symmons DP; on behalf of the British Society for Rheumatology Biologics Register. **Anti-TNF therapy is associated with an increased risk of serious infections** in patients with rheumatoid arthritis especially in the **first 6 months** of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2010 Jul 31.

Galloway JB, Hyrich KL, Mercer LK, et al. on behalf of the BSR Biologics Register. **Risk of septic arthritis** in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Jul 21.

Galloway JB, Mercer LK, Moseley A, et al. Risk of **skin and soft tissue infections (including shingles)** in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2012 Apr 24.

Gaujoux-Viala C, Smolen JS, Landewé R, et al. Current evidence for the management of rheumatoid arthritis with **synthetic disease-modifying antirheumatic drugs**: a systematic literature review informing the **EULAR** recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9. Epub

Geborek P, Bladstrom A, et al.. **Tumour necrosis factor blockers** do not increase overall tumour risk in patients with rheumatoid arthritis, but **may** be associated with an **increased** risk of **lymphomas**. Ann Rheum Dis. 2005 May;64(5):699-703.

Gelinck LB, van der Bijl AE, Beyer WE, et al. The effect of **anti-tumor necrosis factor** alpha treatment on the antibody response to **influenza vaccination**. Ann Rheum Dis. 2007 Oct 26; [Epub ahead of print] The antibody response to influenza vaccination in patients treated with anti-TNF is only modestly impaired. The proportion of patients that achieves a protective titer is not significantly diminished by the use of TNF blocking therapies.

Genevay S, Finckh A, Zufferey P et al. **Adalimumab** in **acute sciatica** reduces the long-term need for surgery: a 3-year follow-up of a randomised double-blind placebo-controlled trial. Ann Rheum Dis. 2012 Apr;71(4):560-2.

Genovese MC, Bathon JM, et al. **Etanercept** versus **methotrexate** in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002 Jun;46(6):1443-50.

Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, Bekker P; 20000223 Study Group. **Combination** therapy with **etanercept and anakinra** in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004 May;50(5):1412-9.

Genovese MC, Becker JC, Schiff M, et al. **Abatacept** for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition (**ATTAIN**). N Engl J Med. 2005 Sep 15;353(11):1114-23.

Genovese M, Covarrubias A, Leon G, et al. **Subcutaneous abatacept** versus intravenous abatacept: A phase IIIb non-inferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011 May 25.

Gladman DD, et al. **Adalimumab** improves joint- and skin-related functional impairment in patients with **psoriatic arthritis**: Patient- reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial (**ADEPT**). Ann Rheum Dis. 2006 Oct 17; [Epub ahead of print]

Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of **four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study)**: A randomized, controlled trial. Arthritis Rheum. 2005 Nov;52(11):3381-90. CONCLUSION: In patients with early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy. (Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial (BeSt). Ann Intern Med. 2007 Mar 20;146(6):406-15. Currently available antirheumatic drugs can be highly effective in patients with early rheumatoid arthritis in a setting of tight disease control. Initial combination therapies seem to provide earlier clinical improvement and less progression of joint damage, but all treatment strategies eventually showed at 2yrs similar clinical improvements. In addition, combination therapy can be withdrawn successfully and less treatment adjustments are needed than with initial monotherapies.)

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. **Comparison of treatment strategies** in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007 Mar 20;146(6):406-15.

Goldbach-Mansky R, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. (anakinra) N Engl J Med. 2006 Aug 10;355(6):581-92.

Goldbach-Mansky R., et al. Comparison of **Tripterygium wilfordii Hook F** Versus Sulfasalazine in the Treatment of Rheumatoid Arthritis: A Randomized Trial. Ann Intern Med 2009; 229-240.

Gómez-Reino JJ, Rodríguez-Lozano C, Campos-Fernández Cet al. Change in the **discontinuation pattern of tumour necrosis factor antagonists** in rheumatoid arthritis over 10 years: data from the Spanish registry BIOBADASER 2.0. Ann Rheum Dis. 2012 Mar;71(3):382-385. (inefficacy being the main reason)

Gómez-Reino J. **Biologic monotherapy as initial treatment** in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2012 Jul;51 Suppl 5:v31-v37.

Gordon KB, et al. Clinical response to **adalimumab** in patients with moderate to severe **psoriasis**: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006 Oct;55(4):598-606. Epub 2006 Aug 10.

Gossec L, Smolen JS, Gaujoux-Viala C, et al. European League Against Rheumatism recommendations for the management of **psoriatic arthritis** with pharmacological therapies. Ann Rheum Dis. 2011 Sep 27.

Gottenberg J, Ravaud P, Bardin T, et al. on behalf of all the investigators of the AIR registry the French Society of Rheumatology.. Risk factors of severe **infections** in patients with rheumatoid arthritis treated with rituximab in the AutoImmunity And **Rituximab** (AIR) registry. Arthritis Rheum. 2010 May 6.

Gottenberg JE, Ravaud P, Cantagrel A, et al. **Positivity for anti-cyclic citrullinated peptide** is associated with a better response to **abatacept**: data from the 'Orencia and Rheumatoid Arthritis' registry. Ann Rheum Dis. 2012 May 21.

Gottlieb AB, et al. **Infliximab** induction therapy for patients with severe plaque-type **psoriasis**: a randomized, double-blind, placebo-controlled trial.J Am Acad Dermatol. 2004 Oct;51(4):534-42.

Gorman JD, Sack KE, et al. Treatment of **ankylosing spondylitis** by inhibition of tumor necrosis factor alpha **etanercept**. N Engl J Med. 2002 May 2;346(18):1349-56.

Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with **glucocorticoids**: a systematic literature review informing the **EULAR** recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1010-4. Epub 2010 May 6.

Griffiths, Christopher E.M., Strober, Bruce E., van de Kerkhof, Peter, et ak, the ACCEPT Study Group, Comparison of **Ustekinumab** and Etanercept for Moderate-to-Severe Psoriasis. N Engl J Med 2010 362: 118-128.

Grigor C, et al. Effect of a treatment strategy of **tight control** for rheumatoid arthritis (the **TICORA study**): a single-blind randomised controlled trial. Lancet. 2004 Jul 17-23;364(9430):263-9.

Graudal N, Jürgens G. Similar effects of **disease modifying anti rheumatic drugs, glucocorticoids and biologics** on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomised placebo or drug controlled studies including 112 comparisons. Arthritis Rheum. 2010 Jun 17. DMARDs, glucocorticoids, biologics and combination treatments significantly reduced radiographic progression at one year with a relative effect of 50-80%.

Greenberg Jeffrey D, Kremer Joel M, Curtis Jeffrey R, et al. , on behalf of the CORRONA Investigators. Tumour necrosis factor antagonist use and associated **risk reduction of cardiovascular events** among patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:576-582

Greenberg JD, Reed G, Decktor D, et al.on behalf of the **CORRONA** Investigators. A comparative effectiveness study of **adalimumab, etanercept and infliximab** in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. Ann Rheum Dis. 2012 Jan 30.

Greenwald MW, Shergy WJ, Kaine JL, et al. Evaluation of the safety of **rituximab in combination with a tumor necrosis factor inhibitor and methotrexate** in patients with active rheumatoid arthritis: results from a randomized controlled trial. Arthritis Rheum. 2011 Mar;63(3):622-32. doi: 10.1002/art.30194.

Gremese E, Carletto A, et al. the Gruppo Italiano di Studio sulle Early Arthritis (GISEA). **Obesity reduces** the response rate to anti TNFα in rheumatoid arthritis. an approach to a personalized medicine. Arthritis Care Res (Hoboken). 2012 Jun 21.

Grijalva CG, Chen L, Delzell E, et al. Initiation of **tumor necrosis factor-alpha antagonists** and the risk of hospitalization for **infection** in patients with autoimmune diseases. [published online November 6, 2011]. JAMA.

Hackmon, Rinat, Sakaguchi, Sachi, Koren, Gideon. Effect of **methotrexate treatment of ectopic pregnancy on subsequent pregnancy**. Can Fam Physician 2011 57: 37-39.

Hashkes PJ, Laxer RM. Medical treatment of **juvenile idiopathic arthritis**. JAMA. 2005 Oct 5;294(13):1671-84. (InfoPOEMs: Nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of corticosteroids, methotrexate, and possibly biologic-modifiers are somewhat beneficial in the management of juvenile idiopathic arthritis (JIA), particularly oligoarthritis. Patients with polyarthritis and a positive rheumatoid factor respond poorly to medications and require aggressive individual management. (LOE = 1a-))

Haraoui B, Cameron L, Ouellet M, White B. **Anti-infliximab antibodies** in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. J Rheumatol. 2006 Jan;33(1):31-6.

Harrold LR, Harrington JT, Curtis JR, et al. **Prescribing practices** in a US cohort of rheumatoid arthritis patients before and after publication of the ACR treatment recommendations. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33380.

Health Canada Aug/09 TNF blockers & risk of **cancer** in children and young adults http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_137-eng.php

Health Canada June/11 **RITUXAN (rituximab) - Fatal Infusion Related Reactions** in Patients with Rheumatoid Arthritis

Heijstek MW, Ott de Bruin LM, Bijl M, et al. EULAR recommendations for **vaccination in paediatric patients with rheumatic diseases**. Ann Rheum Dis. 2011 Oct;70(10):1704-12.

Heijstek MW, van Gageldonk PG, et al. Differences in persistence of **measles, mumps, rubella, diphtheria and tetanus antibodies** between children with **rheumatic disease** and healthy controls: a retrospective cross-sectional study. Ann Rheum Dis. 2012 Jun;71(6):948-54. (lower antibody rates in: mumps, rubella, diphtheria and tetanus)

Henes JC, Schedel J, Kanz L, Koetter I. **Rituximab** and concomitant **leflunomide** for the treatment of rheumatoid arthritis. Rheumatol Int. . [Epub ahead of print]

Hetland ML, Stengaard-Pedersen K, Junker P, et al. **CIMESTRA** study group. **Aggressive combination therapy** with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheum

TOP

arthritis: second-year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis. 2008 Jun;67(6):815-22. Epub 2007 Sep 18.
Hetland ML, Ostergaard M, Ejbjerg B, et al; **CIMESTRA** study group. Short- and long-term efficacy of **intra-articular injections with betamethasone** as part of a treat-to-target strategy in early rheumatoid arthritis: impact of joint area, repeated injections, MRI findings, anti-CCP, IgM-RF and CRP. Ann Rheum Dis. 2012 Jun;71(6):851-6.
Hider SL, et al. Comparing the long-term clinical outcome of treatment with **methotrexate or sulfasalazine** prescribed as the first disease-modifying antirheumatic drug in patients with inflammatory polyarthritis. Ann Rheum Dis. 2006 Nov;65(11):1449-55. Epub 2006 Mar 15.
Hjardem E, Ostergaard M, Podenphant J, et al.. Do rheumatoid arthritis patients in clinical practice benefit from **switching from infliximab to a second tumor necrosis factor** alpha inhibitor? Ann Rheum Dis. 2007 Sep;66(9):1184-9. Epub 2007 Mar 27. Lack of efficacy switchers had a better clinical response to the second treatment. Adverse effect switchers responded equally well to both treatments, with a low risk of discontinuing the second drug as a result of AE. Drug survival of the switchers' second biological therapy was higher than of the first, but lower than that of non-switchers. No difference between various sequences of drugs were found. Danish post-marketing data thus support that RA patients may benefit from switching biological therapy.
Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. **Bioavailability of higher dose methotrexate comparing oral and subcutaneous** administration in patients with rheumatoid arthritis. J Rheumatol. 2004 Apr;31(4):645-8.
Hoekstra M, et al. **Splitting high-dose oral methotrexate** improves bioavailability: a pharmacokinetic study in patients with rheumatoid arthritis. J Rheumatol. 2006 Mar;33(3):481-5. Epub 2006 Jan 15.
Hoes JN, Jacobs JW, Boers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis. 2007 Dec;66(12):1560-7. Epub 2007 Jul 27.
Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral **glucocorticoids** in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009 Dec;68(12):1833-8. Epub 2008 Dec 9.
Hoes JN, van der Goes MC, et al. Glucose tolerance, insulin sensitivity and {beta}-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose **glucocorticoids**. Ann Rheum Dis. 2011 Nov;70(11):1887-94.
Holle JU, Dubrau C, Herlyn K, et al. **Rituximab** for refractory **granulomatosis with polyangiitis** (**Wegener's granulomatosis**): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis. 2012 Mar;71(3):327-33.
Holvast A, et al. Safety & efficacy of influenza vaccination in systemic **lupus** erythematosus patients with quiescent disease. Ann Rheum Dis. 2006 Jul;65(7):913-8. Epub 2005 Dec1.
Horneff G, Ebert A, Fitter S, et al. Safety and effi cacy of once **weekly etanercept** 0.8 mg/kg in a multicentre 12 week trial in active polyarticular course juvenile idiopathic arthritis. Rheumatology (Oxford) 2009; 48: 916–19.
Horneff G, De Bock F, et al. Safety and efficacy of combination of **etanercept and methotrexate** compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis 2009; 68: 519–25.
Huizinga Tom W.J. Pincus Theodore **In the Clinic**: **Rheumatoid Arthritis**. *Ann Intern Med* July 6, 2010 153:ITC1-1; doi:10.1059/0003-4819-153-1-201007060-01001.
Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, et al. Dynamic **exercise programs** (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006853.
Hyrich KL, et al. Comparison of the response to **infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying** antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 May 30;54(6):1786-1794 [Epub ahead of print]
Iacono AT, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med. 2006 Jan 12;354(2):141-50.
Iannone F, Gremese E, et al. **Longterm** Retention of **Tumor Necrosis Factor-α Inhibitor** Therapy in a Large Italian Cohort of Patients with Rheumatoid Arthritis from the GISEA Registry: An Appraisal of Predictors. J Rheumatol. 2012 Apr 1.
Iking-Konert C, Aringer M, Wollenhaupt J, et al. Performance of the new 2011 ACR/EULAR remission criteria with **tocilizumab** using the phase IIIb study **TAMARA** as an example and their comparison with traditional remission criteria. Ann Rheum Dis. 2011 Nov;70(11):1986-90.
Jamnitski A et al. Patients **non-responding to etanercept obtain lower etanercept concentrations** compared with responding patients. Ann Rheum Dis. 2012 Jan;71(1):88-91.
Johnsen AK, Schiff MH, Mease PJ, et al. Comparison of 2 Doses of **Etanercept (50 vs 100 mg)** in Active Rheumatoid Arthritis: a Randomized Double Blind Study. J Rheumatol. 2006 Feb 15; [Epub ahead of print]
Kaine J et al. Evaluation of **abatacept administered subcutaneously** in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase Iiib ALLOW study). Ann Rheum Dis. 2012 Jan;71(1):38-44.
Kalden JR, Schattenkirchner M, et al. The efficacy and safety of **leflunomide** in patients with active rheumatoid arthritis: a five-year followup study. Arthritis Rheum. 2003 Jun;48(6):1513-20.
Källberg Henrik, Ding Bo, Padyukov Leonid, et al. EIRA Study Group. Concise report: **Smoking** is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis 2011;70:508-511 Published Online First: 13 December 2010 doi:10.1136/ard.2009.120899.
Kane S, Ford J, Cohen R, Wagner C. **Absence of Infliximab in Infant Sera and Breast Milk** From Nursing Mothers Receiving Therapy for Crohn's Disease Before and After Delivery. J Clin Gastroenterol. 2009 Jan 12. [Epub ahead of print]n=3. Infliximab was detected in the mothers' sera, but not in the breast milk of nursing mothers or in the sera of the breast-fed newborns. Data from this small series of patients suggest that infliximab was not transferred from mother to child, either in utero or through breast milk. These data suggest that mothers receiving infliximab should not be discouraged from nursing their children.
Kane SV, Acquah LA. **Placental transport of immunoglobulins**: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104:228-233.
Källberg H, Ding B, Padyukov L, et al. EIRA Study Group. **Smoking** is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis. 2010 Dec 13.
Kapetanovic MC, Roseman C, Jönsson G, et al. **Methotrexate but not TNF-blockers reduces antibody response following pneumococcal vaccination** using 7-valent conjugate pneumococcal vaccine in adult patients with established arthritis. Arthritis Rheum. 2011 Aug 10.
Katchamart W, Bourré-Tessier J, Donka T, Drouin J, Rohekar G, Bykerk VP. **Canadian recommendations for use of methotrexate** in patients with rheumatoid arthritis. J Rheumatol [Internet]. 2010 Jul;37(7):1422-30.
Katchamart W, Trudeau J, Phumethum V, Bombardier C. **Methotrexate monotherapy versus methotrexate combination** therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database of Syst Rev [Internet]. 2010 Apr [cited 2011 Apr 11];(4):CD008495.
Kavanaugh A, et al. The **Infliximab** Multinational **Psoriatic Arthritis** Controlled Trial (**IMPACT**): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006 Aug;65(8):1038-43. Epub 2006 Jan 26.
Kavanaugh A, van der Heijde D, McInnes I, et al. **Golimumab**, a human TNF-alpha antibody, administered every 4 weeks as a subcutaneous injection in **psoriatic arthritis**: Clinical efficacy, radiographic, and safety findings through 1year of the randomized, placebo-controlled, **GO-REVEAL**® study. Arthritis Rheum. 2012 Feb 29.
Keeling S, et al. Prospective observational analysis of the efficacy and safety of low-dose (3 mg/kg) infliximab in **ankylosing spondylitis**: 4-year followup. J Rheumatol. 2006 Mar;33(3):558-61. Epub 2006 Feb 1.
Keystone EC, Schiff MH, et al. **Once-weekly** administration of 50 mg **etanercept** in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.
Keystone EC, Genovese MC, Klareskog L, et al. GO-FORWARD Study. **Golimumab**, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the **GO-FORWARD** Study. Ann Rheum Dis. 2009 Jun;68(6):789-96. Epub 2008 Dec 9.
Keystone EC, Kremer JM, Russell A, et al. **Abatacept** in subjects who switch from intravenous to **subcutaneous** therapy: results from the phase IIIb ATTUNE study. Ann Rheum Dis. 2012 Jun;71(6):857-61.
Khanna D, Park GS, Paulus HE, et al. **Reduction of the efficacy of methotrexate** by the use of **folic acid**: post hoc analysis from two randomized controlled studies. Arthritis Rheum. 2005 Oct;52(10):3030-8.
Khanna D, McMahon M, Furst DE. **Safety of tumour necrosis factor-alpha antagonists**. (Pregnancy) Drug Saf. 2004;27(5):307-24.
Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of **glucocorticoids** on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD006356.
Klarenbeek NB, Kerstens PJ, Huizinga TW, et al. **Recent advances in the management of rheumatoid arthritis**. BMJ. 2010 Dec 21;341:c6942. doi: 10.1136/bmj.c6942.
Klarenbeek NB, van der Kooij SM, Güler-Yüksel M, et al. **Discontinuing treatment in patients with rheumatoid arthritis** in sustained clinical remission: exploratory analyses from the BeSt study. Ann Rheum Dis. 2011 Feb;70(2):315-9.
Klareskog Lars, van der Heijde Désirée, de Jager Julien P, et al. for the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the **combination** of **etanercept** and **methotrexate compared** with each treatment **alone** in patients with rheumatoid arthritis: double-blind randomised controlled trial. The Lancet Volume 363, Number 9410 28 February 2004.
Klareskog L, Catrina AI, Paget S. **Rheumatoid arthritis**. Lancet. **2009** Jan 19. [Epub ahead of print]
Klein A, Kaul I, et al. Efficacy and safety of **oral and parenteral methotrexate** therapy in children with juvenile idiopathic arthritis. An observational study with patients of the German Methotrexate Registry. Arthritis Care Res. 2012 May 30.
Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of **tocilizumab** for rheumatoid arthritis in Japan: interim analysis of 3881 patients. Ann Rheum Dis. 2011 Dec;70(12):2148-51.
Komano Y et al. Incidence and risk factors for **serious infection** in patients with rheumatoid arthritis treated with **tumor necrosis factor inhibitors**: A report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. J Rheumatol 2011 Jul; 38:1258. (about double the infection risk)
Korpela M, Laasonen L, Hannonen P, et al.; FIN-RACo Trial Group. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with **disease-modifying antirheumatic drugs**: five-year experience from the FIN-RACo study. Arthritis Rheum. 2004 Jul;50(7):2072-81.
Korswagen LA, Bartelds GM, Krieckaert CL, et al. Venous and arterial **thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies**: a case series and cohort study. Arthritis Rheum. 2011 Apr;63(4):877-83.
Kremer JM, et al. Concomitant **leflunomide** therapy in patients **with** active rheumatoid arthritis despite stable doses of **methotrexate**. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002 Nov 5;137(9):726-3
Kremer JM, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator **abatacept**: Twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Aug;52(8):22

TOP

Kremer JM, et al. Effects of **abatacept** in patients with **methotrexate-resistant** active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006 Jun 20;144(12):865-76. Summary for patients in: Ann Intern Med. 2006 Jun 20;144(12):I18. (but fair number of pts may have been partial MTX responders)
Kremer JL, Blanco R, Brzosko M, et al. **Tocilizumab** inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at 1 year: The **LITHE** study. Arthritis Rheum. 2010 Nov 19.
Kremer JM, Russell AS, Emery P, et al. Long-term safety, efficacy and inhibition of radiographic progression with **abatacept** treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis. 2011 Oct;70(10):1826-30.
Krishnan E, Lingala B, Bruce B, Fries JF. **Disability in rheumatoid arthritis in the era of biological treatments**. Ann Rheum Dis. 2012 Feb;71(2):213-8.
Kroot EJ, et al. The prognostic value of **anti-cyclic citrullinated peptide antibody** in patients with recent-onset rheumatoid arthritis.Arthritis Rheum. 2000 Aug;43(8):1831-5.
Kuriya B, Hernández-Díaz S, Liu J, Bermas BL, Daniel G, Solomon DH. **Patterns of drug use during pregnancy** in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011 Jan 4.
Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of **heart failure** after therapy with a **tumor necrosis** factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.
Lan J , Chen Y , Hsieh TC , et al. Kinetics of viral loads and risk of **HBV** reactivation in HBcAbpositive RA patients undergoing **anti-TNF-α therapy** . Ann Rheum Dis 2011 ; 70:1719–25 .
Lebwohl M, et al. **No** evidence for increased risk of **cutaneous squamous** cell carcinoma in patients with rheumatoid arthritis receiving **etanercept** for up to 5 years. Arch Dermatol. 2005 Jul;141(7):861-4.
Leffers HC, Ostergaard M, Glintborg B, et al. on behalf of all departments of rheumatology in Denmark. Efficacy of **abatacept and tocilizumab** in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish **DANBIO** registry. Ann Rheum Dis. 2011 Jul;70(7):1216-1222.
Lehman AJ, Esdaile JM, Klinkhoff AV, et al.; METGO Study Group. A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination **methotrexate and intramuscular gold** therapy in rheumatoid arthritis: results of the METGO study. Arthritis Rheum. 2005 May;52(5):1360-70.
Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB; **Etanercept Psoriasis** Study Group. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003 Nov 20;349(21):2014-22.
Lequerre T, et al. Management of **Infusion Reactions to Infliximab** in Patients with Rheumatoid Arthritis or Spondyloarthritis: Experience from an Immunotherapy Unit of Rheumatology. J Rheumatol. 2006 Jun 1; [Epub ahead of print]
Lie E, van der Heijde D, Uhlig T, et al. Treatment **strategies** in patients with rheumatoid arthritis for whom **methotrexate monotherapy has failed**: data from the NOR-DMARD register. Ann Rheum Dis. 2011 Dec;70(12):2103-10.
Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of **myocardial infarction** in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011 Jun;70(6):929-34.
Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of **atrial fibrillation** and stroke in rheumatoid arthritis: Danish nationwide cohort study. BMJ. 2012 Mar 8;344:e1257.
Lipsky PE, van der Heijde DM, et al. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. **Infliximab and methotrexate** in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000 Nov 30;343(22):1594-602.
Listing J, Strangfeld A, Kary S, et al. **Infections** in patients with rheumatoid arthritis treated with **biologic agents**. Arthritis Rheum. 2005 Nov;52(11):3403-12.
Lovell DJ, Giannini EH, et al. Pediatric Rheumatology Collaborative Study Group. Long-term efficacy and safety of **etanercept** in **children** with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum. 2003 Jan;48(1):218-26.
Lovell DJ, Giannini EH, et al. **Etanercept** in **children** with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000 Mar 16;342(11):763-9.
Lovell DJ, Reiff A, Ilowite NT, et al. Safety and efficacy of up to **eight years of continuous etanercept** therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008; 58: 1496–504.
Lovell DJ, Ruperto N, Goodman S, et al. **Adalimumab with or without methotrexate** in juvenile rheumatoid arthritis. N Engl J Med 2008; 359: 810–20.
Lukas C, Combe B, Ravaud P, et al. Favorable effect of **very early DMARD treatment** on radiographic progression in early inflammatory arthritis. The ESPOIR cohort study. Arthritis Rheum. 2011 Mar 30. doi:10.1002/art.30371.
Lunt M, Watson KD, Dixon WG, et al; The BSRBR Control Centre Consortium; on behalf of the BSR Biologics Register. **No evidence of association between anti-TNF treatment and mortality** in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2010 Jul 26.
Luqmani R, et al. British Society for Rheumatology and **British Health** Professionals in Rheumatology **Guideline** for the Management of **Rheumatoid Arthritis** (The first 2 years). Rheumatology (Oxford). 2006 Jul 13; [Epub ahead of print]
Ljung L, Simard JF, Jacobsson L, et al. ARTIS Study Group. Treatment with **tumour necrosis factor-inhibitors and the risk of acute coronary syndromes** in early rheumatoid arthritis. Arthritis Rheum. 2011 Aug 26.doi: 10.1002/art.30654.
Mahadevan U, Cucchiara S, Hyams JS, et al. The London position statement of the World Congress of Gastroenterology on **Biological Therapy for IBD with the European Crohn's and Colitis Organisation: Pregnancy and Pediatrics**. Am J Gastroenterol. 2010 Dec 14.
Maini R, St Clair EW, et al. **Infliximab** (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving **concomitant methotrexate**: a randomised phase III trial. **ATTRACT** Study Group. Lancet. 1999 Dec 4;354(9194):1932-9.
Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good Clinical Response, Remission, and Predictors of Remission in Rheumatoid Arthritis Patients Treated with **Tumor Necrosis Factor-alpha Blockers**: The GISEA Study. J Rheumatol. 2007 Aug;34(8):1670-3. Epub 2007 Jul 1. We show that **only a minority** of patients with longstanding RA achieve a good clinical response or remission at the outpatient community level. Predictors of remission identify characteristics commonly observed in subsets with less severe RA.
Mariette X, Tubach F, Bagheri H, et al. **Lymphoma** in patients treated with anti-TNF. Results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2009 Oct 14.
Mariette X, Matucci-Cerinic M, et al. **Malignancies** associated with **tumour necrosis factor inhibitors** in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis. 2011 Nov;70(11):1895-904.
Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF; American Academy of Ophthalmology. Revised recommendations on screening for **chloroquine** and **hydroxychloroquine retinopathy**. Ophthalmology. 2011 Feb;118(2):415-22.
Maxwell L, Singh JA. **Abatacept** for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007277.
McInnes IB, Schett G. The **Pathogenesis of Rheumatoid Arthritis**. N Engl J Med 2011; 365:2205-2219
Mease PJ, Goffe BS, et al. **Etanercept** in the treatment of **psoriatic arthritis** and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.
Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. **Adalimumab** for the treatment of patients with moderately to severely active **psoriatic arthritis**: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Oct;52(10):3279-89.
Mercer LK, Green AC, Galloway JB, et al; **British** Society for Rheumatology **Biologics Register** Control Centre Consortium, Symmons DP, Hyrich KL; on behalf of the British Society for Rheumatology Biologics Register. The influence of anti-TNF therapy upon incidence of **keratinocyte skin cancer** in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2012 Jun;71(6):869-874.
Mertens M, Singh JA. **Anakinra** for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD005121. Anakinra is a relatively safe and modestly efficacious biologic therapy for rheumatoid arthritis.
Micha R, Imamura F, Wyler von Ballmoos M, et al. Systematic Review and Meta-Analysis of **Methotrexate Use and Risk of Cardiovascular Disease**. Am J Cardiol. 2011 Aug 17.
Minden K, Niewerth M, Zink A, et al. **Long-term outcome of patients with JIA treated with etanercept**, results of the biologic register JuMBO. Rheumatology (Oxford). 2012 Mar 24.
Mok C, Kwok C, Ho L, et al. **Life expectancy**, standardized mortality ratios and causes of death of six rheumatic diseases in Hong Kong, China. Arthritis Rheum. 2011 Mar 9. doi: 10.1002/art.30277.
Mor A, Bingham CO 3rd, et al. **Methotrexate combined with isoniazid** treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: experience from an urban arthritis clinic. Ann Rheum Dis. 2008 Apr;67(4):462-5.
Moreland LW, Schiff MH, et al. **Etanercept** therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.
Moreland LW, Baumgartner SW, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein **etanercept**. N Engl J Med. 1997 Jul 17;337(3):141-7.
Moreland LW, et al. **Etanercept** treatment in adults with established rheumatoid arthritis: **7 years** of clinical experience. J Rheumatol. 2006 May;33(5):854-61. Epub 2006 Mar 15.
Moreland LW, O'Dell JR, Paulus HE, et al. **TEAR** Investigators. A randomized comparative effectiveness study of **oral triple therapy versus etanercept plus methotrexate** in early, aggressive rheumatoid arthritis. Arthritis Rheum. 2012 Apr 16.
Morgan SL, Baggott JE, et al. Supplementation with **folic acid during methotrexate** therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. Ann Intern Med. 1994 Dec 1;121(11):833-41.
Mottonen T, Hannonen P, et al. Comparison of **combination** therapy with **single-drug** therapy in early rheumatoid arthritis: a randomised trial. **FIN-RACo trial** group. Lancet. 1999 May 8;353(9164):1568-73.
Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. **Adalimumab** for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005113.
Neovius M, Simard JF, Klareskog L, Askling J; for the ARTIS Study Group. **Sick leave and disability pension** before and after initiation of antirheumatic therapies in clinical practice. Ann Rheum Dis. 2011 Aug;70(8):1407-1414. Obici L, Meini A,
Newton-Cheh Christopher, Lin Angela E., Baggish Aaron L., et al. Case 11-2011 — A 47-Year-Old Man with Systemic Lupus Erythematosus and Heart Failure. N Engl J Med 2011; 364:1450-1460. (Infiltrative cardiomyopathy & possible long-QT syndrome due to **hydroxychloroquine**)
NICE: Ankylosing spondylitis - adalimumab, etanercept and infliximab Adalimumab, etanercept and infliximab for ankylosing spondylitis **May 2008** http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11992
NICE Feb/09 **Rheumatoid Arthritis Guidelines** http://www.nice.org.uk/Guidance/CG79 (Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M; Guideline Development Group. Management of rheumatoid arthritis: sum

TOP

guidance. BMJ. 2009 Mar 16;338:b702. doi: 10.1136/bmj.b702.)
NICE: Rheumatoid arthritis - drugs for treatment **after failure of a TNF inhibitor** Aug/10 http://guidance.nice.org.uk/TA195.)
NICE: National Institute for Health and Clinical Excellence. **Adalimumab, etanercept, infliximab, rituximab and abatacept** for the **treatment of rheumatoid arthritis after the failure of a TNF inhibitor**. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Aug. http://www.nice.org.uk/nicemedia/live/13108/50409/50409.pdf
NICE: **Tocilizumab** for rheumatoid arthritis Aug/10 http://guidance.nice.org.uk/TA198
NICE: National Institute for Health and Clinical Excellence (NICE). Etanercept, infliximab and adalimumab for the treatment of **psoriatic arthritis**. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Aug. 35 p. (Technology appraisal guidance; no. 199). http://www.nice.org.uk/nicemedia/live/13110/50424/50424.pdf
NICE: National Institute for Health and Clinical Excellence (NICE). **Certolizumab** pegol for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Feb. (Technology appraisal guidance; no. 186). http://www.nice.org.uk/nicemedia/live/12808/47528/47528.pdf
Nigrovic PA, Mannion M, Prince FH, et al. **Anakinra** as first-line disease-modifying therapy in **systemic juvenile idiopathic arthritis**: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011 Feb;63(2):545-55. doi: 10.1002/art.30128.
Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007 Jun 5;146(11):797-808. **Anti-CCP antibodies** are more specific than RF for diagnosing rheumatoid arthritis & may better predict erosivedisease.
Nordal E, Zak M, Aalto Ket al. **Juvenile idiopathic arthritis**; Ongoing disease activity and changing categories in a long-term Nordic cohort study. Arthritis Rheum. 2011 May 10.
Nuki G, Bresnihan B, et al. European Group Of Clinical Investigators. Long-term safety and maintenance of clinical improvement following treatment with **anakinra** (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Nov;46(11):2838-46.
Obici L, Meini A, Cattalini M, et al. Favourable and sustained response to **anakinra** in **tumour necrosis factor receptor-associated periodic syndrome (TRAPS)** with or without AA amyloidosis. Ann Rheum Dis. 2011 Aug;70(8):1511-2.
O'Dell JR, Leff R, et al. Treatment of rheumatoid arthritis with **methotrexate and hydroxychloroquine**, **methotrexate and sulfasalazine**, or a **combination** of the **three** medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 May;46(5):1164-70.
O'Dell JR, Haire CE, et al. Treatment of rheumatoid arthritis with **methotrexate alone**, **sulfasalazine and hydroxychloroquine**, or a **combination** of all **three** medications. N Engl J Med. 1996 May 16;334(20):1287-91.
O'Dell JR, Blakely KW, et al. Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of **minocycline** and **hydroxychloroquine**. Arthritis Rheum. 2001 Oct;44(10):2235-41.
O'dell JR, Petersen K, Leff R, et al. **Etanercept in Combination with Sulfasalazine, Hydroxychloroquine, or Gold** in the Treatment of Rheumatoid Arthritis. J Rheumatol. 2005 Dec 15; [Epub ahead of print]
Okuyama A, Nagasawa H, Suzuki K, et al. **Fc{gamma} receptor IIIb polymorphism and use of glucocorticoids** at baseline are associated with **infusion reactions to infliximab** in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Feb;70(2):299-304.
Olivieri I, Palazzi C, Peruz G, Padula A. Management Issues with Elderly-Onset Rheumatoid Arthritis : An Update. Drugs Aging. 2005;22(10):809-822.
Ornetti P, Chevillotte H, Zerrak A, Maillefert JF. **Anti-Tumour Necrosis** Factor-alpha Therapy for Rheumatoid and Other Inflammatory Arthropathies : Update on Safety in **Older Patients**. Drugs Aging. 2006;23(11):855-60.
Ornbjerg LM, et al. Impact of **tumour necrosis factor inhibitor** treatment on **radiographic progression** in rheumatoid arthritis patients in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis. 2012 Apr 24.
Osiri M, Shea B, Welch V, Suarez-Almazor ME, Strand V, Tugwell P, et al. **Leflunomide** for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev [Internet]. 2009 [cited 2011 Apr 11];(4):CD002047.
Østergaard M, Emery P, Conaghan PG, et al. Significant improvement in synovitis, osteitis, and bone erosion following **golimumab and methotrexate** combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. Arthritis Rheum. 2011 Dec;63(12):3712-22.
Otten Marieke H., Prince Femke H. M., Armbrust Wineke, et al. Original Contribution Factors Associated With Treatment Response to **Etanercept** in **Juvenile Idiopathic Arthritis**. JAMA. 2011;Published online November 6, 2011.
Paller AS, Siegfried EC, Langley RG, et al.; **Etanercept Pediatric Psoriasis** Study Group. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008 Jan 17;358(3):241-51.
Papp KA, Tyring S, Lahfa M, et al.; **Etanercept Psoriasis** Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005 Jun;152(6):1304-12.
Pavelka K, Jarosova K, et al. Increasing the **infliximab dose** in rheumatoid arthritis patients: a randomized, double blind study failed to confirm its efficacy. Ann Rheum Dis. 2009 Apr 6. [Epub ahead of print]
Peters MJ, Symmons DP, McCarey D et al. EULAR evidence-based recommendations for **cardiovascular risk** management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2009 Sep 22.
Pharmacist's Letter. Selected Issues in the Effective and Safe Use of **Live Vaccines**. Oct 2007.
Pikwer M, Bergström U, et al. **Breast-feeding**, but not oral contraceptives, is associated with a reduced risk of rheumatoid arthritis. Ann Rheum Dis. 2008 May 14. [Epub ahead of print]
Pikwer M, Bergström U, Nilsson JÅ et al. **Early menopause** is an independent predictor of rheumatoid arthritis. Ann Rheum Dis. 2012 Mar;71(3):378-81.
Plant D, Prajapati R, Hyrich KL, et al. Investigation of established rheumatoid-arthritis (RA) susceptibility genetic markers as predictors of response to **anti-TNF therapy** in a large UK cohort replicates association with the **PTPRC gene**. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33381.
Plosker GL, Croom KF. **Sulfasalazine**: a review of its use in the management of rheumatoid arthritis. Drugs. 2005;65(13):1825-49.
Poor G, Strand V. Efficacy and safety of **leflunomide 10 mg versus 20 mg** once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. Rheumatology (Oxford). 2004 Mar 16 [Epub ahead of print]
Prakken B, Albani S, Martini A. **Juvenile idiopathic arthritis (JIA)**. Lancet 2011; 377: 2138–49.
Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation --- United States, 2003—2005 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5540a2.htm?s_cid=mm5540a2_x
Prey S, Paul C. Effect of **folic or folinic acid** supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br J Dermatol. 2008 Oct 20. [Epub ahead of print] Supplementation with folic acid is an effective measure to reduce hepatic adverse effects associated with methotrexate treatment. There is no difference between folinic acid and folic acid, but the lower cost of the latter promotes its use.
Prince FH, Otten MH, van Suijlekom-Smit LW. Diagnosis and management of **juvenile idiopathic arthritis**. BMJ. 2010 Dec 3;341:c6434. doi: 10.1136/bmj.c6434.
Quartier Pierre, Allantaz Florence, Cimaz Rolando, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist **anakinra** in patients with **systemic-onset juvenile** idiopathic arthritis (**ANAJIS** trial). Ann Rheum Dis 2011;70:747-754 Published Online First: 20 December 2010 doi:10.1136/ard.2010.134254.
Raaschou P, Simard JF, Neovius M, Askling J; Anti-Rheumatic Therapy in Sweden Study Group (ARTIS). Does **cancer** that occurs during or after **anti-tumor necrosis factor therapy** have a worse prognosis? A national assessment of overall and site-specific cancer survival in rheumatoid arthritis patients treated with biologic agents. Arthritis Rheum. 2011 Jul;63(7):1812-22.
Rahman MU, Buchanan J, et al. Changes in **patient characteristics in anti-tumour necrosis factor clinical trials** for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis. 2011 Sep;70(9):1631-40.
Ravindran V, Rachapalli S, Choy EH. Safety of medium- to long-term **glucocorticoid therapy** in rheumatoid arthritis: a meta-analysis. Rheumatology (Oxford). 2009 Jul;48(7):807-11. Epub 2009 May 15.
Reich K, Nestle FO, Papp K, et al.; **EXPRESS** study investigators. Infliximab induction and maintenance therapy for moderate-to-severe **psoriasis**: a phase III, multicentre, double-blind trial. Lancet. 2005 Oct 15-21;366(9494):1367-74.
Rezaei H, Saevarsdottir S, Forslind K et al. In early rheumatoid arthritis, patients with a good initial response to **methotrexate** have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial. Ann Rheum Dis. 2012 Feb;71(2):186-91.
Ribeiro AC, Guedes LK, Moraes JC, et al. **Reduced seroprotection after pandemic H1N1 influenza** adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis. 2011 Dec;70(12):2144-7.
Richards BL, Whittle SL, Buchbinder R. **Antidepressants for pain management** in rheumatoid arthritis. Cochrane Database Syst Rev. 2011 Nov 9;11:CD008920. There is currently insufficient evidence to support the routine prescription of antidepressants as analgesics in patients with RA as no reliable conclusions about their efficacy can be drawn from eight placebo RCTs.
Richards BL, Whittle SL, Buchbinder R. **Muscle relaxants for pain** management in rheumatoid arthritis. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008922. DOI: 10.1002/14651858.CD008922
Richards BL, Whittle SL, Buchbinder R. **Neuromodulators for pain** management in rheumatoid arthritis. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008921. DOI: 10.1002/14651858.CD008921.
Rigby W, Ferraccioli G, Greenwald M, et al. **Rituximab** improved physical function and quality of life in patients with rheumatoid arthritis naïve to methotrexate (**IMAGE** study). Arthritis Care Res (Hoboken). 2010 Dec 8.
Robert N, Wong GW, Wright JM. Effect of **cyclosporine on blood pressure**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007893. There appears to be a dose-related effect with lower doses (1-4 mg/kg/d) increasing mean BP by an average of 5 mmHg and higher doses (>10 mg/kg/d) increasing mean BP by 11 mmHg on average.
Rudwaleit M, van der Heijde D, et al. The development of **Assessment of SpondyloArthritis international Society** classifi cation criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68:
Ruperto N, Murray KJ, Gerloni V, et al. A randomized trial of parenteral **methotrexate** comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of meth

TOP

Arthritis Rheum 2004; 50: 2191–201.
Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of **infliximab plus methotrexate** for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56: 3096–106.
Ruperto N, Lovell DJ, Quartier P, et al. **Abatacept** in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008; 372: 383–91.
Ruperto N, Lovell DJ, et al. Long-term efficacy and safety of **infliximab plus methotrexate** for the treatment of polyarticular-course juvenile rheumatoid arthritis: fi ndings from an open-label treatment extension. Ann Rheum Dis 2010; 69: 718–22.
Ruperto N, Lovell DJ, Quartier P, et al. Long-term safety and efficacy of **abatacept** in children with juvenile idiopathic arthritis. Arthritis Rheum 2010; 62: 1792–802.
Ruperto N, Quartier P, Wulffraat N, et al. for the Paediatric Rheumatology International Clinical Trials Organisation (**PRINTO**). A phase II study to evaluate dosing and preliminary safety and efficacy of **canakinumab** in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33342.
Ryu YS, Park SH, Kim JM, et al. A case of **leukoencephalopathy associated with adalimumab**-treated rheumatoid arthritis and a review of literature. Rheumatol Int. 2011 Nov 8.
Saad AA, Symmons DP, Noyce PR, et al. Risks and benefits of 12 tumor necrosis factor-alpha inhibitors in the management of **psoriatic arthritis**: systematic review and meta-analysis of randomized controlled trials. J Rheumatol 2008;35:883-90.
Saag KG, Teng GG, et al. American College of Rheumatology-**ACR 2008** recommendations for the use of **nonbiologic and biologic disease-modifying antirheumatic drugs** in rheumatoid arthritis. Arthritis Rheum 2008 Jun 15;59(6):762-84.
Salliot C, van der Heijde D. **Long-term safety of methotrexate** monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009 Jul;68(7):1100-4. Epub 2008 Dec 5.
Salmon-Ceron D, Tubach F, Lortholary O, for RATIO group. Drug-specific risk of non-tuberculosis **opportunistic infections** in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Dec 21. Various and severe OIs, especially those with intracellular micro-organisms, may develop in patients receiving anti-TNF treatment. Monoclonal anti-TNF antibody rather than soluble TNF receptor therapy and steroid use >10 mg/day are independently associated with OI.
Sarnes E, Crofford L, Watson M, et al. Incidence and US Costs of **Corticosteroid-Associated Adverse Events**: A Systematic Literature Review. Clin Ther. 2011 Oct 12.
Savage RL. **Leflunomide in combination** therapy for rheumatoid arthritis. Drug Saf. 2010 Jun 1;33(6):523-6.
Schanz S, Schmalzing M, Guenova E, et al. **Interstitial granulomatous dermatitis** with arthritis responding to **tocilizumab**. Arch Dermatol. 2012 Jan;148(1):17-20
Schiff MH, et al. Safety Analyses of **Adalimumab** (HUMIRA(R)) in Global Clinical Trials and US Postmarketing Surveillance of Patients With Rheumatoid Arthritis. Ann Rheum Dis. 2006 Feb 13; [Epub ahead of print]
Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of **abatacept** in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis. 2009 Nov;68(11):1708-14. Epub 2008 Dec 15.
Schiff M. **Abatacept** treatment for rheumatoid arthritis. Rheumatology (Oxford). 2011 Mar;50(3):437-49.
Schiff M, Keiserman M, et al. Clinical response & tolerability to **abatacept** in patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the **ATTEST** Study. Ann Rheum Dis. 2011 Nov;70(11):2003-7.
Schipper LG, Vermeer M, Kuper HH, et al. A **tight control** treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis. 2012 Jun;71(6):845-50.
Schmajuk G, Trivedi AN., Solomon DH., et al. Receipt of **Disease-Modifying Antirheumatic Drugs** Among Patients With Rheumatoid Arthritis in **Medicare Managed** Care Plans. *JAMA*. 2011;305(5):480-486.doi:10.1001/jama.2011.67
Schmitz S, Adams R, Walsh CD, et al. A **mixed treatment comparison of the efficacy of anti-TNF agents** in rheumatoid arthritis for methotrexate non-responders demonstrates differences between treatments: a Bayesian approach. Ann Rheum Dis. 2012 Feb;71(2):225-30.
Schoels M, Wong J, Scott DL, et al. **Economic aspects of treatment options in rheumatoid arthritis**: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):995-1003.
Schumacher HR, Chen LX. **Injectable corticosteroids** in treatment of arthritis of the knee. Am J Med. 2005 Nov;118(11):1208-14.
Schuna AA. **Rituximab** for the treatment of rheumatoid arthritis. Pharmacotherapy. 2007 Dec;27(12):1702-10.
Scott DL, et al. European Leflunomide Study Group. Treatment of active rheumatoid arthritis with **leflunomide**: two year follow up of a double blind, placebo controlled trial **versus sulfasalazine**. Ann Rheum Dis. 2001 Oct;60(10):913-23.
Scott DL, Wolfe F, Huizinga TW. **Rheumatoid arthritis**. Lancet. 2010 Sep 25;376(9746):1094-108.
Scott DL, Kingsley GH. **Tumor necrosis factor inhibitors** for rheumatoid arthritis. N Engl J Med. 2006 Aug 17;355(7):704-12.
Semb AG, Kvien TK, Demicco D, et al. Effect of **intensive lipid lowering** on cardiovascular outcome in patients with and without inflammatory joint disease. Arthritis Rheum. 2012 May 10.
Setoguchi S, et al. **Tumor necrosis factor** alpha antagonist use and **cancer** in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2757-64. Comparing biologic DMARD users with MTX users, the propensity score-adjusted pooled hazard ratio was 1.37 (95% confidence interval 0.71-2.65) for hematologic malignancies and 0.91 (95% confidence interval 0.65-1.26) for solid tumors. Our results indicate that users of biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with MTX users.
Silva F, Seo P, Schroeder DR, et al; for the **Wegener's Granulomatosis Etanercept Trial Research Group. Solid malignancies** among patients with Wegener's granulomatosis treated with etanercept: Long-term follow-up of a multicenter longitudinal cohort. Arthritis Rheum. 2011 Apr 11.
Silverman E. et al. **Leflunomide or Methotrexate** for **Juvenile Rheumatoid Arthritis**. N Engl J Med 2005;352:1655-66.
Silverman E, Spiegel L, Hawkins D, et al. Long-term open-label preliminary study of the safety and efficacy of **leflunomide** in patients with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2005; 52: 554–62.
Simard JF, Neovius M, Hagelberg S, Askling J. **Juvenile idiopathic arthritis and risk of cancer**: a nationwide cohort study. Arthritis Rheum 2010; 62: 3776–82.
Simsek I, Erdem H, Pay S, Sobaci G, Dinc A. **Optic neuritis occurring with anti-tumour necrosis factor alpha** therapy.Ann Rheum Dis. 2007 Sep;66(9):1255-8. Epub 2007 Apr 24.
Singh JA, Christensen R, Wells GA, et al. **Biologics for rheumatoid arthritis**: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007848.
Singh, Jasvinder A, Christensen, Robin, Wells, George A, et al. A network meta-analysis of randomized controlled trials of **biologics for rheumatoid arthritis**: a Cochrane overview. CMAJ 2009 0: cmaj.091391.
Singh JA, Noorbaloochi S, Singh G. **Golimumab** for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008341.
Singh JA, Beg S, Lopez-Olivo MA. **Tocilizumab** for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Jul 7;7:CD008331. Tocilizumab is beneficial in decreasing RA disease activity and improving function. Tocilizumab treatment was associated with significant increase in cholesterol levels and in total adverse events. Larger safety studies are needed to address these safety concerns.
Singh JA, Wells GA, Christensen R, et al. **Adverse effects of biologics**: a network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD008794. DOI: 10.1002/14651858.CD008794.pub2. Overall, in the short term biologics were associated with significantly higher rates of total adverse events, withdrawals due to adverse events and TB reactivation. Some biologics had a statistically higher association with certain adverse outcomes compared to control, but there was no consistency across the outcomes so caution is needed in interpreting these results.
Singh JA, Furst DE, Bharat A, et al. **2012 update** of the 2008 American College of Rheumatology recommendations for the use of **disease-modifying antirheumatic drugs and biologic agents** in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39.
Smolen JS, Kalden JR, Scott DL, et al.. Efficacy and safety of **leflunomide** compared with placebo and **sulphasalazine** in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet. 1999 Jan 23;353(9149):259-66.
Smolen JS, Emery P, Keystone EC, et al. Consensus Statement on the Use of **Rituximab** in Patients With Rheumatoid Arthritis. Ann Rheum Dis. 2006 Nov 15; [Epub ahead of print]
Smolen JS, Kay J, Doyle MK, et al. GO-AFTER study investigators. **Golimumab** in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (**GO-AFTER** study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21. Epub 2009 Jun 26.
Smolen JS, Landewé R, Breedveld FC, et al. **EULAR** recommendations for the management of rheumatoid arthritis with **synthetic and biological disease-modifying antirheumatic drugs**. Ann Rheum Dis. 2010 May 5. [Epub ahead of print]
Snijders GF, van den Ende CH, van Riel PL, et al. on behalf of NOAC study group. The effects of **doxycycline** on reducing symptoms in knee osteoarthritis: results from a triple-blinded randomised controlled trial. Ann Rheum Dis. 2011 Jul;70(7):1191-1196.
Soliman Moetaza M, Ashcroft Darren M, Watson Kath D, et al. , on behalf of the British Society for Rheumatology Biologics Register. Impact of **concomitant use of DMARDs on the persistence with anti-TNF therapies** in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:583-589
Solomon DH, Avorn J, Katz JN, et al. **Immunosuppressive medications** and hospitalization for **cardiovascular events** in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Nov 29;54(12):3790-3798. Monotherapy with oral glucocorticoids was associated with an increased risk of cardiovascular events (OR 1.5, 95% CI 1.1 - 2.1), and a similar trend in the direction of risk was seen with glucocorticoid combination therapy (OR 1.3, 95% CI 0.8-2.0). Cytotoxic immunosuppressive agents other than MTX (azathioprine, cyclosporine, and leflunomide) were also associated with an increased risk of cardiovascular events (with both monotherapy and combination treatment, OR 1.8, 95% CI 1.1-3.0). When compared with RA patients receiving MTX monotherapy, those receiving biologic immunosuppressive agents had neither an increased nor decreased risk of experiencing a cardiovascular event, whereas use of oral glucocorticoids and cytotoxic immunosuppressive agents was associated with significant increases in the risk of cardiovascular events.
Solomon Daniel H., Massarotti Elena, Garg Rajesh, et al. Association Between **Disease-Modifying Antirheumatic Drugs and Diabetes Risk** in Patients With Rheumatoid Arthritis and Psoriasis. JAMA. 2011;305(24):2525-2531.
Solomon DH, Mercer E, Kavanaugh A. Observational studies on the risk of **cancer associated with TNF-Inhibitors** in RA: A review of their methodologies and results. Arthritis Rheum. 2011 Aug 26. doi: 10.1002/art.30653.

TOP

Song I-H, Hermann KG, Haibel H, et al. Effects of **etanercept versus sulfasalazine** in early axial **spondyloarthritis** on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 2011;70:590-596 doi:10.1136/ard.2010.139667

Song IH, Althoff CE, Haibel H, et al. Frequency and duration of drug-free remission after 1 year of treatment with **etanercept versus sulfasalazine** in early **axial spondyloarthritis**: 2 year data of the ESTHER trial. Ann Rheum Dis. 2012 Mar 22.

Sterry W, Ortonne JP, Kikham B, Brocq O, Robertson D, Pederson RD, et al. 1 Comparison of two **etanercept** regimens for treatment of psoriasis and **psoriatic arthritis**: **PRESTA** randomised double blind multicentre trial. BMJ 2010;340:c147.

St Clair EW, van der Heijde DM, Smolen JS, et al.; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of **Early Onset** Study Group. Combination of **infliximab and methotrexate** therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43.

Strand V, Cohen S, et al. Treatment of active rheumatoid arthritis with **leflunomide** compared with placebo and **methotrexate**. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med. 1999 Nov 22;159(21):2542-50.

Strand V, Smolen JS, van Vollenhoven RF, et al. **Certolizumab pegol plus methotrexate** provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. Ann Rheum Dis. 2011 Mar 17.

Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A. Risk of **herpes zoster** in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009 Feb 18;301(7):737-44. Treatment with monoclonal anti-**TNF-alpha antibodies** may be associated with increased risk of herpes zoster, but this requires further study.

Strangfeld A, Eveslage M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011 Nov;70(11):1914-20.

Summers KM, Kockler DR. **Rituximab** Treatment of Refractory Rheumatoid Arthritis (December). Ann Pharmacother. 2005 Oct 25; [Epub ahead of print]

Suter Lisa G.; Fraenkel Liana; Braithwaite R. Scott. Cost-effectiveness of Adding **Magnetic Resonance Imaging** (MRI) to Rheumatoid Arthritis Management. Arch Intern Med. 2011;171(7):657-667.

Svensson B, Boonen A, Albertsson K, et al. **Low-dose prednisolone** in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum. 2005 Nov;52(11):3360-70.

Symmons D, et al. Patients with stable long-standing rheumatoid arthritis **continue to deteriorate** despite intensified treatment with traditional disease modifying anti-rheumatic drugs--results of the British Rheumatoid Outcome Study Group Randomized controlled clinical trial.
Rheumatology (Oxford). 2006 May;45(5):558-65. Epub 2005 Nov 1.

Rituximab (Rituxan) for Rheumatoid Arthritis. Pharmacist's Letter Aug, 2006. (Roche patient Assisance program 1-888-748-8926)

Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with **rituximab plus methotrexate** in early active rheumatoid arthritis: the **IMAGE** trial. Ann Rheum Dis. 2011 Jan;70(1):39-46.

Tan CS, Koralnik IJ. **Progressive multifocal leukoencephalopathy** (PML) and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010 Apr;9(4):425-37.

Tanaka Y, et al. for the RRR study investigators. **Discontinuation of infliximab** after attaining **low disease activity** in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. Ann Rheum Dis. 2010 Apr 1.

Ter Wee MM, Lems WF, Usan H et al. The effect of **biological agents on work participation** in rheumatoid arthritis patients: a systematic review. Ann Rheum Dis. 2012 Feb;71(2):161-71.

Tesfa1 D, Ajeganova S, Hägglund1 H, et al. **Late-onset neutropenia following rituximab** therapy in rheumatic diseases: Association with B-lymphocyte depletion and infections. Arthritis Rheum. 2011 May 10. doi: 10.1002/art.30427.

Thompson AE, Rieder SW, Pope JE. **TNF therapy and the risk of serious infection** and malignancy in patients with early rheumatoid arthritis: A meta-analysis of randomized controlled trials. Arthritis Rheum. 2011 Feb 25. doi: 10.1002/art.30310.

Tubach F, Salmon D, Ravaud P, et al. Research Axed on Tolerance of Biotherapies Group. **Risk of tuberculosis** is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective french research axed on tolerance of biotherapies registry. Arthritis Rheum. 2009 Jun 29;60(7):1884-1894.

Tugwell P, Pincus T, et al. Combination therapy with **cyclosporine and methotrexate** in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. N Engl J Med. 1995 Jul 20;333(3):137-41.

Tugwell P, Singh JA, Wells GA. **Biologicals for rheumatoid arthritis**. BMJ. 2011 Jul 28;343:d4027.

Tynjälä P, Vähäsalo P, Tarkiainen M, et al. Aggressive Combination Drug Therapy in **Very Early Polyarticular Juvenile Idiopathic** Arthritis (**ACUTE-JIA**): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 May 28.

Tyring S, Gottlieb A, Papp K, Gordon K, et al. **Etanercept** and clinical outcomes, fatigue, and depression in **psoriasis**: double-blind placebo-controlled randomised phase III trial. Lancet. 2006 Jan 7;367(9504):29-35.

van Assen S, et al. Humoral responses after **influenza vaccination** are severely reduced in patients with rheumatoid arthritis treated with **rituximab**. Arthritis Rheum. 2009 Dec 28;62(1):75-81.

van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for **vaccination in adult patients** with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;**70**:414-422. Online: 3 Dec 2010 doi:10.1136/ard.2010.137216

van den Broek M, Klarenbeek NB, Dirven L, et al. **Discontinuation of infliximab** and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the **BeSt** study. Ann Rheum Dis. 2011 Aug;70(8):1389-94.

van den Broek M, Dirven L, Klarenbeek N, et al. The association of **treatment response and joint damage with ACPA-status** in recent-onset RA: a subanalysis of the 8-year follow-up of the **BeSt study**. Ann Rheum Dis. 2012 Feb;71(2):245-8.

van der Heijde D, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: **Two-year** clinical and radiographic results from the **TEMPO** study, a double-blind, randomized trial. Arthritis Rheum. 2006 Mar 29;54(4):1063-1074 [Epub ahead of print]

van der Heijde D, et al. **Once-weekly** 50-mg dosing of **Etanercept** (Enbrel(R)) is as effective as 25-mg twice-weekly dosing in patients with **ankylosing spondylitis**. Ann Rheum Dis. 2006 Sep 12; [Epub ahead of print]

van der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease Activity, Physical Function, and Radiographic Progression After Longterm Therapy with **Adalimumab** Plus Methotrexate: 5-Year Results of **PREMIER**. J Rheumatol. 2010 Oct 1.

van der Heijde Désirée, Sieper Joachim, Maksymowych Walter P, et al. for the Assessment of SpondyloArthritis international Society. **2010 Update of the international ASAS recommendations** for the use of **anti-TNF agents** in patients with **axial spondyloarthritis**. Ann Rheum Dis 2011;70:905-908 doi:10.1136/ard.2011.151563.

van der Linden MP, van der Woude D, Ioan-Facsinay A, et al. Value of **anti-modified citrullinated vimentin** and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2232-41.

van der Linden MP, le Cessie S, Raza K, et al. Long-term **impact of delay in assessment of patients with early arthritis**. Arthritis Rheum. 2010 Dec;62(12):3537-46. doi: 10.1002/art.27692.

van der Woude D, Young A, Jayakumar K,et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free **remission** in rheumatoid arthritis: Results from two large early arthritis cohorts. Arthritis Rheum. 2009 Aug;60(8):2262-71. Sustained DMARD-free remission in RA patients treated with conventional therapy is not uncommon (15%). Symptom duration at presentation and the absence of autoantibodies are associated with sustained DMARD-free remission.

van Everdingen AA, Jacobs JW, et al. **Low-dose prednisone** therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med. 2002 Jan 1;136(1):1-12.

van Lümig PPM et al. Relevance of laboratory investigations in **monitoring patients with psoriasis on etanercept or adalimumab**. Br J Dermatol 2011 Mar 24

van Riel PL, et al. Add **Enbrel or Replace Methotrexate** Study Investigators. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis. 2006 Nov;65(11):1478-83. Epub 2006 Feb 7.

van Rossum MA, et al. **Sulfasalazine** in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch **Juvenile** Chronic Arthritis Study Group. Arthritis Rheum. 1998 May;41(5):808-16.

van Sijl AM, van den Oever IA, Peters MJ, et al. Subclinical **renal dysfunction** is independently associated with cardiovascular events in rheumatoid arthritis: **the CARRE Study**. Ann Rheum Dis. 2012 Mar;71(3):341-4.

van Vollenhoven RF et al. Addition of **infliximab** compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (**Swefot** trial): 1-year results of a randomised trial. *Lancet* 2009 Aug 8; 374:459.

van Vollenhoven RF, Geborek P, Forslind K, et al, for the **Swefot** study group. **Conventional combination treatment versus biological** treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012; online March 29.

Vermeer M, Kuper HH, Hoekstra M et al. Implementation of a **treat-to-target strategy in very early** rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study **(DREAM Study).** Arthritis Rheum. 2011 Oct;63(10):2865-72.

Verstappen SM, Bakker MF, et al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with **methotrexate** tight control therapy (the CAMERA study). Ann Rheum Dis. 2009 Jul 5.

Verstappen SM, McCoy MJ, Roberts C, et al. The beneficial effects of a **3 week** course of **intramuscular glucocorticoid** injections in patients with very early inflammatory polyarthritis: Results of the STIVEA trial. Ann Rheum Dis. 2009 Oct 12.

Verstappen Suzanne M M, King Yvonne, Watson Kath D, et al. BSRBR Control Centre Consortium, BSR Biologics Register. **Anti-TNF therapies and pregnancy**: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:823-826 Published Online First: 28 February 2011 doi:10.1136/ard.2010.140822.

Verstappen SM, Lunt M, Bunn DK, Scott DG, Symmons DP. In patients with **early inflammatory polyarthritis**, ACPA positivity, younger age and inefficacy of the first non-biological DMARD are predictors for receiving biologic
results from the Norfolk Arthritis Register. Ann Rheum Dis. 2011 Aug;70(8):1428-32.

TOP

Welsh P, Peters MJ, Sattar N. **Vitamin D** in rheumatoid arthritis: A magic bullet or a mirage? The need to improve the evidence base prior to calls for supplementation. Arthritis Rheum. 2011 Mar 11. doi: 10.1002/art.30341.
Vinet E, Pineau C, Gordon C, Clarke AE, Bernatsky S. **Biologic therapy and pregnancy** outcomes in women with rheumatic diseases. Arthritis Rheum. 2009 May 15;61(5):587-92.
Visser K, Katchamart W, Loza E, et al. Multinational **evidence-based recommendations for the use of methotrexate** in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis. 2008 Nov 25. [Epub ahead of print]
Visser K, van der Heijde D. Optimal dosage and route of administration of **methotrexate** in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009 Jul;68(7):1094-9. Epub 2008 Nov 25. Starting on methotrexate 15 mg/week orally, escalating with 5 mg/month to 25-30 mg/week, or the highest tolerable dose, with a subsequent switch to subcutaneous administration in the case of an insufficient response, seems to be the optimal evidence-based dosing and routing recommendation for methotrexate in RA.
Vo Kevin H, Waddell James Aubrey, Suda Katie J. Rapid Development of Infusion-Related Severe **Hypotension During Rituximab** Therapy. Articles Ahead of Print published on 1 May 2011, DOI 10.1345/aph.1P733. Ann Pharmacother ;45:e29.
Vriezekolk JE, van Lankveld WG, Geenen R, et al. Longitudinal association between **coping and psychological distress** in rheumatoid arthritis: a systematic review. Ann Rheum Dis. 2011 Jul;70(7):1243-50.
Vroom F, et al. Disease-modifying antirheumatic drugs in **pregnancy**: current status and implications for the future. Drug Saf. 2006;29(10):845-63.
Wasko MC, Hubert HB, Lingala VB, et al. **Hydroxychloroquine and risk of diabetes** in patients with rheumatoid arthritis. JAMA. 2007 Jul 11;298(2):187-93.
Wassenberg S, Rau R, Steinfeld P, et al. Very **low-dose prednisolone** in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2005 Nov;52(11):3371-80.
Wasserman AM. **Diagnosis and management of rheumatoid arthritis**. Am Fam Physician. 2011 Dec 1;84(11):1245-52.
Weiss-Smith S, Deshpande G, Chung S, et al. The **FDA drug safety surveillance program: adverse event reporting** trends. Arch Intern Med 2011;171:591-3. The drugs most frequently cited were biologic agents etanercept, adalimumab and infliximab (the first, third and fourth most frequently reported suspect drugs).
Wegener's Granulomatosis Etanercept Trial (**WGET**) Research Group. **Etanercept** plus standard therapy for **Wegener's** granulomatosis. N Engl J Med. 2005 Jan 27;352(4):351-61. (Stone JH, et al. Solid malignancies among patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 2006 May;54(5):1608-18.)
Weinblatt ME, Kremer JM, et al. A trial of **etanercept**, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis **receiving methotrexate**. N Engl J Med. 1999 Jan 28;340(4):253-9.
Weinblatt ME, et al. Long term efficacy and safety of **adalimumab plus methotrexate** in patients with rheumatoid arthritis: **ARMADA** 4 year extended study. Ann Rheum Dis. 2006 Jun;65(6):753-9. Epub 2005 Nov 24.
Weinblatt ME, et al.. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45. Erratum in: Arthritis Rheum. 2003 Mar;48(3):855. Arthritis Rheum. 2004 Mar-Apr;22(2):144.
Weinblatt ME, et al. Selective co-stimulation modulation using **abatacept** in patients with active rheumatoid arthritis while receiving etanercept: a randomized clinical trial. Ann Rheum Dis. 2006 Aug 25; [Epub ahead of print]
Weinblatt M, et al. Safety of the selective costimulation modulator **abatacept** in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006 Aug 31;54(9):2807-2816 [Epub ahead of print] Abatacept in combination with synthetic DMARDs was well tolerated and improved physical function and physician- and patient-reported disease outcomes. However, abatacept in combination with biologic background therapies was associated with an increase in the rate of serious adverse events. Therefore, abatacept is not recommended for use in combination with biologic therapy.
Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. An **oral spleen tyrosine kinase (Syk) inhibitor** for rheumatoid arthritis. N Engl J Med. 2010 Sep 30;363(14):1303-12.
Welsh P, Peters MJ, Sattar N. **Vitamin D** in rheumatoid arthritis: A magic bullet or a mirage? The need to improve the evidence base prior to calls for supplementation. Arthritis Rheum. 2011 Mar 11. doi: 10.1002/art.30341.
Westhovens R, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: A large, randomized,placebo-controlled trial. Arthritis Rheum. 2006 Mar 29;54(4):1075-1086 [Epub ahead of print] CONCLUSION: The risk of serious infections in patients receiving the approved infliximab dose of 3 mg/kg plus MTX was similar to that in patients receiving MTX alone. Patients receiving the unapproved induction regimen of 10 mg/kg infliximab plus MTX followed by a 10 mg/kg maintenance regimen had an increased risk of serious infections through week 22.
Westlake SL, Colebatch AN, Baird J, et al.. The effect of **methotrexate on cardiovascular disease** in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford). 2009 Nov 27. [Epub ahead of print]
Whiting Penny F., Smidt Nynke, Sterne Jonathan A.C., Et al. Systematic Review: Accuracy of **Anti–Citrullinated Peptide Antibodies** for Diagnosing Rheumatoid Arthritis. *Ann Intern Med* April 6, 2010 152:456-464.
Whittle SL, Richards BL, Husni E, et al. **Opioid therapy** for treating rheumatoid arthritis pain. Cochrane Database Syst Rev. 2011 Nov 9;11:CD003113. There is limited evidence that weak oral opioids may be effective analgesics for some patients with RA, but adverse effects are common and may offset the benefits of this class of medications.
Wolbink GJ, et al. Development of **antiinfliximab antibodies** and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):711-5.
Woo P, Southwood TR, et al. Randomized, placebo-controlled, crossover trial of low-dose oral **methotrexate** in **children** with extended oligoarticular or systemic arthritis. Arthritis Rheum. 2000 Aug;43(8):1849-57.
Wong SP, Chu CM, Kan CH, Tsui HS, Ng WL. Successful treatment of leflunomide-induced acute pneumonitis with **cholestyramine** wash-out therapy. J Clin Rheumatol. 2009 Dec;15(8):389-92.
Yazici Y, Curtis JR, Ince A, et al. Efficacy of **tocilizumab** in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012 Feb;71(2):198-205.
Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of **tocilizumab** in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008; 371: 998–1006.
Young JD, McGwire BS. **Infliximab** and reactivation of **cerebral toxoplasmosis**. N Engl J Med. 2005 Oct 6;353(14):1530-1; discussion 1530-1.
Zink A, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: Comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006 Oct 30;54(11):3399-3407 [Epub ahead of print] Only 21-33% of the patients in the RABBIT register would have been eligible for the major trials.
Zochling J, van der Heijde D, Burgos-Vargas R, et al. ASAS/EULAR recommendations for the management of **ankylosing spondylitis**. Ann Rheum Dis 2006; 65: 442–52.
Zulian F, Martini G, Vallongo C, et al. **Methotrexate in juvenile localized scleroderma**: A randomised, double-blind, placebo-controlled trial. Arthritis Rheum. 2011 Jan 28.

TOP

Rev. 2008 Jan 23;(1):CD001155.
Wells GA, Cranney A, Boucher M, et al. **Bisphosphonates** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women: a meta-analysis [Technology report no 69]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
Wimalawansa SJ, Grimes JP, Wilson AC, et al. Transdermal **nitroglycerin therapy may not prevent early postmenopausal bone loss**. J Clin Endocrinol Metab. 2009 Sep;94(9):3356-64.
Winzenberg TM, Powell S, Shaw KA, Jones G. **Vitamin D** supplementation for improving bone mineral density in **children**. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006944. DOI: 10.1002/14651858.CD006944.pub2. These results do not support vitamin D supplementation to improve bone density in healthy children with normal vitamin Dlevels, but suggest that supplementation of deficient children may be clinically useful.
Whitaker M, Guo J, Kehoe T, Benson G. **Bisphosphonates for Osteoporosis – Where Do We Go from Here**? N Engl J Med. 2012 May 9.
Wysowski DK. Reports of **esophageal cancer** with oral bisphosphonate use. N Engl J Med. 2009 Jan 1;360(1):89-90.
Yu EW, Bauer SR, Bain PA, et al. **Proton pump inhibitors** and risk of fractures: a meta-analysis of 11 international studies. Am J Med. 2011 Jun;124(6):519-26.
Zhu K, Devine A, Lewis JR, et al. "**Timed Up and Go**" (TUG) test and bone mineral density measurement for fracture prediction. Arch Intern Med. 2011;171(18):1655-1661.

Web Links:

Calculating Bone Mineral Densitometry, BMD fracture risk http://www.halls.md/bone-mineral-densitometry/bmd.htm
National Osteoporosis Foundation (NOF) http://www.nof.org/
Osteoporosis Canada – www.osteoporosis.ca
QFractureScore http://www.qfracture.org/
Simple Calculated Osteoporosis Risk Estimation (SCORE) tool http://osteoed.org/tools.php (sensitivity 91%, specificity 40%)[BMD]

TOP

Behavioural & Psychological Symptoms of DEMENTIA (BPSD) Treatment Chart

[1] Therapeutic Choices 5rd Edition, 2007
[2] Ontario Guidelines for the Management of Anxiety Disorders in Primary Care Fall 2000 1st Edition
[3] Micromedex 2010
[4] **Treatment Guidelines**: Drugs for Psychiatric Disorders. **The Medical Letter**: July, **2003**; p. 69-76.
[5] Kawas CH. Clinical practice. Early Alzheimer's disease. N Engl J Med. 2003 Sep 11; 349(11): 1056-63.
[6] Ritchie K, Lovestone S. The dementias. Lancet. 2002 Nov 30; 360(9347): 1759-66.
Corrada MM, Brookmeyer R, Berlau D, Paganini-Hill A, Kawas CH. Prevalence of dementia after age 90: results from the 90+ study. Neurology. 2008 Jul 29;71(5):337-43. Epub 2008 Jul 2. In a very large sample of participants aged 90 and older, prevalence of all-cause dementia doubled every 5 years for women but not men. The overall prevalence of all-cause dementia was higher in women (45%, 95% CI = 41.5-49.0) than men (28%, 95% CI = 21.7-34.2).
[7] Doody RS. Current treatments for Alzheimer's disease: **cholinesterase inhibitors**. J Clin Psychiatry. 2003;64 Suppl 9:11-7. s. 2000 Nov;60(5):1095-122.
[8] Cummings JL. Use of **cholinesterase inhibitors** in clinical practice: **evidence-based** recommendations. Am J Geriatr Psychiatry. 2003 Mar-Apr;11(2):131-45.
[9] Gauthier S. Advances in the pharmacotherapy of **Alzheimer's** disease. CMAJ. 2002 Mar 5;166(5):616-23.
[10] DeLaGarza VW. Pharmacologic treatment of **Alzheimer's disease**: an update. Am Fam Physician. 2003 Oct 1; 68(7): 1365-72.
[11] Kindermann SS, Dolder CR, Bailey A, Katz IR, Jeste DV. Pharmacological treatment of **psychosis and agitation** in elderly patients with dementia: four decades of experience. Drugs Aging. 2002; 19(4): 257-76.
[12] Lanctot KL, Herrmann N, Yau KK, et al. Efficacy and safety of **cholinesterase inhibitors** in Alzheimer's disease: a **meta-analysis**. CMAJ. 2003 Sep 16;169(6):557-64.
[13] Trinh NH, Hoblyn J, et al. Efficacy of **cholinesterase inhibitors** in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a **meta-analysis**. JAMA. 2003 Jan 8;289(2):210-6.
[14] Wilkinson DG, Passmore AP, et al. A multinational, randomised, 12-week, comparative study of **donepezil** and **rivastigmine** in patients with mild to moderate Alzheimer's disease. Int J Clin Pract. 2002 Jul-Aug;56(6):441-6.
[15] AGS Clinical Practice Committee. Guidelines abstracted from the **American Academy of Neurology's Dementia Guidelines** for Early Detection, Diagnosis, and Management of Dementia. J Am Geriatr Soc. 2003 Jun; 51(6): 869-73.
[16] U.S. Preventive Services Task Force. **Screening for dementia**: recommendation and rationale. Ann Intern Med. 2003 Jun 3; 138(11): 925-6. No abstract available. Summary for patients in: Ann Intern Med. 2003 Jun 3;138(11):I60.
[17] Patterson CJ, Gauthier S, Bergman H, Cohen CA, et al. The recognition, assessment and management of dementing disorders: conclusions from the **Canadian Consensus Conference on Dementia**. CMAJ. 1999 Jun 15; 160(12 Suppl): S1-15.
[18] Bullock R. Cholinesterase inhibitors and **vascular dementia**: another string to their bow? CNS Drugs. 2004; 18(2): 79-92.
[19] Department of Veterans Affairs; Drug Review March 2004 http://www.vapbm.org/reviews/CholinestInh.pdf
[20] Cummings JL. **Alzheimer's disease**. N Engl J Med. **2004** Jul 1;351(1):56-67.
[21] Sink KM, Holden KF, Yaffe K. Pharmacological treatment of **neuropsychiatric** symptoms of dementia: a review of the evidence. **JAMA. 2005** Feb 2;293(5):596-608. (InfoPOEMs: Pharmacologic agents are minimally, if at all, effective in managing the neuropsychiatric symptoms of dementia. The atypical antipsychotics olanzapine (Zyprexa) and risperidone (Risperdal) are the most effective, but these agents may increase the risk of stroke. The decision to use any of these drugs must be made on the basis of individual circumstances. (LOE = 1a-))
[22] Desai AK, Grossberg GT. Diagnosis and treatment of Alzheimer's disease. Neurology. 2005 Jun 28;64(12 Suppl 3):S34-9.
[23] Clinical **Handbook of Psychotropic Drugs** 13th Edition, Bezchlibnyk-Butler K, Jeffries J. 2003
[24] Bentue-Ferrer D, Tribut O, Polard E, Allain H. Clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists. CNS Drugs. 2003; 17(13): 947-63.
[25] Birks JS, Harvey R. **Donepezil** for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2003;(3):CD001190.
[26] Black S, et al. **Donepezil** 307 **Vascular** Dementia Study Group. Efficacy & tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke. 2003 Oct;34(10):2323-30.
[27] Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. **Donepezil** is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc. 2003 Jul;51(7):937-44.
[28] Feldman H, Gauthier S, et al. Donepezil MSAD Study Investigators. Efficacy of **donepezil** on maintenance of activities of daily living with moderate to severe Alzheimer's disease & the effect on caregiver burden. J Am Geriatr Soc. 2003 Jun;51(6):737-44.
[29] Wimo A, Winblad B, Engedal K, et al. Donepezil Nordic Study Group. An economic evaluation of **donepezil** in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomized trial. Dement Geriatr Cogn Disord. 2003;15(1):44-54.
[30] Winblad B, Engedal K, Soininen H, Verhey F, et al. Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of **donepezil** in patients with mild to moderate AD. Neurology. 2001 Aug 14;57(3):489-95.
[31] Mohs RC, Doody RS, Morris JC, Ieni JR, et al. "312" Study Group. A 1-year, placebo-controlled preservation of function survival study of **donepezil** in AD patients. Neurology. 2001 Aug 14;57(3):481-8. Erratum in: Neurology 2001 Nov 27;57(10):1942.
[32] Homma A, et al. Clinical efficacy & safety of **donepezil** on cognitive & global function in Alzheimer's. A 24-wk, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Gp. Dement Geriatr Cogn Disord. 2000 Nov-Dec;11(6):299-313.
[33] Rogers SL, Doody RS, et al. Long-term efficacy and safety of **donepezil** in the treatment of Alzheimer's disease: final analysis (**up to 4.9yrs**) of a US multicentre open-label study. Eur Neuropsychopharmacol. 2000 May;10(3):195-203
[34] Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, Pratt RD; Donepezil 308 Study Group. **Donepezil** in **vascular** dementia: a randomized, placebo-controlled study. Neurology. 2003 Aug 26; 61(4): 479-86.
[35] Auriacombe S, Pere JJ, Loria-Kanza Y, Vellas B. Efficacy and safety of **rivastigmine** in patients with Alzheimer's disease who failed to benefit from treatment with **donepezil**. Curr Med Res Opin. 2002; 18(3): 129-38.
[36] Courtney C, Farrell D, Gray R, et al.; **AD2000** Collaborative Group. **Long-term donepezil** treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004 Jun 26;363(9427):2105-15. (Author reply: Oct 2,2004)
[37] Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, Richardson S; Donepezil "402" Study Group. Efficacy of **donepezil** in **early-stage** Alzheimer disease: a randomized placebo-controlled trial. Arch Neurol. 2004 Dec;61(12):1852-6.
[38] Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., et al., for the Alzheimer's Disease Cooperative Study Group Vitamin E & Donepezil for the Treatment of **Mild Cognitive Impairment.** N Engl J Med 2005 June 9;352:2379-88. (Conclusions: Vitamin E had no benefit in patients with mild cognitive impairment. Although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment, the rate of progression to Alzheimer's disease after three years was not lower among patients treated with donepezil than among those given placebo.) (InfoPOEMs: Vitamin E does not slow progression of mild cognitive impairment to full-fledged Alzheimer's disease. Donepezil provides an early benefit that is gone by 3yr. A secondary analysis found that donepezil appeared more beneficial for pts with the apolipoprotein E4 (APOE) gene. This finding requires prospective confirmation before we begin to test all pts with mild cognitive impairment for APOE & use it to guide therapy.(LOE = 1b))
Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL; Alzheimer's Disease Cooperative Study Group. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology. 2009 Jun 16;72(24):2115-21.
[39] Holmes C, Wilkinson D, Dean C, Vethanayagam S, et al. The efficacy of donepezil in the treatment of **neuropsychiatric** symptoms in Alzheimer disease. Neurology. 2004 Jul 27;63(2):214-9.
[40] Suh DC, Thomas SK, Valiyeva E, Arcona S, Vo L. Drug Persistency of Two Cholinesterase Inhibitors : Rivastigmine versus Donepezil in Elderly Patients with Alzheimer's Disease. Drugs Aging. 2005;22(8):695-707.
[41] Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, Nagel J, Lane R. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin. 2005 Aug;21(8):1317-27.
[42] Winblad B,et al.; Severe Alzheimer's Disease Study Group. **Donepezil** in patients with **severe Alzheimer's disease**: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1;367(9516):1057-65. INTERPRETATION: Donepezil improves cognition and preserves function in individuals with severe Alzheimer's disease who live in nursing homes. (Editorial: a case of too little, too late & points out the limitations of using last observation carried forward & questions the clinical sig. of the findings.)
[43] Birks J. Cholinesterase inhibitors for Alzheimer's disease: review. Cochrane Database Syst Rev 2006;1: CD005593.
[44] Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. **Cholinesterase inhibitors** for patients with Alzheimer's disease: **systematic review** of randomised clinical trials. BMJ. **2005** Aug 6;331(7512):321-7. (InfoPOEMs: The evidence supporting the effectiveness of cholinesterase inhibitors is based on exceedingly **small effects found in poorly analyzed studies**. Studies of Alzheimer's drugs need to be carefully scrutinized for methodologic errors that inflate the appearance of benefit. (LOE = 1a))
[45] Feldman H, Gauthier S, et al. Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of **donepezil** in **moderate to severe** Alzheimer's disease. Neurology. 2001 Aug 28;57(4):613-20.
[46] Tariot PN, Cummings JL, Katz IR, Mintzer J, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of **donepezil** in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc. 2001 Dec;49(12):1590-9.
[47] Health Canada Public Advisory April 2005 -Information about Reminyl in patients with mild cognitive impairment (mortality: 1.3% galantamine vs 0.1% placebo group) http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/reminyl_hpc_e.html
Doody RS et al. Donepezil treatment of patients with MCI: A 48-week randomized, placebo-controlled trial. Neurology 2009 May 5; 72:1555.
[48] Olin J, Schneider L. **Galantamine** for Alzheimer's disease. Cochrane Database Syst Rev. 2002;(3):CD001747.
[49] Scott LJ, Goa KL. **Galantamine**: a review of its use in Alzheimer's disease. Drugs. 2000 Nov;60(5):1095-122.
[50] Kurz AF, Erkinjuntti T, et al. Long-term safety and cognitive effects of **galantamine** in the treatment of probable vascular dementia or Alzheimer's disease with cerebrovascular disease. Eur J Neurol. 2003 Nov;10(6):633-40.
[51] Small G, Erkinjuntti T, Kurz A, Lilienfeld S. **Galantamine** in the treatment of cognitive decline in patients with vascular dementia or Alzheimer's disease with cerebrovascular disease. CNS Drugs. 2003;17(12):905-14.
[52] Mintzer JE, Kershaw P. The efficacy of **galantamine** in the treatment of Alzheimer's disease: comparison of patients previously treated with acetylcholinesterase inhibitors to patients with no prior exposure. Int J Geriatr Psychiatry. 2003 Apr;18(4):292-7.
[53] Blesa R, Davidson M, Kurz A, Reichman W, et al. **Galantamine** provides sustained benefits in patients with 'advanced moderate' Alzheimer's disease for at least 12 months. Dement Geriatr Cogn Disord. 2003;15(2):79-87.

TOP

[54] Erkinjuntti T, Kurz A, Gauthier S, et al. Efficacy of **galantamine** in probable **vascular** dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet. 2002 Apr 13;359(9314):1283-90.
[55] Wilcock GK, et al. Efficacy & safety of **galantamine** in mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ. 2000 Dec 9;321(7274):1445-9. Erratum: BMJ 2001 Feb 17;322(7283):405.
[56] Tariot PN, Solomon PR, Morris JC, Kershaw P, et al. A 5-month, randomized, placebo-controlled trial of **galantamine** in AD. The Galantamine USA-10 Study Group. Neurology. 2000 Jun 27;54(12):2269-76.
[57] Raskind MA, Peskind ER, Wessel T, et al. **Galantamine** in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology. 2000 Jun 27;54(12):2261-8.
[58] Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of **galantamine** are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6.
[59] Pirttila T, Wilcock G, Truyen L, Damaraju CV. Long-term efficacy and safety of **galantamine** in patients with mild-to-moderate Alzheimer's disease: multicenter trial. Eur J Neurol. 2004 Nov;11(11):734-41.
[60] Health Canada Public Advisory April 2005 -Information about Reminyl in patients with mild cognitive impairment (mortality: 1.3% galantamine vs 0.1% placebo group) http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/reminyl_hpc_e.html
Winblad B, Gauthier S, Scinto L, Feldman H, Wilcock GK, Truyen L, Mayorga AJ, Wang D, Brashear HR, Nye JS; GAL-INT-11/18 Study Group. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology. 2008 May 27;70(22):2024-35.
Doody RS et al. Donepezil treatment of patients with MCI: A 48-week randomized, placebo-controlled trial. Neurology 2009 May 5; 72:1555.
[61] Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. **Rivastigmine** for Alzheimer's disease. Cochrane Database Syst Rev. 2000;(4):CD001191.
[62] Rigaud AS, Andre G, Vellas B, Touchon J, Pere JJ; French Study Group. No additional benefit of **HRT** on response to **rivastigmine** in menopausal women with AD. Neurology. 2003 Jan 14;60(1):148-9.
[63] Farlow M, Anand R, Messina J Jr, Hartman R, Veach J. A 52-week study of the efficacy of **rivastigmine** in patients with mild to moderately severe Alzheimer's disease. Eur Neurol. 2000;44(4):236-41.
[64] Rosler M, Anand R, et al. Efficacy and safety of **rivastigmine** in patients with Alzheimer's disease: international randomised controlled trial. BMJ. 1999 Mar 6;318(7184):633-8. Erratum: BMJ 2001 Jun 16;322(7300):1456.
[65] Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. **Rivastigmine** in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients. Am J Alzheimers Dis Other Demen. 2003 Sep-Oct; 18(5): 265-72.
[66] Aupperle PM, Koumaras B, Chen M, Rabinowicz A, Mirski D. Long-term effects of **rivastigmine** treatment on neuropsychiatric and behavioral disturbances in nursing home residents with moderate to severe Alzheimer's disease: results of a 52-week open-label study. Curr Med Res Opin. 2004 Oct;20(10):1605-12.
[67] Farlow MR, Lilly ML. **Rivastigmine**: An open-label, observational study of safety and effectiveness in treating patients with Alzheimer's Disease for up to **5 years**. BMC Geriatr. 2005 Jan 19;5(1):3 [Epub ahead of print]
[68] Lai MW, Moen M, Ewald MB. Pesticide-like poisoning from a prescription drug. N Engl J Med. 2005 Jul 21;353(3):317-8.
[69] Wild R, Pettit T, Burns A. Cholinesterase inhibitors for dementia with **Lewy bodies**. Cochrane Database Syst Rev. 2003;(3):CD003672.
[70] McKeith I, Del Ser T, Spano P, et al. Efficacy of **rivastigmine** in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet. 2000 Dec 16;356(9247):2031-6.
[71] Wilcock GK. **Memantine** for the treatment of dementia. Lancet Neurol. 2003 Aug; 2(8): 503-5.
Wilcock G, Mobius HJ, Stoffler A; MMM 500 group. A double-blind, placebo-controlled multicentre study of **memantine** in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol. 2002 Nov; 17(6): 297-305.
Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F. Efficacy and safety of **memantine** in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke. 2002 Jul; 33(7): 1834-9.
Memantine for Alzheimer's disease. Med Lett Drugs Ther. 2003 Sep 15; 45(1165): 73-4.
Areosa SA, Sherriff F. **Memantine** for dementia. Cochrane Database Syst Rev. 2003; (3): CD003154.
Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003 Apr 3;348(14):1333-41.
Tariot PN, et al. Memantine Study Group. **Memantine** treatment in patients with moderate to severe Alzheimer disease **already receiving donepezil**: a randomized controlled trial. JAMA. 2004 Jan 21; 291(3): 317-24.
Perras C. Memantine for treatment of moderate to severe Alzheimer's disease. Issues Emerg Health Technol. 2005 Mar;(64):1-4.
Gauthier S, Wirth Y, et al. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. Int J Geriatr Psychiatry. 2005 May;20(5):459-64.
Hanney M, Prasher V, Williams N, et al, on behalf of the **MEADOWS** trial researchers. **Memantine** for dementia in adults older than 40 years with **Down's syndrome** (MEADOWS): a randomised, double-blind, placebo-controlled trial. Lancet 2012; online Jan 10.
[72] Reisberg B, Doody R, Stöffler A et al. A 24-Week Open-Label Extension Study of Memantine in Moderate to Severe Alzheimer Disease. Archives of Neurology 2006;63:1-6
(Kirby J, et al. A systematic review of the clinical and cost-effectiveness of memantine in patients with moderately severe to severe Alzheimer's disease. Drugs Aging. 2006;23(3):227-40.) (Cummings JL, Schneider E, Tariot PN, Graham SM; Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients Receiving donepezil treatment. Neurology. 2006 Jul 11;67(1):57-63.)
[73] Herrmann N, Li A, Lanctot K. Memantine in dementia: a review of the current evidence. *Expert Opin Pharmacother* 2011; 12(5): 787-800.
Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data-analysis. *Int J Geriatr Psychiatry* 2008; 23: 537-545.
Maidment I, Fox CG, Boustani M, Rodriguez J, Brown RC, Katona CL. Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis. *Ann Pharmacother* 2008; 43:32-38.
Herrmann N, Cappell J, Eryavec GM, Lanctot KL. Changes in nursing burden following memantine for agitation and aggression in LTC residents with moderate-severe Alzheimers' disease. *CNS Drugs* 2011; 25(5): 425-433.
[74] Devanand DP, Marder K, Michaels KS, et al. A randomized, placebo-controlled dose-comparison trial of **haloperidol** for psychosis and disruptive behaviors in Alzheimer's disease. Am J Psychiatry. 1998 Nov; 155(11): 1512-20.
Devanand DP, Pelton GH, Cunqueiro K, Sackeim HA, Marder K. A 6-month, randomized, double-blind, placebo-controlled pilot **discontinuation trial following response to haloperidol** treatment of psychosis and agitation In Alzheimer's disease. Int J Geriatr Psychiatry. 2011 Sep;26(9):937-43.
[75] June 2005 Health Canada & April 2005 FDA Issues Public Health Advisory for Antipsychotic Drugs used for Treatment of Behavioral Disorders in Elderly Patients
http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_63_e.html (Singh S, Wooltorton E. Increased mortality among elderly patients with dementia using atypical antipsychotics. CMAJ. 2005 Aug 2;173(3):252.) (Medical Letter August 1,2005 -Atypical antipsychotics in the Elderly FDA n=5106 17 RCTs mortality rate of 4.5% with atypical antipsychotic therapy vs 2.6% with placebo, most deaths were due to cardiovascular & infectious causes such as pneumonia.) Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005 Oct 19;294(15):1934-43. (InfoPOEMs: The use of atypical antipsychotic drugs for even short periods (less than 8 to 12 weeks) is associated with a significantly increased risk of death. Antipsychotic drugs should be used only in individual situations of an identifiable risk of harm and when alternate therapies have failed. (LOE = 1a)){15 trials (9 unpublished) of atypical antipsychotics vs placebo for ~10-12weeks n=5110; 3.5 vs 2.3% death rate}(Wang PS et al. Risk of Death in Elderly Users of Conventional vs Atypical Antipsychotic Medications. N Engl J Med 2005;353:2335-41. Conclusion: If confirmed, these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should no be used to replace atypical agents discontinued in response to the FDA warning. (InfoPOEMs: It seems reasonable to conclude that conventional and atypical antipsychotic agents are both associated with an increased risk of death in elderly pts. The limitations of this study do not allow us to confidently conclude that older agents are less safe than newer agents, though. (LOE = 2b))) (Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ. 2007 Feb 27;176(5):627-32. Among elderly patients, the risk of death associated with conventional antipsychotic medications is comparable to and possibly greater than the risk of death associated with atypical antipsychotic medications. Until further evidence is available, physicians should consider all antipsychotic medications to be equally risky in elderly patients.) (Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N, Gurwitz JH, Rochon PA. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007 Jun 5;146(11):775-86. Atypical antipsychotic use is associated with an increased risk for death compared with nonuse among older adults with dementia. The risk for death may be greater with conventional antipsychotics than with atypical antipsychotics.)
Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic Drug Use and Risk of **Pneumonia** in Elderly People. J Am Geriatr Soc. 2008 Feb 7; [Epub ahead of print] Use of antipsychotics in elderly people is associated with greater risk of pneumonia. This risk is highest shortly after the initiation of treatment, with the greatest increase in risk found for atypical antipsychotics.
FDA Conventional Antipsychotic Warning June/08 http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm
Rochon PA, Normand SL, et al. Antipsychotic therapy and short-term **serious events** in older adults with dementia. Arch Intern Med. 2008 May 26;168(10):1090-6. Relative to those who received no antipsychotic therapy, community-dwelling older adults newly dispensed an **atypical antipsychotic therapy were 3.2 times** more likely (95% confidence interval, 2.77-3.68) and those who received **conventional antipsychotic therapy were 3.8 times** more likely (95% confidence interval, 3.31-4.39) to develop any serious event during the 30 days of follow-up. The pattern of serious events was similar but less pronounced among older adults living in a nursing home. Serious events, as indicated by a hospital admission or death, are frequent following the short-term use of antipsychotic drugs in older adults with dementia. Antipsychotic drugs should be used with caution even when short-term therapy is being prescribed.
Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ. 2008 Aug 28;337:a1227. doi: 10.1136/bmj.a1227. **All antipsychotics are associated with an increased risk of stroke**, and the risk might be higher in patients receiving atypical antipsychotics than those receiving typical antipsychotics. People with dementia seem to be at a higher risk of an associated stroke than people without dementia and use of antipsychotics should, when possible, be avoided in these patients.
Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. CMAJ. 2008 Aug 26;179(5):438-46.
Ballard C, Hanney ML, Theodoulou M, et al; the **DART-AD** investigators. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009 Jan 8.

TOP

[Epub ahead of print] There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients.

Ray WA, Chung CP, Murray KT et al. Atypical antipsychotic drugs and the risk of **sudden cardiac death**. New Engl J Med 2009; 360: 225-235. Both typical and atypical antipsychotic drugs increase the risk of sudden cardiac death. The absolute risk of sudden cardiac death in patients taking these drugs is 1.8 per 100 persons taking the drugs for 10yrs, which is approximately twice as high as for patients in the general population. Newer drugs are not safer than older drugs with respect to cardiovascular outcomes, & thioridazine, clozapine, & risperidone in high doses appear to be slightly more risky. (LOE = 2b)

Rossom RC, Rector TS, Lederle FA, et al. Are All Commonly Prescribed Antipsychotics Associated with Greater **Mortality** in Elderly Male Veterans with Dementia? J Am Geriatr Soc. 2010 May 7.

Commonly prescribed doses of haloperidol, olanzapine, and risperidone, but not quetiapine, were associated with a short-term increase in mortality.

Foley Debra L.; Morley Katherine I.. Systematic Review of Early **Cardiometabolic Outcomes** of the First Treated Episode of Psychosis. Arch Gen Psychiatry. 2011;0(2011):archgenpsychiatry.2011.2.

Huybrechts KF, Rothman KJ, Silliman RA., et al. **Risk of death and hospital admission** for major medical events after initiation of psychotropic medications in older adults admitted to nursing homes. CMAJ 2011 0: cmaj.101406

Parker C et al. **Antipsychotic drugs and risk of venous thromboembolism**: nested case-control study. BMJ 2010; 341: c4245

Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of **death in older residents in nursing homes prescribed specific antipsychotic drugs**: population based cohort study. BMJ 2012;344:e977. (worse with **haloperidol**)

Pariente A, Fourrier-Réglat A, Ducruet T, Farrington P, et al. Antipsychotic use and **myocardial infarction** in older patients with treated dementia [published online Mar 26, 2012]. Arch Intern Med doi:10.1001/archinternmed.2012.28.

[76] Hien le TT, Cumming RG, Cameron ID, et al. Atypical antipsychotic medications and **risk of falls** in residents of aged care facilities. J Am Geriatr Soc. 2005 Aug;53(8):1290-5. CONCLUSION: Despite fewer extrapyramidal side effects, atypical antipsychotic medications are not associated with fewer falls than the older, more-established antipsychotics.

[77] Schneider LS, Tariot PN, Dagerman KS, et al. **CATIE-AD** Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med. 2006 Oct 12;355(15):1525-38. (n=421 36weeks risperidone 1mg/d, olanzapine 5.5mg/d, & quetiapine 56.5mg/d) Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) (P=0.52). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) (P=0.002). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, & 5% of patients who received placebo discontinued their assigned treatment owing to intolerability (P=0.009). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo (P=0.22). (InfoPOEMs: Atypical antipsychotics are minimally, if at all, effective for patients with Alzheimer's disease (AD), and they have significant adverse effects. They should not be routinely used for the treatment of psychosis, agitation, or aggression in these patients. (LOE = 1b))

[78] Lee PE, Gill SS, Freedman M, Bronskill SE, Hillmer MP, Rochon PA. **Atypical antipsychotic** drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. BMJ. 2004 Jul 10;329(7457):75. CONCLUSIONS: Although atypical antipsychotic drugs are being used with increasing frequency, few randomised trials have evaluated their use for BPSD. Limited evidence supports the perception of improved efficacy and adverse event profiles compared with typical antipsychotic drugs.

[79] Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry. 2004 Jun;161(6):1113-5.

[80] Cummings JL, Street J, Masterman D, Clark WS. Efficacy of **olanzapine** in the treatment of psychosis in dementia with lewy bodies. Dement Geriatr Cogn Disord. 2002; 13(2): 67-73.

[81] Street JS, Clark WS, Kadam DL, Mitan SJ, et al. A. Long-term efficacy of **olanzapine** in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. Int J Geriatr Psychiatry. 2001 Dec; 16 Suppl 1: S62-70.

[82] Street JS, et al. **Olanzapine** treatment of psychotic & behavioral symptoms in patients with Alzheimer's in nursing care facilities: a double-blind, randomized, placebo-controlled trial. HGEU Study Group. Arch Gen Psychiatry. 2000 Oct; 57(10): 968-76.

[83] De Deyn PP, Carrasco MM, Deberdt W, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Feb;19(2):115-26.

[84] De Deyn PP, Carrasco MM, Deberdt W, Jeandel C, Hay DP, Feldman PD, Young CA, Lehman DL, Breier A. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Feb;19(2):115-26.

[85] Deberdt WG, Dysken MW, Rappaport SA, Feldman PD, et al.. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry. 2005 Aug;13(8):722-30. CONCLUSIONS: Patients' neuropsychiatric functioning improved with olanzapine, risperidone, and placebo treatment. There was a substantial response in the placebo group, and no significant differences emerged among treatments.

[86] Kennedy J, Deberdt W, Siegal A, et al. **Olanzapine** does **not** enhance **cognition** in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. Int J Geriatr Psychiatry. 2005 Oct 26;20(11):1020-1027 [Epub ahead of print]

[87] Lim CJ, Trevino C, Tampi RR. Can Olanzapine Cause Delirium in the Elderly? (January). Ann Pharmacother. 2005 Dec 20; [Epub ahead of print]

[88] Consensus Development Conference on Antipsychotic Drugs and Obesity and **Diabetes**; Diabetes Care.2004; 27: 596-558.

[89] Sajatovic M, Mullen JA, Sweitzer DE. Efficacy of quetiapine and risperidone against depressive symptoms in outpatients with psychosis. J Clin Psychiatry. 2002 Dec; 63(12): 1156-63.

[90] Ballard C, Margallo-Lana M, Juszczak E, et al. **Quetiapine** and **rivastigmine** and **cognitive decline in Alzheimer's disease**: randomised double blind placebo controlled trial. BMJ. 2005 Apr 16;330(7496):874. Epub 2005 Feb 18. CONCLUSIONS: Neither quetiapine nor rivastigmine are effective in the treatment of agitation in people with dementia in institutional care. Compared with placebo, quetiapine is associated with significantly greater **cognitive decline**.

[91] Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of **risperidone** for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry. 2003 Feb; 64(2): 134-43.

[92] Katz IR, Jeste DV, Mintzer JE, et al. Comparison of **risperidone** and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry. 1999 Feb; 60(2): 107-15.

[93] De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of **risperidone**, placebo, and **haloperidol** for behavioral symptoms of dementia. Neurology 1999;53:946-55.

[94] Fontaine CS, Hynan LS, Koch K, et al. A double-blind comparison of **olanzapine versus risperidone** in the acute treatment of dementia-related behavioral disturbances in extended care facilities. J Clin Psychiatry. 2003 Jun; 64(6): 726-30.

[95] De Deyn PP, Katz IR, et al. Management of agitation, aggression, and psychosis associated with dementia: A pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. Clin Neurol Neurosurg. 2005 May 24; [Epub ahead of print]

Komossa K, Rummel-Kluge C, Schwarz S, et al. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2011 Jan 19;1:CD006626. Risperidone seems to produce somewhat more extrapyramidal side effects and clearly more prolactin increase than most other SGAs. It may also differ from other compounds in efficacy and in the occurrence of other adverse effects such as weight gain, metabolic problems, cardiac effects, sedation and seizures. Nevertheless, the large proportion of participants leaving studies early and incomplete reporting of outcomes makes it difficult to draw firm conclusions.

[96] Clinical **Handbook of Psychotropic Drugs** 13th Edition, Bezchlibnyk-Butler K, Jeffries J. 2003

[97] Bentue-Ferrer D, Tribut O, Polard E, Allain H. Clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists. CNS Drugs. 2003; 17(13): 947-63.

[98] Pollock BG, et al. Comparison of **citalopram**, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry. 2002 Mar;159(3):460-5.

[99] Nyth AL, et al. A controlled multicenter clinical study of **citalopram** and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand. 1992 Aug;86(2):138-45.

[100] Nyth AL, Gottfries CG. The clinical efficacy of **citalopram** in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. Br J Psychiatry. 1990 Dec;157:894-901.

Seitz DP, Adunuri N, Gill SS, et al. Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev. 2011 Feb 16;2:CD008191. Currently there are relatively few studies of antidepressants for the treatment of agitation and psychosis in dementia. The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies. Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics.

[101] Petracca GM, Chemerinski E, Starkstein SE. A double-blind, placebo-controlled study of **fluoxetine** in depressed patients with Alzheimer's disease. Int Psychogeriatr. 2001 Jun; 13(2): 233-40.

[102] Olafsson K, Jorgensen S, Jensen HV, Bille A, Arup P, Andersen J. **Fluvoxamine** in the treatment of demented elderly patients: a double-blind, placebo-controlled study. Acta Psychiatr Scand. 1992 Jun; 85(6): 453-6.

[103] Katona CL, Hunter BN, Bray J. A double-blind comparison of the efficacy and safely of **paroxetine** and **imipramine** in the treatment of depression with dementia. Int J Geriatr Psychiatry. 1998 Feb; 13(2): 100-8.

[104] Schatzberg AF, Kremer C, Rodrigues HE, Murphy GM Jr; Mirtazapine vs. Paroxetine Study Group. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. Am J Geriatr Psychiatry. 2002 Sep-Oct; 10(5): 541-50.

[105] Lyketsos CG, et al. Randomized, placebo-controlled, double-blind clinical trial of **sertraline** in the treatment of depression complicating Alzheimer's: initial results from the Depression in Alzheimer's Disease study. Am J Psychiatry. 2000 Oct;157(10):1686-9.

[106] Lyketsos CG, DelCampo L, et al. Treating depression in Alzheimer disease: efficacy and safety of **sertraline** therapy, and the benefits of depression reduction: the DIADS. Arch Gen Psychiatry. 2003 Jul; 60(7): 737-46.

[107] Modell JG, Katholi CR, Modell JD, et. al. Comparative **sexual side effects** of bupropion fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997;61(4):476-87.

[108] Gonzalez M, Llorca G, Izquierdo JA, et.al. J Sex Marital Ther 1997;23(3):176-94.

[109] Which **SSRI**? Med Lett Drugs Ther. 2003 Nov 24;45(1170):93-95.

[110] Mulsant BH, Pollock BG, Nebes R, et al. A twelve-week, double-blind, randomized comparison of **nortriptyline** and **paroxetine** in older depressed inpatients and outpatients. Am J Geriatr Psychiatry. 2001 Fall; 9(4): 406-14.

[111] Shumaker SA, et al; **Estrogen plus progestin** & the incidence of dementia & mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study: randomized controlled trial. JAMA.2003May28;289(20): 2651-62.

Mulnard RA, et al. **Estrogen replacement** therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA. 2000 Feb 23; 283(8): 1007-15. Erratum: JAMA 2000 Nov 22-29;284(20):2597.

TOP

[112] Etminan M, Gill S, Samii A. Effect of non-steroidal a**nti-inflammatory** drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. BMJ. 2003 Jul 19; 327(7407): 128.
Ad2000 Collaborative Group. **Aspirin 75mg/d in Alzheimer's disease** (AD2000): a randomised open-label trial. Lancet Neurol. 2007 Dec 6; [Epub ahead of print] n=310. Although aspirin is commonly used in dementia, in patients with typical AD 2 years of treatment with low-dose aspirin has no worthwhile benefit and increases the risk of serious bleeds.
Martyn C. **Anti-inflammatory** drugs and Alzheimer's disease. BMJ. 2003 Aug 16;327(7411):353-4.
Tabet N, Feldmand H. **Ibuprofen** for Alzheimer's disease. Cochrane Database Syst Rev. 2003;(2):CD004031. (Naproxen 220 mg BID and celecoxib 200 mg BID or placebo. do not prevent AD in early results from a randomized controlled trial. **ADAPT** Research Group Neurology. 2007 Apr 25; [Epub ahead of print] These results do not support the hypothesis that celecoxib or naproxen prevent Alzheimer dementia, at least within the early years after initiation of treatment. Masked long-term follow-up of these participants will be essential. Kang JH, Cook N, Manson J, Buring JE, Grodstein F. Low dose aspirin and cognitive function in the **Women's Health Study** cognitive cohort. BMJ. 2007 Apr 27; [Epub ahead of print] n=6377 mean 9.6yr. Long term use of low dose aspirin (100mg on alternate days) does not provide overall benefits for cognition among generally healthy women aged 65 or more.)
ADAPT Research Group. Cognitive Function Over Time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): Results of a Randomized, Controlled Trial of Naproxen and Celecoxib. Arch Neurol. 2008 May 12. [Epub ahead of print] Use of naproxen or celecoxib did not improve cognitive function. There was weak evidence for a detrimental effect of naproxen.
Arvanitakis Z, Grodstein F, Bienias JL, Schneider JA, Wilson RS, Kelly JF, Evans DA, Bennett DA. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. Neurology. 2008 Jun 3;70(23):2219-25. These data do not support a strong relation between nonsteroidal anti-inflammatory drugs and Alzheimer disease or cognition. Consistent findings across clinical and pathologic outcomes provide additional confidence in these results.
Price JF, Stewart MC, et al. **AAA Trialists**. Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial. BMJ. 2008 Sep 1;337:a1198. doi: 10.1136/bmj.a1198. Low dose aspirin (100 mg daily) or placebo for five years. Low dose aspirin does not affect cognitive function in middle aged to elderly people at increased cardiovascular risk.
Jaturapatporn D, Isaac MG, McCleery J, et al. Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer`s disease. Cochrane Database Syst Rev. 2012 Feb 15;2:CD006378. Based on the studies carried out so far, the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven. Therefore, these drugs cannot be recommended for the treatment of AD.

[113] Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of **Ginkgo** biloba for dementia. North American EGb Study Group. JAMA. 1997 Oct 22-29;278(16):1327-32.
van Dongen MC, et al. The efficacy of **ginkgo** for elderly people with dementia & age-associated memory impairment: new results of a randomized trial. J Am Geriatr Soc. 2000 Oct;48(10):1183-94.
Birks J, Grimley EV, Van Dongen M. **Ginkgo** biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2002;(4):CD003120.
Dekosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP, Kuller LH, Robbins JA, Tracy RP, Woolard NF, Dunn L, Snitz BE, Nahin RL, Furberg CD; for the Ginkgo Evaluation of memory (**GEM**) Study Investigators. Ginkgo biloba for Prevention of Dementia: A Randomized Controlled Trial. JAMA. 2008 Nov 19;300(19):2253-2262. In this study, G biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.
Snitz Beth E.; O'Meara Ellen S.; Carlson Michelle C.; et al. for the Ginkgo Evaluation of Memory (**GEM**) Study Investigators. Ginkgo biloba for Preventing Cognitive Decline in Older Adults: A Randomized Trial. JAMA. 2009;302(24):2663-2670. Compared with placebo, the use of G biloba, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment.
Geng J, Dong J, Ni H, et al. **Ginseng** for cognition. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD007769. DOI: 10.1002/14651858.CD007769.pub2. Currently, there is a lack of convincing evidence to show a cognitive enhancing effect of Panax ginseng in healthy participants and no high quality evidence about its efficacy in patients with dementia. Randomized, double-blind, placebo-controlled, parallel group trials with large sample sizes are needed to further investigate the effect of ginseng on cognition in different populations, including dementia patients.

[114] Rockwood K, Kirkland S, Hogan DB, MacKnight C, Merry H, Verreault R, Wolfson C, McDowell I. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol. 2002 Feb;59(2):223-7.
Scott HD, Laake K. **Statins** for the prevention of Alzheimer's disease. Cochrane Database Syst Rev. 2001;(4):CD003160.
Rea TD, Breitner JC, Psaty BM, et al. **Statin** use and the risk of incident dementia: the cardiovascular health study. Arch Neurol. 2005 Jul;62(7):1047-51. CONCLUSIONS: In this cohort study, statin therapy was not associated with a decreased risk of dementia.
Arvanitakis Z, Schneider JA, Wilson RS, et al. Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. Neurology. 2008 Jan 16; [Epub ahead of print] Overall, **statins were not** related to incident Alzheimer disease (AD) or change in cognition, or continuous measures of AD pathology or infarction.
Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, Schwam E,Schindler R, Hey-Hadavi J, Demicco DA, Breazna A; On behalf of the **LEADe** Investigators. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease. LEADe. Neurology. 2010 Mar 3.
McGuinness B, O`Hare J, Craig D, et al. Statins for the treatment of dementia. Cochrane Database Syst Rev. 2010 Aug 4;8:CD007514. There is insufficient evidence to recommend statins for the treatment of dementia. Analysis from the studies available, including one large RCT, indicate statins have no benefit on the outcome measures ADAS-Cog or MMSE. We need to await full results from CLASP 2008 before we can be certain.
Mielke MM, Zandi PP, Shao H, et al. The 32-year relationship between **cholesterol and dementia** from midlife to late life. Neurology. 2010 Nov 10.
Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of **simvastatin to treat Alzheimer disease**. Neurology. 2011 Aug 9;77(6):556-63. (no benefit)

[115] Tabet N, Birks J, Grimley Evans J. **Vitamin E** for Alzheimer's disease. Cochrane Database Syst Rev. 2000;(4):CD002854. (Pham DQ, Plakogiannis R. **Vitamin e** supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: part 2. Ann Pharmacother. 2005 Dec;39(12):2065-71. Epub 2005 Nov 15.)
Ronald C. Petersen, Ph.D., M.D., Ronald G. et al., for the Alzheimer's Disease Cooperative Study Group **Vitamin E** and Donepezil for the Treatment of Mild Cognitive Impairment Published at www.nejm.org April 13, 2005

[116] Malouf R, Areosa Sastre A. **Vitamin B12** for cognition. Cochrane Database Syst Rev. 2003;(3):CD004326.
Aisen PS, Schneider LS, Sano M, et al. Alzheimer Disease Cooperative Study (ADCS). High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA. 2008 Oct 15;300(15):1774-83. This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.
Hooshmand B, Solomon A, Kåreholt I, et al. Homocysteine and holotranscobalamin and the risk of Alzheimer disease: A longitudinal study. Neurology. 2010 Oct 19;75(16):1408-14.

[117] Forette F, et al. Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002 Oct 14;162(18):2046-52.
Peila R, et al. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. Stroke. 2006 May;37(5):1165-70. Epub 2006 Apr 6.)

[118] Adapted from: Primary Care Management & Pharmacological Management of BPSD, International Psychogeriatric Association, Module 1-8 2002. http://www.ipa-online.org/ipaonlinev3/ipaprograms/bpsdrev/6BPSDfinal.pdf

[119] Hien le TT, Cumming RG, Cameron ID, et al. Atypical antipsychotic medications and risk of falls in residents of aged care facilities. J Am Geriatr Soc. 2005 Aug;53(8):1290-5.

[120] Feldman HH, Ferris S, Winblad B, Sfikas N, Mancione L, He Y, Tekin S, Burns A, Cummings J, del Ser T, Inzitari D, Orgogozo JM, Sauer H, Scheltens P, Scarpini E, Herrmann N, Farlow M, Potkin S, Charles HC, Fox NC, Lane R. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol. 2007 Jun;6(6):501-12.

[121] Massoud F, Belleville S, Bergman H, et al. Mild cognitive impairment and cognitive impairment, no dementia: Part B, therapy. Alzheimers Dement 2007;3:283- 91. Jean L, Bergeron ME, Thivierge S, Simard M. Cognitive intervention programs for individuals with mild cognitive impairment: systematic review of the literature. Am J Geriatr Psychiatry 2010;18:281-96.
Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133-42.

Additional references:

Acosta-Baena Natalia, Sepulveda-Falla Diego, Lopera-Gomez Carlos Mario, et al. **Pre-dementia** clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study, The Lancet Neurology, Vol10, Issue 3, Mar 2011.

AHA-ASA-American Heart Association/American Stroke Association. Scientific statement: **Vascular contributions to cognitive impairment and dementia**. *Stroke* 2011; DOI:10.1161/?STR.0b013e3182299496. http://stroke.ahajournals.org/content/early/2011/07/21/STR.0b013e3182299496.full.pdf+html

Alagiakrishnan K, Marrie T, Rolfson D, et al. Gaps in patient care practices to **prevent hospital-acquired delirium**. Can Fam Physician. 2009 Oct;55(10):e41-6.

TOP

Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging and Alzheimer's Association workgroup. Alzheimers Dement 2011 April 20 (Epub ahead of print).

Alexopoulos GS, Streim J, et al.; Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients. Using antipsychotic agents in older patients. J Clin Psychiatry. 2004;65 Suppl 2:5-99;discussion 100-102;quiz 103-4.

Almaraz AC, Driver-Dunckley ED, Woodruff BK, et al. Efficacy of rivastigmine for cognitive symptoms in **Parkinson** disease with dementia. Neurologist. 2009 Jul;15(4):234-7. Rivastigmine therapy for PDD is associated with significant tradeoffs in efficacy and adverse effects. Carefully monitored trials of rivastigmine may provide meaningful benefits for a minority of PDD patients.

Amariglio RE, Townsend MK, Grodstein F, et al. **Specific Subjective Memory Complaints** in Older Persons May Indicate Poor Cognitive Function. J Am Geriatr Soc. 2011 Sep 15. doi: 10.1111/j.1532-5415.2011.03543.x.

Amato MP, Hakiki B, Goretti B, et al. Association of **MRI metrics** and cognitive impairment in radiologically isolated syndromes. Neurology. 2012 Jan 31;78(5):309-314.

Ancelin ML, et al. Non-degenerative mild **cognitive impairment** in elderly people and use of **anticholinergic** drugs: longitudinal cohort study. BMJ. 2006 Feb 25;332(7539):455-9. Epub 2006 Feb 1. CONCLUSIONS: Elderly people taking anticholinergic drugs had significant deficits in cognitive functioning and were highly likely to be classified as mildly cognitively impaired, although not at increased risk for dementia. Doctors should assess current use of anticholinergic drugs in elderly people with mild cognitive impairment before considering administration of acetylcholinesterase inhibitors.

Anderson Craig, Teo Koon, Gao Peggy, et al. and for the **ONTARGET and TRANSCEND Investigators, Renin-angiotensin system blockade** and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies, The Lancet Neurology, Volume 10, Issue 1, January 2011, Pages 43-53, ISSN 1474-4422, DOI: 10.1016/S1474-4422(10)70250-7. (no clear benefits)

Anticholinergic Cognitive Burden (ACB) scale http://www.indydiscoverynetwork.org/AnticholinergicCognitiveBurdenScale.html

Axona (Accera) Medical Letter June 29, 2009. (Medical food containing medium-chain triglycerides –insufficient evidence.

Balasa M., Gelpi E., Antonell A., et al. and For the Neurological Tissue Bank/University of Barcelona/Hospital Clínic NTB/UB/HC Collaborative Group. Clinical features and APOE genotype of pathologically proven **early-onset Alzheimer** disease Neurology May 17, 2011 76:1720-1725. (1/3 present with atypical features)

Baldi I et al. Neurobehavioral effects of long-term exposure to **pesticides**: Results from the 4-year follow-up of the PHYTONER Study. Occup Environ Med 2010 Nov 22

Ballard C, Waite J. The effectiveness of **atypical antipsychotics** for the treatment of **aggression and psychosis in Alzheimer's disease**. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003476.

Ballard C, Hanney ML, Theodoulou M, et al; the **DART-AD** investigators. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009 Jan 8. [Epub ahead of print] There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients.

Ballard C, Gauthier S, Corbett A, et al. **Alzheimer's** disease. Lancet. 2011 Mar 19;377(9770):1019-31.

Ballard C, Corbett A. Management of **neuropsychiatric symptoms** in people with dementia. CNS Drugs. 2010 Sep 1;24(9):729-39. doi:10.2165/11319240-000000000-00000.

Banerjee S, Hellier J, Dewey M, et al. **Sertraline** (150mg/day) **or mirtazapine** (45mg/day) for depression in dementia (**HTA-SADD**): a randomised, multicentre, double-blind, placebo-controlled trial. Lancet 2011; July 18.

Barak Y, Plopski I, Tadger S, et al. **Escitalopram versus risperidone** for the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease: a randomized double-blind pilot study. Int Psychogeriatr. 2011 Apr 15:1-5.

Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults. The **late-life dementia risk index**. Neurology. 2009 May 13. [Epub ahead of print]

Barnes Deborah E, Yaffe Kristine, The projected effect of **risk factor reduction** on Alzheimer's disease prevalence, The Lancet Neurology, online 19 July 2011

Barnes DE, Yaffe K, Byers AL, et al. **Midlife vs Late-Life Depressive Symptoms** and Risk of Dementia: Differential Effects for Alzheimer Disease and Vascular Dementia. Arch Gen Psychiatry. 2012 May;69(5):493-8.

Barthel H, Gertz HJ, Dresel S, et al. for the **Florbetaben** Study Group. Cerebral amyloid-β PET with florbetaben ((18)F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. Lancet Neurol. 2011 Apr 8.

Bartorelli L, et al.; Upgrade Study Group. Effects of **switching** from an AChE inhibitor to a dual AChE-BuChE inhibitor in patients with Alzheimer's disease. Curr Med Res Opin. 2005 Nov;21(11):1809-18.

Barzilay Joshua I.; Gao Peggy; O'Donnell Martin; et al. for the ONTARGET and TRANSCEND Investigators. **Albuminuria and Decline in Cognitive Function**: The ONTARGET/TRANSCEND Studies. Arch Intern Med. 2011;171(2):142-150.

Bayer-Carter JL, Green PS, Montine TJ, et al. **Diet intervention** and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. Arch Neurol. 2011 Jun;68(6):743-52.

Belle SH, et al. Resources for Enhancing Alzheimer's Caregiver Health (**REACH**) II Investigators. Enhancing the quality of life of dementia caregivers from different **ethnic or racial groups**: a randomized, controlled trial. Ann Intern Med. 2006 Nov 21;145(10):727-38.

Bergh S, Selbæk G, Engedal K. **Discontinuation of antidepressants** in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial. BMJ. 2012 Mar 9;344:e1566.

Bergman J, Dwolatzky T, Brettholz I, Lerner V. Beneficial effect of **donepezil** in the treatment of elderly patients with **tardive movement** disorders. J Clin Psychiatry. 2005 Jan;66(1):107-10.

Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive care **delirium** screening checklist: evaluation of a new **screening tool**. Intensive Care Med 2001;27:859-64.

Bernick C, Cummings J, Raman R, et al. **Age and Rate of Cognitive Decline** in Alzheimer Disease: Implications for Clinical Trials. Arch Neurol. 2012 Mar 19.

Berthier ML, et al. A randomized, placebo-controlled study of **donepezil** in **poststroke aphasia**. Neurology. 2006 Nov 14;67(9):1687-9. n=16

Birks J, Harvey RJ. **Donepezil** for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2006; 1: CD001190.

Birks J, Grimley Evans J, Iakovidou V, Tsolaki M, Holt FE. **Rivastigmine** for Alzheimer's disease. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD001191.

Black SE, Doody R, Li H, et al. **Donepezil** preserves cognition and global function in patients with **severe Alzheimer disease**. Neurology. 2007 Jul 31;69(5):459-69.

Blennow K, Zetterberg H, Rinne JO, et al. Effect of Immunotherapy With **Bapineuzumab** on Cerebrospinal Fluid Biomarker Levels in Patients With Mild to Moderate Alzheimer Disease. Arch Neurol. 2012 Apr 2.

Boyle PA, Buchman AS, Wilson RS, et al. Effect of **purpose in life** on the relation between Alzheimer disease pathologic changes on cognitive function in advanced age. Arch Gen Psychiatry. 2012 May;69(5):499-504.

Breen DA, Breen DP, Moore JW, Breen PA, O'Neill D. **Driving and dementia**. BMJ. 2007 Jun 30;334(7608):1365-9.

Breitbart W, Alici Y. Agitation and **delirium** at the end of life: "We couldn't manage him". JAMA. 2008 Dec 24;300(24):2898-910, E1.

Breitbart W, et al. A double-blind trial of **haloperidol**, chlorpromazine, and lorazepam in the treatment of **delirium** in hospitalized AIDS patients. Am J Psychiatry. 1996 Feb;153(2):231-7.

Brodaty H, Ames D, Snowdon J, et al. **Risperidone** for psychosis of Alzheimer's disease and mixed dementia: results of a double-blind, placebo-controlled trial. Int J Geriatr Psychiatry. 2005 Dec;20(12):1153-7.

Brown Jeremy, Pengas George. Self administered cognitive **screening test** (**TYM**) for detection of Alzheimer's disease: cross sectional study. BMJ 2009;338:b2030, doi: 10.1136/bmj.b2030 (Published 9 June 2009) http://www.bmj.com/cgi/data/bmj.b2030/DC1/1

Buchhave P, Minthon L, Zetterberg H, et al. **Cerebrospinal Fluid Levels of β-Amyloid 1-42**, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia. Arch Gen Psychiatry. 2012 Jan;69(1):98-106.

Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total **daily physical activity** and the risk of AD and cognitive decline in older adults. Neurology 2012;78: 1323–1329.

Burns A, Bernabei R, Bullock R, et al. Safety and efficacy of **galantamine** (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. Lancet Neurol. 2008 Nov 28. [Epub ahead of print] Galantamine can be started and used safely in elderly patients with severe AD. Galantamine improved cognitive function but failed to significantly improve the co-primary parameter of overall activities of daily living.

Burns A, Iliffe S. **Dementia**. BMJ. **2009 Feb** 5;338:b75. doi: 10.1136/bmj.b75.

Burns A, Iliffe S. **Alzheimer's disease**. BMJ. **2009 Feb** 5;338:b158. doi: 10.1136/bmj.b158.

Burrell JR, Hornberger M, Carpenter RH, et al. **Saccadic abnormalities** in frontotemporal dementia. Neurology. 2012 Jun 5;78(23):1816-23.

Callahan CM, et al. Effectiveness of **collaborative care** for older adults with Alzheimer disease in primary care: a randomized controlled trial.JAMA. 2006 May 10;295(18):2148-57.

Campbell NL, Boustani MA, Lane KA, et al. Use of **anticholinergics** and the risk of **cognitive impairment** in an African American population. Neurology. 2010 Jul 13;75(2):152-9.

Canadian Coalition for Seniors' Mental Health (**CCSMH**) National Guidelines for **Delirium & Depression** Mental Health 2006: http://www.ccsmh.ca/en/default.cfm http://www.ccsmh.ca/pdf/final%20supplement.pdf

Canessa N, Ferini-Strambi L. **Sleep-disordered breathing** and cognitive decline in older adults. JAMA. 2011 Aug 10;306(6):654-5.

Cardarelli R, Kertesz A, Knebl JA. **Frontotemporal dementia**: a review for primary care physicians. Am Fam Physician. 2010 Dec 1;82(11):1372-7.

TOP

Cardiovascular and Cerebrovascular Events in the Randomized, Controlled **Alzheimer's** Disease Anti-Inflammatory Prevention Trial (**ADAPT**). PLoS Clin Trials. 2006 Nov 17;1(7):e33 [Epub ahead of print] For celecoxib, ADAPT data do not show the same level of risk as those of the APC trial. The data for **naproxen**, although not definitive, are suggestive of increased cardiovascular and cerebrovascular risk. (Nissen SE. ADAPT: The Wrong Way to Stop a Clinical Trial. PLoS Clin Trials. 2006 Nov 17;1(7):e35 [Epub ahead of print]

Carson S, McDonagh MS, Peterson K. A systematic review of the efficacy and safety of atypical antipsychotics in patients with psychological and behavioral symptoms of dementia. J Am Geriatr Soc. 2006 Feb;54(2):354-61.

Carrière I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with **anticholinergic** properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009 Jul 27;169(14):1317-24.

Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the **APOE epsilon4** effect. N Engl J Med. 2009 Jul 16;361(3):255-63.

Caselli RJ, Dueck AC, Locke DE, et al. Cerebrovascular risk factors and preclinical memory decline in healthy **APOE** {varepsilon}4 **homozygotes**. Neurology. 2011 Mar 22;76(12):1078-84.

Chen Yong; Briesacher Becky A.; Field Terry S.; et al. Unexplained Variation Across US **Nursing Homes in Antipsychotic Prescribing Rates**. Arch Intern Med. 2010;170(1):89-95.

Chertkow H. **Diagnosis and treatment of dementia: introduction**. Introducing a series based on the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. CMAJ. 2008 Jan 29;178(3):316-21.

Chertkow H, Massoud F, Nasreddine Z, et al. Diagnosis and treatment of dementia: 3. **Mild cognitive impairment and cognitive impairment without dementia**. CMAJ. 2008 May 6;178(10):1273-85.

Clark Christopher M., Schneider Julie A., Bedell Barry J., et al., for the AV45-A07 Study Group. Use of **Florbetapir-PET for Imaging β-Amyloid** Pathology. *JAMA*. 2011;305(3):275-283.doi:10.1001/jama.2010.2008

Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing. 2011 Jan;40(1):23-9. (opiates and benzos)

Cohen-Bittan J, Boddaert J, Guettrot-Imbert G, et al. **Atypical dementia**. Lancet. 2010 Aug 21;376(9741):656.

Cooper C, Selwood A, Blanchard M, Walker Z, Blizard R, Livingston G. **Abuse of people** with dementia by family carers: representative cross sectional survey. BMJ. 2009 Jan 22;338:b155. doi: 10.1136/bmj.b155.

Cooper C, Katona C, Lyketsos K, et al. A Systematic Review of Treatments for **Refractory Depression in Older People**. Am J Psychiatry. 2011 Mar 31.

Dangour AD et al. Effect of 2-y n–3 long-chain **polyunsaturated fatty acid supplementation** on cognitive function in older people: A randomized, double-blind, controlled trial. Am J Clin Nutr 2010 Apr 21.

Dartigues JF, Féart C. **Risk factors** for Alzheimer disease: Aging beyond age? Neurology. 2011 Jul 19;77(3):206-7.

Davies NM, Kehoe PG, Ben-Shlomo T, Martin RM. Associations of anti-hypertensive treatments (**ARBS**) with **Alzheimer's disease**, vascular dementia, and other dementias. J Alzheimer's Dis 2011; 26:699-708.

Daviglus ML, Plassman BL, Pirzada A, et al. **Risk Factors and Preventive Interventions** for Alzheimer Disease: State of the Science. Arch Neurol. 2011 May 9.

De Deyn P, Jeste DV, Swanink R, Kostic D, Breder C, Carson WH, Iwamoto T. **Aripiprazole** for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study. J Clin Psychopharmacol. 2005 Oct;25(5):463-7.

De Meyer Geert; Shapiro Fred; Vanderstichele Hugo; et al.; for the Alzheimer's Disease Neuroimaging Initiative. Diagnosis-Independent Alzheimer **Disease Biomarker** Signature in Cognitively Normal Elderly People. Arch Neurol. 2010;67(8):949-956.

Dekosky ST, Williamson JD, Fitzpatrick AL, et al.; for the Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for Prevention of Dementia: A Randomized Controlled Trial. JAMA. 2008 Nov 19;300(19):2253-2262. (n=3,069 6.1yrs) In this study, G biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.

Deramecourt V, Slade JY, Oakley AE, et al. **Staging and natural history of cerebrovascular pathology** in dementia. Neurology 2012;78:1043–1050.

Devanand DP, Schupf N, Stern Y, et al. Plasma A{beta} and **PET PiB binding** are inversely related in mild cognitive impairment. Neurology. 2011 Jul 12;77(2):125-31.

Devanand DP, Pelton GH, Cunqueiro K, Sackeim HA, Marder K. A 6-month, randomized, double-blind, placebo-controlled pilot **discontinuation trial following response to haloperidol** treatment of psychosis and agitation In Alzheimer's disease. Int J Geriatr Psychiatry. 2011 Sep;26(9):937-43.

Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of **quetiapine** in critically ill patients with **delirium**: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2010 Feb;38(2):419-27. In ICU patients with delirium, the addition of scheduled quetiapine to as-needed haloperidol results in faster resolution of delirium, decreased time spent in delirium, and less agitation. This study was too small to detect significant differences in adverse events, if they exist. (LOE = 1b)

Devore EE, Grodstein F, van Rooij FJ, et al. **Dietary antioxidants** and long-term risk of dementia. Arch Neurol. 2010 Jul;67(7):819-25.

Devore EE, Kang JH, Breteler MM, Grodstein F. **Dietary intakes of berries and flavonoids** in relation to cognitive decline. Ann Neurol. 2012 Apr 26.

Dickerson BC, Stoub TR, Shah RC, et al. **Alzheimer-signature MRI biomarker** predicts AD dementia in cognitively normal adults. Neurology. 2011 Apr 19;76(16):1395-402.

Dickerson BC, Wolk DA. **MRI cortical thickness biomarker** predicts AD-like CSF and cognitive decline in normal adults. Neurology 2012;78:84 –90.

Dichgans M, Markus HS, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. Lancet Neurol. 2008 Feb 22; [Epub ahead of print] Donepezil had no effect on the primary endpoint, the V-ADAS-cog score in CADASIL patients with cognitive impairment. Improvements were noted on several measures of executive function, but the clinical relevance of these findings is not clear.

Dhillon S. Spotlight on **rivastigmine transdermal patch**: in dementia of the Alzheimer's type. Drugs Aging. 2011 Nov 1;28(11):927-30.

Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of ginkgo biloba for the prevention of cognitive decline. Neurology. 2008 Feb 27; [Epub ahead of print] n=118 42 month In unadjusted analyses, **ginkgo biloba** extract (GBE) neither altered the risk of progression from normal to Clinical Dementia Rating (CDR) = 0.5, nor protected against a decline in memory function. Secondary analysis taking into account medication adherence showed a protective effect of GBE on the progression to CDR = 0.5 and memory decline.

Dolder Christian R, Davis Lauren Nicole, McKinsey Jonathan. Use of **Psychostimulants in Patients with Dementia** . Ahead of Print on 1 Oct2010, DOI 10.1345/aph.1P341. Ann Pharmacother ;44:1624-1632.

Dorsey E. Ray; Rabbani Atonu; Gallagher Sarah A.; et al. Impact of **FDA Black Box Advisory** on Antipsychotic Medication Use. Arch Intern Med. 2010;170(1):96-103.

Driver JA, Beiser A, Au R, Kreger BE, Splansky GL, Kurth T, et al. **Inverse association between cancer and Alzheimer's** disease: results from the Framingham Heart Study. BMJ 2012;344:e1442.

Drugs for Cognitive Loss and Dementia. Treatment Guidelines from the Medical Letter. Feb 2007 & revised **Mar 2010**.

Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the **diagnosis of Alzheimer's disease**: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007 Aug;6(8):734-46. These new criteria are centred on a clinical core of early and significant episodic memory impairment. They stipulate that there must also be at least one or more abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of amyloid beta or tau proteins.

Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, et al. Revising the **definition of Alzheimer's disease**: a new lexicon. Lancet Neurol. 2010 Oct 8.

Ehlenbach William J.; Hough Catherine L.; Crane Paul K.; et al. Association Between Acute Care and Critical Illness **Hospitalization and Cognitive Function** in Older Adults. JAMA. 2010;303(8):763-770.

Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of **delirium** in critically ill patients: validation of the confusion assessment method for the Intensive Care Unit (**CAM-ICU**). Crit Care Med 2001;29:1370-9.

Emre M, Tsolaki M, Bonuccelli Uet al; 11018 Study Investigators. **Memantine** for patients with **Parkinson's disease dementia** or dementia with **Lewy bodies**: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010 Oct;9(10):969-77.

Espeland MA, Tindle HA, Bushnell CA, et al. for the Women's Health Initiative Memory Study. Brain Volumes, Cognitive Impairment, and **Conjugated Equine Estrogens**. J Gerontol A Biol Sci Med Sci. 2009 Sep 3.

Etgen Thorleif; Sander Dirk; Huntgeburth Ulrich; et al. **Physical Activity** and Incident Cognitive Impairment in Elderly Persons: The INVADE Study. Arch Intern Med. 2010;170(2):186-193.

Farlow M, Salloway S, Tariot P, et al. Effectiveness & tolerability of **high-dose (23 mg/d)** versus standard-dose (10 mg/d) **donepezil** in moderate to severe Alzheimer's disease: 24-week, randomized, double-blind study. Clin Ther. 2010Jul;32(7):1234-1251.

FDA Aug/11 Antidepressant **citalopram** (*Celexa*, Forest Laboratories) should not be used in doses higher than 40 mg per day because of concerns that it can cause potentially fatal changes in heart rhythm (eg. ↑ QT)

FDA Apr/12 approved **Amyvid (florbetapir F 18 injection)** which binds to beta-amyloid plaques in patients' brains, an active diagnostic for detection of the tell-tale sign of Alzheimer's disease.

Féart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, Scarmeas N, Barberger-Gateau P. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA. 2009 Aug 12;302(6):638-48.

Feldman HH, Jacova C, Robillard A, et al. **Diagnosis and treatment of dementia**: 2. Diagnosis. CMAJ. 2008 Mar 25;178(7):825-36.

Ferrara N, Corbi G, Capuano A, Filippelli A, Rossi F. **Memantine-induced hepatitis** with cholestasis in a very elderly patient. Ann Intern Med. 2008 Apr 15;148(8):631-2.

Ferri CP, Prince M, Brayne C, Brodaty H, et al.; Alzheimer's Disease International. **Global prevalence of dementia**: a Delphi consensus study. Lancet. 2006 Dec 17;366(9503):2112-7.

Fialova D, et al. R; AdHOC Project Research Group. Potentially **inappropriate medication** use among elderly home care patients in Europe. JAMA. 2005 Mar 16;293(11):1348-58.

Fillit HM, Doody RS, Binaso K, et al. Recommendations for **best practices** in the treatment of Alzheimer's disease in managed care. Am J Geriatr Pharmacother. 2006;4 Suppl A:S9-S24; quiz S25-S28.

Fleisher AS, Chen K, Liu X, et al. Using Positron Emission Tomography and **Florbetapir F 18** to Image Cortical Amyloid in Patients With Mild Cognitive Impairment or Dementia Due to Alzheimer Disease. Arch Neurol. 2011 Jul 11.

TOP

Fleisher AS, Truran D, Mai JT, et al. For the Alzheimer's Disease Cooperative Study. Chronic **divalproex** sodium use and brain atrophy in Alzheimer disease. Neurology. 2011 Sep 27;77(13):1263-1271.

Fong TG et al. **Delirium accelerates** cognitive decline in Alzheimer disease. Neurology 2009 May 5; 72:1570.

Fong Tamara G.; Jones Richard N.; Rudolph James L.; et al. Development and Validation of a Brief **Cognitive Assessment Tool**: **The Sweet 16**. Arch Intern Med. 2010;0(2010):archinternmed.2010.423. http://hospitalelderlifeprogram.org

Forlenza OV, Diniz BS, Radanovic M, et al. Disease-modifying properties of long-term **lithium treatment for amnestic mild cognitive impairment**: randomised controlled trial. Br J Psychiatry. 2011 May;198:351-6.

Fossey J, et al. Effect of enhanced **psychosocial care** on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. BMJ. 2006 Apr 1;332(7544):756-61. Epub 2006 Mar 16. Erratum in: BMJ. 2006 Apr 1;332(7544):61.

Fox C, Richardson K, Maidment ID, et al. **Anticholinergic Medication Use** and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study. J Am Geriatr Soc. 2011 Jun 24

Frank Christopher, Feldman Sid, Schulz Mary. Resources for people with dementia: The Alzheimer Society and beyond (**First Link**). Can Fam Physician December 2011 57: 1387-1391.

Frisoni GB. **PET and (18)F ligands** in the diagnosis of Alzheimer's disease. Lancet Neurol. 2011 Apr 8.

Fuchs A, Wiese B, Altiner A, Wollny A, Pentzek M. Cued recall and other cognitive tasks to facilitate dementia recognition in primary care (**VAT-Visual Association Test**). J Am Geriatr Soc. 2012 Jan;60(1):130-5.

Galasko DR, Peskind E, Clark CM, et al. for the Alzheimer's Disease Cooperative Study. **Antioxidants** for Alzheimer Disease: A Randomized Clinical Trial With Cerebrospinal Fluid Biomarker Measures. Arch Neurol. 2012 Mar 19.

Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC. The **AD8**: a brief informant **interview to detect dementia**. Neurology. 2005 Aug 23;65(4):559-64.

Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of **mild cognitive impairment** by definition: a population study. Arch Neurol. 2011 Jun;68(6):761-7.

Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. CMAJ. 2005 Jun 21;172(13):1703-11.

Gauthier S, et al. International Psychogeriatric Association Expert Conference on mild cognitive impairment. **Mild cognitive impairment**. Lancet. 2006 Apr 15;367(9518):1262-70.

Gauthier S, Herrmann N, Ferreri F, Agbokou C. Use of **memantine** to treat Alzheimer's disease. CMAJ. 2006 Aug 29;175(5):501-2.

Gauthier S, et al. EXTEND Investigators. A large, naturalistic, **community-based** study of **rivastigmine** in mild-to-moderate AD: the **EXTEND** Study. Curr Med Res Opin. 2006 Nov;22(11):2251-65.

Gill Sudeep S; et al. **Syncope** and Its Consequences in Patients With Dementia Receiving Cholinesterase Inhibitors: A Population-Based Cohort Study Arch Intern Med. 2009;169(9):867-873.

Gitlin Laura N.; Winter Laraine; Dennis Marie P.; et al. A **Biobehavioral Home-Based Intervention** and the Well-being of Patients With Dementia and Their Caregivers: The **COPE** Randomized Trial. JAMA. 2010;304(9):983-991.

Givens Jane L.; Jones Richard N.; Shaffer Michele L.; et al. Survival and Comfort After **Treatment of Pneumonia** in Advanced Dementia. Arch Intern Med. 2010;170(13):1102-1107.

Godin O, Tzourio C, Maillard P, et al. **Antihypertensive Treatment** and Change in Blood Pressure Are Associated With the Progression of White Matter Lesion Volumes: The Three-City (3C)-Dijon Magnetic Resonance Imaging Study. Circulation. 2011 Jan 25;123(3):266-73.

Goldfeld Keith S.; Stevenson David G.; Hamel Mary Beth; et al. **Medicare Expenditures Among Nursing Home Residents** With Advanced Dementia. *Arch Intern Med*. 2011;171(9):824-830.

Gorelick PB, Scuteri A, Black SE et al. **Vascular contributions** to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association-AHA/American Stroke Association-ASA.Stroke.2011Sep;42(9):2672-713.

Gozalo P, Teno JM, Mitchell SL, et al. **End-of-life transitions** among nursing home residents with cognitive issues. N Engl J Med. 2011 Sep 29;365(13):1212-21.

Graff MJ, Adang EM, Vernooij-Dassen MJ, et al. Community **occupational therapy** for older patients with dementia and their care givers: cost effectiveness study. BMJ. 2008 Jan 19;336(7636):134-8. Epub 2008 Jan 2. Community occupational therapy intervention for patients with dementia and their care givers is successful and cost effective, especially in terms of informal care giving.

Green RC, Roberts JS, Cupples LA, et al.; REVEAL Study Group. Disclosure of **APOE genotype** for risk of Alzheimer's disease. N Engl J Med. 2009 Jul 16;361(3):245-54.

Green RC.; Schneider LS.; et al. the Tarenflurbil Phase 3 Study Group. Effect of **Tarenflurbil** on Cognitive Decline and Activities of Daily Living in Patients With Mild Alzheimer Disease: A Randomized Controlled Trial. JAMA. 2009;302(23):2557-2564.

Growdon JH, Hyman BT. **Plasma {beta}-Amyloid** Linked to Cognitive Decline. Arch Neurol. 2011 Jun;68(6):799-801.

Gu Y, Schupf N, Cosentino SA, et al. **Nutrient intake** (ω-3 PUFA) and plasma β-amyloid. Neurology. 2012 Jun 5;78(23):1832-40.

Gupta VB, Laws SM, Villemagne VL,et al; For the AIBL Research Group. Plasma **apolipoprotein E** and Alzheimer disease risk: The **AIBL** study of aging. Neurology. 2011 Mar 22;76(12):1091-1098.

Haan M, Espeland MA, Klein BE, et al. Cognitive function and **retinal** and ischemic **brain** changes: the Women's Health Initiative (WHI). Neurology 2012;78:942–949.

Haddad P. **Weight** change with atypical antipsychotics in the treatment of schizophrenia. J Psychopharmacol. 2005 Nov;19(6 Suppl):16-27.

Han L, Agostini JV, Allore HG. **Cumulative anticholinergic exposure** is associated with poor memory and executive function in older men. J Am Geriatr Soc. 2008 Dec;56(12):2203-10. Cumulative anticholinergic exposure across multiple medications over 1 year may negatively affect verbal memory and executive function in older men. Prescription of drugs with anticholinergic effects in older persons deserves continued attention to avoid deleterious adverse effects.

Hanney M, Prasher V, Williams N, et al, on behalf of the **MEADOWS** trial researchers. **Memantine** for dementia in adults older than 40 years with **Down's syndrome** (MEADOWS): randomised, double-blind, placebo-controlled trial. Lancet 2012; Jan 10.

Hanson LC, Ersek M, Gilliam R, et al. **Oral feeding** options for people with dementia: a systematic review. J Am Geriatr Soc. 2011 Mar;59(3):463-72. doi: 10.1111/j.1532-5415.2011.03320.x.

Hashimoto K. Can **Minocycline Prevent** the Onset of Alzheimer's Disease? Annals of Neurology. 2011; 1-4 [online].

Hayden KM, Norton MC, Darcey D, et al. Cache County Study Investigators. Occupational exposure to **pesticides** increases the risk of incident AD: the Cache County study. Neurology. 2010 May 11;74(19):1524-30.

Head D, Bugg JM, Goate AM, et al. **Exercise** Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition. Arch Neurol. 2012 Jan 9.

Health Canada May/10: Novartis, in consultation with Health Canada, is informing healthcare providers and consumers that serious adverse events including **death** were associated with medication errors/misuse of the **Exelon Patch**.

Heister D, Brewer JB, Magda S, et al; For the Alzheimer's Disease Neuroimaging Initiative. **Predicting MCI** outcome with clinically available **MRI and CSF biomarkers**. Neurology. 2011 Oct 25;77(17):1619-1628.

Helmer C et al. **Chronic kidney disease**, cognitive decline, and incident dementia:The 3C Study. Neurology. 2011 Dec 6;77(23):2043-51.

Hernandez RK, Farwell W, Cantor MD, Lawler EV. Cholinesterase Inhibitors and Incidence of **Bradycardia** in Patients with Dementia in the Veterans Affairs New England Healthcare System. J Am Geriatr Soc. 2009 Sep 28.

Henderson VW, St John JA, Hodis HN, et al; For the **WISH** Research Group. Long-term **soy isoflavone** supplementation and cognition in women: A randomized, controlled trial. Neurology. 2012 Jun5;78(23):1841-1848.

Herrmann N, Rapoport MJ, Sambrook R, et al. Canadian Outcomes Study in Dementia (COSID) Investigators. Predictors of **driving cessation** in mild-to-moderate dementia. CMAJ. 2006 Sep 12;175(6):591-5.

Herrmann N, Lanctôt KL. Pharmacologic management of **neuropsychiatric symptoms of Alzheimer disease**. Can J Psychiatry. 2007 Oct;52(10):630-46.

Herrmann N Md, Gauthier S Md. Diagnosis and treatment of dementia: 6. Management of **severe Alzheimer disease**. CMAJ. 2008 Dec 2;179(12):1279-1287.

Herrmann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctôt KL. **Serotonergic Function** (citalopram) and Treatment of Behavioral and Psychological Symptoms of **Frontotemporal Dementia**. Am J Geriatr Psychiatry. 2011 Aug 27.

Herrmann N, Black SE, Li A, Lanctôt KL. **Discontinuing cholinesterase inhibitors**: results of a survey of Canadian dementia experts. Int Psychogeriatr 2011;23:539-45.

Herholz Karl, Ebmeier Klaus. Clinical **amyloid imaging** in Alzheimer's disease. The Lancet Neurology 1 July 2011 (Volume 10 Issue 7 Pages 667-670 DOI: 10.1016/S1474-4422(11)70123-5)

Hindin SB, Zelinski EM. **Extended practice and aerobic exercise interventions** benefit untrained cognitive outcomes in older adults: a meta-analysis. J Am Geriatr Soc. 2012 Jan;60(1):136-41.

Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Thorpe L et al. Diagnosis and treatment of dementia: 4. Approach to management of **mild to moderate dementia**. CMAJ. 2008 Oct 7;179(8):787-93.

Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Man-Son-Hing M, Lanctôt K, Morgan D, Thorpe L. Diagnosis and treatment of dementia: 5. **Nonpharmacologic and pharmacologic** therapy for **mild to moderate dementia**. CMAJ. 2008 Nov 4;179(10):1019-26.

Holmes C, Cunningham C, Zotova E, et al. Proinflammatory **cytokines**, sickness behavior, and Alzheimer disease. Neurology. 2011 Jul 19;77(3):212-8.

Holroyd-Leduc JM, Khandwala F, Sink KM. How can **delirium** best be prevented and managed in older patients in hospital? CMAJ. 2009 Aug 17. [Epub ahead of print]

Holmes C, Wilkinson D, Dean C, et al. The efficacy of **donepezil** in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology 2004;63:214-9.

Holsinger T, Deveau J, Boustani M, Williams JW Jr. **Does this patient have dementia**? JAMA. 2007 Jun 6;297(21):2391-404.

Howard RJ, et al. **Donepezil** for the treatment of agitation in Alzheimer`s disease. (**CALM-AD**) N Engl J Med. 2007 Oct 4;357(14):1382-92. In this 12-week trial, donepezil was not more effective than placebo in treating **agitation** in patients with Alzheimer's disease.

Howard R et al. **Donepezil and memantine** for moderate-to-severe Alzheimer's disease. (**DOMINO**) *N Engl J Med* 2012 Mar 8; 366:893.

Husebo BS, Ballard C, Aarsland D. **Pain treatment of agitation** in patients with dementia: a systematic review. Int J Geriatr Psychiatry. 2011 Oct;26(10):1012-8. doi: 10.1002/gps.2649.

Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of **treating pain** to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. BMJ 2011;343;d4065.

Huybrechts KF, Rothman KJ, Silliman RA., et al. **Risk of death and hospital admission** for major medical events after initiation of psychotropic medications in older adults admitted to nursing homes. CMAJ 2011 0: cmaj.101406

TOP

Hyman BT. **Amyloid**-Dependent and Amyloid-Independent Stages of Alzheimer Disease. Arch Neurol. 2011 Apr 11.
Iliffe S, Pealing L. **Subjective memory problems**. BMJ. 2010 Mar 19;340:c1425.
Inouye SK. **Delirium in older persons**. N Engl J Med. 2006 Mar 16;354(11):1157-65.
Inzitari M, Pozzi C, Ferrucci L, Chiarantini D, Rinaldi LA, Baccini M, Pini R, Masotti G, Marchionni N, Di Bari M. **Subtle neurological abnormalities** as risk factors for cognitive and functional decline, cerebrovascular events, and mortality in older community-dwelling adults. Arch Intern Med. 2008 Jun 23;168(12):1270-6. In this sample of older community-dwelling persons without overt neurological diseases, multiple SNAs were associated with cognitive and functional decline and independently predicted mortality and CVEs.
Irwin DJ, McMillan CT, Toledo JB, et al. Comparison of **Cerebrospinal Fluid Levels of Tau and Aβ 1-42** in Alzheimer Disease and Frontotemporal Degeneration Using 2 Analytical Platforms. Arch Neurol. 2012 Apr 9.
Isik AT, Babacan Yildiz G, Bozoglu E, Yay A, Aydemir E. **Cardiac safety of donepezil** in elderly patients with Alzheimer disease. Intern Med. 2012;51(6):575-8.
Iverson DJ, Gronseth GS, Reger MA, et al. Practice parameter update: evaluation and management of **driving risk** in dementia: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010 Apr 20;74(16):1316-24. http://www.neurology.org/cgi/rapidpdf/WNL.0b013e3181da3b0fv1.pdf
Iwashyna Theodore J.; Ely E. Wesley; Smith Dylan M.; et al. Long-term Cognitive Impairment and Functional Disability Among Survivors of **Severe Sepsis**. *JAMA*. 2010;304(16):1787-1794.
Irizarry M, Jin S; He F et al. Incidence of **New-Onset Seizures** in Mild to Moderate Alzheimer Disease Arch Neurol. 2012;69(3):368-372.
Jack CR Jr, Vemuri P, Wiste HJ, et al. for the Alzheimer's Disease Neuroimaging Initiative. Evidence for Ordering of **Alzheimer Disease Biomarkers**. Arch Neurol. 2011 Aug 8.
Jagust WJ. **Amyloid Imaging**: Liberal or Conservative? Let the Data Decide. Arch Neurol. 2011 Jul 11.
Jaturapatporn D, Isaac MG, McCleery J, et al. **Aspirin, steroidal and non-steroidal anti-inflammatory** drugs for the treatment of Alzheimer`s disease. Cochrane Database Syst Rev. 2012 Feb 15;2:CD006378. Based on the studies carried out so far, the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven. Therefore, these drugs cannot be recommended for the treatment of AD.
Jokinen H, Gouw AA, Madureira S, et al. On behalf of the LADIS Study Group. Incident **lacunes** influence cognitive decline: The LADIS study. Neurology. 2011 May 31;76(22):1872-1878.
Kales HC, Zivin K, Kim HM, Valenstein M, Chiang C, Ignacio R, Ganoczy D, Cunningham F, Schneider LS, Blow FC. Trends in **antipsychotic use in dementia** 1999-2007. Arch Gen Psychiatry. 2011 Feb;68(2):190-7.
Kales HC , Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C , Cunningham F, Schneider LS, Blow FC: Risk of **mortality among individual antipsychotics** in patients with dementia. Am J Psychiatry 2011; 168:71–79.
Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, Eikelenboom P, van Gool WA. **Haloperidol** prophylaxis for elderly hip-surgery patients at risk for **delirium**: a randomized placebo-controlled study. J Am Geriatr Soc. 2005 Oct;53(10):1658-66. (InfoPOEMs: Low-dose haloperidol was no more effective than placebo in preventing delirium in elderly patients undergoing hip surgery. However, when delirium occurred, it was milder and shorter in patients receiving haloperidol. Furthermore, haloperidol shortened the hospital length of stay among patients who became delirious. (LOE = 1b-))
Kamble P, Chen H, Sherer JT, et al. Use of **antipsychotics among elderly nursing home residents** with dementia in US: an analysis of National Survey Data. Drugs Aging.2009;26(6):483-92.doi:10.2165/00002512-200926060-00005.
Kantarci K, Lowe V, Przybelski SA, et al. **APOE modifies** the association between **AB load** and cognition in cognitively normal older adults. Neurology 2012;78:232–240.
Kapusta Peter, Regier Loren, Bareham Julia, et al. **RxFiles**: **Behaviour management in dementia**. Can Fam Physician December 2011 57: 1420-1422.
Kennedy J, Deberdt W, Siegal A, et al. **Olanzapine does not enhance cognition** in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. Int J Geriatr Psychiatry. 2005 Nov;20(11):1020-7.
Khachaturian et al. **Antihypertensive** Medication Use and Incident Alzheimer Disease: The Cache County Study. Arch Neurol. 2006 Mar 13; [Epub ahead of print]
Kim DH, Brown RT, Ding EL, et al. Dementia medications and risk of falls, **syncope**, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc. 2011 Jun;59(6):1019-31.(syncope for ChEIs)
Kirby J, et al. A systematic review of the clinical and cost-effectiveness of **memantine** in patients with moderately severe to severe Alzheimer's disease. Drugs Aging. 2006;23(3):227-40.
Klassen BT, Hentz JG, Shill HA, et al. **Quantitative EEG** as a predictive biomarker for Parkinson disease dementia. Neurology. 2011 Jul 12;77(2):118-24.
Knopman DS, Penman AD, Catellier DJ, et al. **Vascular risk factors** and longitudinal changes on brain MRI: The ARIC study. Neurology. 2011 May 31;76(22):1879-85.
Knopman DS, Jack CR Jr, Wiste HJ, et al. Short-term clinical outcomes for stages of **NIA-AA preclinical Alzheimer disease**. Neurology. 2012 May 15;78(20):1576-82.
Koivunen J, Scheinin N, Virta JR, et al. **Amyloid PET imaging** in patients with mild cognitive impairment: A 2-year follow-up study. Neurology. 2011 Mar 22;76(12):1085-90.
Kolanowski A, Litaker M, Buettner L, et al. A randomized clinical trial of **theory-based activities** for the behavioral symptoms of dementia in nursing home residents. J Am Geriatr Soc. 2011 Jun;59(6):1032-41. doi: 10.1111/j.1532-5415.2011.03449.x.
Köpke S, Mühlhauser I, Gerlach A, et al. Effect of a guideline-based **multicomponent intervention on use of physical restraints** in nursing homes: a randomized controlled trial. JAMA. 2012 May 23;307(20):2177-84.
Koyama A, Okereke OI, Yang T, et al. **Plasma Amyloid-β** as a Predictor of Dementia and Cognitive Decline: A Systematic Review and Meta-analysis. Arch Neurol. 2012 Mar 26. Krupp LB, Christodoulou C, Melville P, et al. Multicenter randomized clinical trial of **donepezil** for memory impairment in multiple sclerosis. Neurology. 2011 Apr 26;76(17):1500-7. (not work)
Kwok CS, Loke YK, Hale R, et al. **Atrial fibrillation** and incidence of dementia: A systematic review and meta-analysis. Neurology 2011; 76:914-922.
Landau Susan M.; Marks Shawn M.; Mormino Elizabeth C.; et al. Association of **Lifetime Cognitive Engagement** and Low {beta}-Amyloid Deposition. Arch Neurol. 2012
Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. **Exercise** is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006 Jan 17;144(2):73-81.
Lautenschlager NT, et al. Effect of **physical activity** on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008 Sep 3;300(9):1027-37. In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.
Lee JH, Kim SH, Kim GH, et al. Identification of pure **subcortical vascular dementia** using 11C-Pittsburgh compound B. Neurology. 2011 Jul 5;77(1):18-25.
Leonard R, Tinetti ME, Allore HG, Drickamer MA. Potentially **modifiable resident characteristics** that are associated with physical or verbal aggression among nursing home residents with dementia. Arch Intern Med. 2006 Jun 26;166(12):1295-300. If the associations we have estimated are causal, then treatment of depression, delusions, hallucinations, and constipation may reduce physical aggression among nursing home residents.
Llewellyn David J.; Lang Iain A.; Langa Kenneth M.; et al. **Vitamin D** and Risk of Cognitive Decline in Elderly Persons Arch Intern Med. 2010;170(13):1135-1141. Conclusion: Low levels of vitamin D were associated with substantial cognitive decline in the elderly population studied over a 6-year period, which raises important new possibilities for treatment and prevention.
Li NC, Lee A, Whitmer RA, et al. Use of **angiotensin receptor blockers** and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ. 2010 Jan 12;340:b5465. doi:10.1136/bmj.b5465.
Li J, Wang YJ, Zhang M, et al. On behalf of the Chongqing Ageing Study Group. **Vascular risk factors** promote conversion from mild cognitive impairment to Alzheimer disease. Neurology. 2011 Apr 26;76(17):1485-1491.
Lieb Wolfgang; Beiser Alexa S.; Vasan Ramachandran S.; et al. Association of Plasma **Leptin** Levels With Incident Alzheimer Disease and MRI Measures of Brain Aging. JAMA. 2009;302(23):2565-2572.
Lim WS, Gammack JK, Van Niekerk J, Dangour AD. **Omega 3 fatty acid** for the prevention of dementia. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005379.
Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. **Hearing loss** and incident dementia. Arch Neurol. 2011 Feb;68(2):214-20.
Liperoti R, Pedone C, Lapane KL, et al. **Venous Thromboembolism** Among Elderly Patients Treated With **Atypical** and Conventional Antipsychotic Agents. Arch Intern Med. 2005 Dec 12;165(22):2677-2682.
Liu-Ambrose Teresa; Nagamatsu Lindsay S.; Graf Peter; et al. **Resistance Training** and Executive Functions: A 12-Month Randomized Controlled Trial. Arch Intern Med. 2010;170(2):170-178.
Livingston G, et al. Old Age Task Force of the World Federation of Biological Psychiatry. **Systematic review of psychological approaches** to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry. 2005 Nov;162(11):1996-2021.
Lo RY, Hubbard AE, Shaw LM, et al. for the Alzheimer's Disease **Neuroimaging Initiative. Longitudinal Change of Biomarkers** in Cognitive Decline. Arch Neurol. 2011 Jun 13.
Lo RY, Jagust WJ, for the Alzheimer's Disease Neuroimaging Initiative. Predicting missing **biomarker data** in a longitudinal study of Alzheimer disease. Neurology 2012;78: 1376–1382.
Lonergan E, Luxenberg J, Areosa Sastre A, Wyller TB. **Benzodiazepines** for delirium. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006379. No adequately controlled trials could be found to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients, and at this time benzodiazepines cannot be recommended for the control of this condition. Because of the scarcity of trials with randomization of patients, placebo control, and adequate concealment of allocation of subjects, it is clear that further research is required to determine the role of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.
Lonergan E, Luxenberg J, Valproate preparations for agitation in dementia. *Cochrane Database of Systematic Reviews* 2009; Issue 3.
Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, Clegg A. The **clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine** for Alzheimer's disease. Health Technol Assess. 2006 Jan;10(1):1-176.
Loy C, Schneider L. **Galantamine** for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2006; 1: CD001747.
Lu D, Song H, Hao Z, Wu T, McCleery J. **Naftidrofuryl** for dementia. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD002955. DOI: 10.1002/14651858.CD002955.pub4. Oral administration of naftidrofuryl is well-tolerated by patients with dementia.The low-quality evidence shows that, by use of naftidrofuryl, people with dementia may benefit on performance, behaviour, cognition, and mood. However, the benefit on global impression is inconsistent and unconvincing.
Lu PH, Masterman DA, Mulnard R, et al. Effects of Testosterone on Cognition and Mood in Male Patients With Mild **Alzheimer Disease** and Healthy Elderly Men. Arch Neurol. 2005 Dec 12; [Epub ahead of print]

TOP

Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL; Alzheimer's Disease Cooperative Study Group. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology. 2009 Jun 16;72(24):2115-21.

Lyketsos CG, et al.; Task Force of **American Association for Geriatric Psychiatry**. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from **Alzheimer** disease. Am J Geriatr Psychiatry. 2006 Jul;14(7):561-72.

Machulda MM, Jones DT, Vemuri P, et al. Effect of **APOE {varepsilon}4 Status** on Intrinsic Network Connectivity in Cognitively Normal Elderly Subjects. Arch Neurol. 2011 May 9.

Mackin P, Thomas SH. **Atypical antipsychotic drugs**. BMJ. 2011 Mar 4;342:d1126. doi: 10.1136/bmj.d1126.

Maher AR et al. Efficacy and comparative effectiveness of **atypical antipsychotic medications for off-label uses in adults**. JAMA 2011 Sep 28; 306:1359.

Malouf R, Grimley Evans J. **Folic acid with or without vitamin B12** for the prevention & treatment of healthy elderly and demented people. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004514. The small number of studies which have been done provide no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvement in the response of people with Alzheimer`s disease to cholinesterase inhibitors. In another, long-term use appeared to improve the cognitive function of healthy older people with high homocysteine levels. More studies are needed on this important issue.

Mangialasche Francesca, Solomon Alina, Winblad Bengt et al; **Alzheimer's disease: clinical trials and drug development**, The Lancet Neurology, Volume 9, Issue 7, July 2010

Manly JJ, Schupf N, Stern Y, et al. **Telephone-based identification** of mild cognitive impairment and dementia in a multicultural cohort. Arch Neurol. 2011 May;68(5):607-14.

Marcantonio Edward R. In the Clinic: **Delirium**. Ann Intern Med June 7, 2011 154:ITC6-1; doi:10.1059/0003-4819-154-11-201106070-01006.

Marsh L. Treatment of **Lewy-body dementias and psychopathology**. Lancet Neurol. 2010 Oct;9(10):943-5. Epub 2010 Aug 20. PubMed PMID: 20729149.

Mattsson N, Rosén E, Hansson O, et al. Age and diagnostic performance of Alzheimer disease **CSF biomarkers**. Neurology. 2012 Feb 1.

Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. **Cognition-based interventions** for healthy older people and people with mild cognitive impairment. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD006220. DOI: 10.1002/14651858.CD006220.pub2. There is evidence that cognitive interventions do lead to performance gains but none of the effects observed could be attributable specifically to cognitive training, as the improvements observed did not exceed the improvement in active control conditions. This does not mean that longer, more intense or different interventions might not be effective, but that those which have been reported thus far have only limited effect. We therefore suggest more standardized study protocols in order to maximize comparability of studies and to maximize the possibility of data pooling - also in other cognitive domains than memory.

Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with **atrial fibrillation**: results of the **ONTARGET** and **TRANSCEND** studies. CMAJ 2012

Matsuzaki T, Sasaki K, Tanizaki Y, et al. **Insulin resistance** is associated with the pathology of Alzheimer disease. The Hisayama Study. Neurology. 2010 Aug 25.

Matsuzaki T, Sasaki K, Hata J, et al. Association of Alzheimer disease pathology with **abnormal lipid metabolism**: The Hisayama Study. Neurology. 2011 Sep 13;77(11):1068-75.

Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, ET AL. **CSF biomarkers** and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA. 2009 Jul 22;302(4):385-93.

Mayeux R. Clinical practice. **Early Alzheimer's disease**. N Engl J Med. 2010 Jun 10;362(23):2194-201.

Mazza M, Capuano A, Bria P, Mazza S. **Ginkgo biloba and donepezil**: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. Eur J Neurol. 2006 Sep;13(9):981-5.

McCarten JR, Anderson P, Kuskowski MA et al. **Screening for cognitive impairment** in an elderly veteran population: acceptability and results using different versions of the Mini-Cog. J Am Geriatr Soc. 2011 Feb;59(2):309-13.

McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment & dementia in patients without apparent prior cerebrovascular disease. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD004034. There was no convincing evidence from the trials identified that blood pressure lowering prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease. There were significant problems identified with analysing the data, however, due to the number of patients lost to follow-up and the number of placebo patients given active treatment. This introduced bias. More robust results may be obtained by analysing one year data to reduce differential drop-out or by conducting a meta- analysis using individual patient data.

McGuinness B, O`Hare J, Craig D, et al. Statins for the treatment of dementia. Cochrane Database Syst Rev. 2010 Aug 4;8:CD007514. There is insufficient evidence to recommend statins for the treatment of dementia. Analysis from the studies available, including one large RCT, indicate statins have no benefit on the outcome measures ADAS-Cog or MMSE. We need to await full results from CLASP 2008 before we can be certain.

McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining **inappropriate** practices in prescribing for elderly people: a national consensus panel. CMAJ. 1997 Feb 1;156(3):385-91.

McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of **homocysteine** lowering and cognitive performance. N Engl J Med. 2006 Jun 29;354(26):2764-72.

McShane R, Areosa Sastre A, Minakaran N. **Memantine** for dementia. Cochrane Database Syst Rev 2006; 2: CD003154.

Medical Letter. Treatment Guidelines. **Drugs for Cognitive Loss and Dementia**. Mar 2010.

Meeuwsen EJ, Melis RJ, Van Der Aa GC, et al. Effectiveness of dementia follow-up care by **memory clinics** or general practitioners: randomised controlled trial. BMJ. 2012 May 15;344:e3086.

Middleton LE, Manini TM, Simonsick EM, et al. **Activity energy expenditure** and incident cognitive impairment in older adults. (**Health ABC**) Arch Intern Med. 2011 Jul 25;171(14):1251-7.

Middleton LE, Grinberg LT, Miller B, et al. **Neuropathologic features** associated with Alzheimer disease diagnosis: Age matters. Neurology. 2011 Nov 8;77(19):1737-44.

Mielke MM, Zandi PP, Shao H, et al. The 32-year relationship between **cholesterol and dementia** from midlife to late life. Neurology. 2010 Nov 10.

Mintzer JE, Tune LE, Breder CD, et al. **Aripiprazole** for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. Am J Geriatr Psychiatry. 2007 Nov;15(11):918-31.

Mitchell SL. A **93-year-old man with advanced dementia and eating problems**. JAMA. 2007 Dec 5;298(21):2527-36. Epub 2007 Nov 6.

Mitchell SL et al. The clinical course of **advanced dementia**. N Engl J Med 2009 Oct 15; 361:1529.

Mitchell AJ, Shiri-Feshki M. Rate of **progression** of **mild cognitive impairment to dementia**--meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009 Apr;119(4):252-65.

Mitchell SL, Black BS, Ersek M, et al. Advanced Dementia: **State of the Art and Priorities** for the Next Decade. Ann Intern Med. 2012 Jan 3;156(1_Part_1):45-51.

Mintzer J, et al. **Risperidone** in the treatment of psychosis of Alzheimer disease: results from a prospective clinical trial. Am J Geriatr Psychiatry. 2006 Mar;14(3):280-91. (Negative trial)

Mittelman MS, Haley WE, Clay OJ, Roth DL. Improving **caregiver** well-being delays nursing home placement of patients with Alzheimer disease. Neurology. 2006 Nov 14;67(9):1592-9.

Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. **Estimating prognosis** for nursing home residents with advanced dementia. JAMA. 2004 Jun 9;291(22):2734-40.

Mitchell Susan L.; Miller Susan C.; Teno Joan M.; et al. **Prediction of 6-Month Survival** of Nursing Home Residents With Advanced Dementia Using ADEPT vs Hospice Eligibility Guidelines. *JAMA*. 2010;304(17):1929-1935.

Moghekar A, Goh J, Li M, et al. **Cerebrospinal fluid aβ and tau** level fluctuation in an older clinical cohort. Arch Neurol. 2012 Feb;69(2):246-50.

Molnar, Frank J., Simpson, Christopher S. Approach to assessing **fitness to drive** in patients with cardiac and cognitive conditions. Can Fam Physician 2010 56: 1123-1129. (See also www.mocatest.org)

Moncada LV. Management of **falls in older persons**: a prescription for prevention. Am Fam Physician. 2011 Dec 1;84(11):1267-76.

Moniz Cook ED, Swift K, et al. **Functional analysis-based interventions** for challenging behaviour in dementia. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD006929. DOI:10.1002/14651858.CD006929.pub2. The delivery of FA has been incorporated within wide ranging multi-component programmes and study designs have varied according to setting - i.e. family care, care homes and hospital, with surprisingly few studies located in care homes. Our findings suggest potential beneficial effects of multi-component interventions, which utilise FA. Whilst functional analysis for challenging behaviour in dementia care shows promise, it is too early to draw conclusions about its efficacy.

Montlahuc C, Soumaré A, Dufouil C, et al. **Self-rated health and risk of incident dementia**: a community-based elderly cohort, the 3C Study. Neurology 2011;77:1457–1464

Mori E, Ikeda M, et al. **Donepezil for dementia with Lewy bodies**: A randomized, placebo-controlled trial. Annals of Neurology 2012.

Morrens M, Wezenberg E, Verkes RJ, Hulstijn W, Ruigt GS, Sabbe BG. Psychomotor and memory effects of haloperidol, olanzapine, and paroxetine in healthy subjects after short-term administration. J Clin Psychopharmacol. 2007 Feb;27(1):15-21. Short-term administration of olanzapine, and not of haloperidol, impedes several aspects of psychomotor function and verbal memory in healthy volunteers.

Morris MC, et al. Associations of **vegetable and fruit consumption** with age-related cognitive change. Neurology. 2006 Oct 24;67(8):1370-6.

Mukundan A, Faulkner G, Cohn T, Remington G. **Antipsychotic switching** for people with schizophrenia who have neuroleptic-induced **weight or metabolic problems**. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD006629. DOI: 10.1002/14651858.CD006629.pub2. Evidence from this review suggests that switching antipsychotic medication to one with lesser potential for causing weight gain or metabolic problems could be an effective way to manage these side effects, but the data were weak due to the limited number of trials in this area and small sample sizes. Poor reporting of data also hindered using some trials and outcomes. There was no difference in mental state, global state and other treatment related adverse events between switching to another medication and continuing on the previous one. When the three switching strategies were compared none of them had an advantage over the others in their effects on the primary outcomes considered in this review. Better designed trials with adequate power would provide more convincing evidence for using medication switching as an intervention strategy.

Murray ME, Graff-Radford NR, Ross OA, et al. **Neuropathologically defined subtypes of Alzheimer's disease** with distinct clinical characteristics: a retrospective study. Lancet Neurol. 2011 Sep;10(9):785-96.

Nelson JC, Devanand DP. A Systematic Review and Meta-Analysis of Placebo-Controlled **Antidepressant** Studies in People with **Depression and Dementia** J Am Geriatr Soc. 2011 Apr;59(4):577-85.

Newhouse P, Kellar K, Aisen P, et al. **Nicotine treatment** (transdermal 15mg/day) of mild cognitive impairment: A 6-month double-blind pilot clinical trial. Neurology. 2012 Jan 10;78(2):91-101.

TOP

NHS CKS Dementia Clinical Knowledge Summary 2010 http://www.cks.nhs.uk/dementia/management/scenario_screening_diagnosis_and_assessment/suspecting_dementia/early_recognition_of_dementia_is_a_challenge

NIA: Jack Clifford R., Albert Marilyn S., Knopman David S.. Introduction to the **recommendations** from the National Institute on Aging and the **Alzheimer's** Association workgroup on diagnostic guidelines for Alzheimer's disease. http://www.alz.org/documents_custom/Intro_Diagnostic_Recommendations_Alz_proof.pdf

NIA:McKhann Guy M, Knopman David S., Chertkow Howard. The **diagnosis of dementia due to Alzheimer's disease**: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. http://www.alz.org/documents_custom/Diagnostic_Recommendations_Alz_proof.pdf

NIA: Albert Marilyn S., DeKosky Steven T., Dickson Dennis. The diagnosis of **mild cognitive impairment due to Alzheimer's disease**: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup. http://www.alz.org/documents_custom/Diagnositic_Recommendations_MCI_due_to_Alz_proof.pdf

NIA: Sperling Reisa A., Aisen Paul S., Beckett Laurel A..Toward defining the **preclinical stages of Alzheimer's disease**: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. http://www.alz.org/documents_custom/Diagnostic_Recommendations_Alz_Preclinical.pdf

NIH: National Institutes of Health. State-of-the-Science Conference statement: **preventing Alzheimer's disease and cognitive decline**. April 26-28, 2010. National Institutes of Health http://consensus.nih.gov/2010/alzstatement.htm Accessed Aug 24, 2010.

NIH NATIONAL INSTITUTES OF HEALTH STATE-OF-THE-SCIENCE CONFERENCE STATEMENT NIH State-of-the-Science Conference: **Preventing Alzheimer's Disease** and Cognitive Decline April 26–28, 2010 http://consensus.nih.gov/2010/docs/alz/alz_stmt.pdf

NICE National Institute for Health and Clinical Excellence. **Donepezil, galantamine, rivastigmine (review) and memantine** for the treatment of Alzheimer's disease. London (UK): National Institute for Health and Clinical Excellence; 2006 Nov. 64 p. (Technology appraisal guidance; no. 111). http://www.nice.org.uk/guidance/TA111/guidance/pdf/English

NICE: National Collaborating Centre for Acute and Chronic Conditions. **Delirium: diagnosis, prevention and management**. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Jul. 29 p. (Clinical guideline; no. 103). http://www.nice.org.uk/nicemedia/live/13060/49913/49913.pdf

NICE- Delirium: diagnosis, prevention and management. (Clinical guidline 103.) **2010**. http://www.nice.org.uk/CG103

NICE: Technical Appraisal Guidance 111 Mar 2011. **Donepezil, galantamine, rivastigmine and memantine** for the treatment of Alzheimer's disease http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf **Donepezil, galantamine and rivastigmine** are now recommended as options for managing mild as well as moderate Alzheimer's disease, and **Memantine** is now recommended as an option for managing moderate Alzheimer's disease for people who cannot take acetylcholinesterase (AChE) inhibitors, and as an option for managing severe Alzheimer's disease.

Nourhashemi Fati, Andrieu Sandrine, Gillette-Guyonnet Sophie, et al., on behalf of the **PLASA** Group. Effectiveness of a **specific care plan** in patients with Alzheimer's disease: cluster randomised trial (PLASA study). BMJ 2010;340.

O'Kee e E, Mukhtar O, O'Kee e ST. **Orientation to time** as a guide to the presence and severity of cognitive impairment in older hospital patients. J Neurol Neurosurg Psychiatry. 2011;82:500-4.

Ohara T, Doi Y, Ninomiya T, et al. **Glucose tolerance status** and risk of dementia in the community: The Hisayama Study. Neurology. 2011 Sep 20;77(12):1126-34.

Okonkwo OC, Xu G, Dowling NM, et al. **Family history of Alzheimer** disease predicts hippocampal atrophy in healthy middle-aged adults. Neurology. 2012 May 29;78(22):1769-76.

Oldenbeuving AW, de Kort PL, Jansen BP, et al. **Delirium in the acute phase after stroke**: Incidence, risk factors, and outcome. Neurology. 2011 Mar 15;76(11):993-9.

O'Mahony Rachel, Murthy Lakshmi, Akunne A, et al. , for the Guideline Development Group. Synopsis of the National Institute for Health (**NIH**) and Clinical Excellence Guideline for **Prevention of Delirium**. Ann Intern Med June 7, 2011 154:746-751.

Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of Amyloid Removal in Patients With Alzheimer Disease Treated With **Gantenerumab**. Arch Neurol. 2011 Oct 10.

Oveisgharan S, Hachinski V. **Hypertension**, executive dysfunction, and progression to dementia: the Canadian study of health and aging. Arch Neurol 2010; 67:187-192.

Pariente A, Fourrier-Réglat A, Ducruet T, Farrington P, et al. Antipsychotic use and **myocardial infarction** in older patients with treated dementia [published online Mar 26, 2012]. Arch Intern Med doi:10.1001/archinternmed.2012.28.

Pariente A, Fourrier-Réglat A, Bazin F, et al. Effect of **treatment gaps** in elderly patients with dementia treated with **cholinesterase inhibitors**. Neurology. 2012 Mar 27;78(13):957-63.

Parker C et al. **Antipsychotic drugs and risk of venous thromboembolism**: nested case-control study. BMJ 2010; 341: c4245

Patterson C, Feightner JW, Garcia A, Hsiung GY, MacKnight C, Sadovnick AD. Diagnosis and treatment of dementia: 1. **Risk assessment and primary prevention** of Alzheimer disease. CMAJ. 2008 Feb 26;178(5):548-56.

Peltz CB, Corrada MM, Berlau DJ, Kawas CH. **Incidence of dementia in oldest-old** with amnestic MCI and other cognitive impairments. Neurology. 2011 Nov 22;77(21):1906-12.

Perneczky R, Tsolakidou A, Arnold A, et al. **CSF soluble amyloid precursor proteins** in the diagnosis of incipient Alzheimer disease. Neurology. 2011 Jul 5;77(1):35-8.

Perras C, Shukla VK, Lessard C, et al.Cholinesterase Inhibitors for Alzheimer's Disease:A Systematic Review of Randomized Controlled Trials [Technology report no 58]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; Sept 2005. 129pages. CCOHTA https://www.ccohta.ca/publications/pdf/217_cholinesterase_tr_e.pdf

Peters R, Beckett N, Forette F, et al. **HYVET** investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (**HYVET-COG**): a double-blind, placebo controlled trial. Lancet Neurol. 2008 Aug;7(8):683-9. Epub 2008 Jul 7. Antihypertensive treatment in elderly patients does not statistically reduce incidence of dementia. This negative finding might have been due to the short follow-up, owing to the early termination of the trial, or the modest effect of treatment. Nevertheless, the HYVET findings, when included in a meta-analysis, might support antihypertensive treatment to reduce incident dementia.

Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133-42.

Petersen RC. Clinical practice. **Mild cognitive impairment**. N Engl J Med. 2011 Jun 9;364(23):2227-34.

Pharmacist's Letter Oct 2006. **Drug treatment of Dementia** due to Alzheimer's Disease.

Pharmacist's Letter. **Fall prevention in the elderly**. April 2010.

Phelan EA, Borson S, Grothaus L, Balch S, Larson EB. Association of **incident dementia with hospitalizations**. JAMA. 2012;307(2):165-172.

Phillips VL, Diwan S. The incremental effect of dementia-related problem **behaviors** on the time to nursing home placement in poor, frail, demented older people.J Am Geriatr Soc. 2003 Feb;51(2):188-93.

Piguet Olivier, Hornberger Michael, Mioshi Eneida, et al. **Behavioural-variant frontotemporal dementia**: diagnosis, clinical staging, and management, The Lancet Neurology, In Press, Corrected Proof, Available online 10 Dec 2010, ISSN 1474-4422

Plassman Brenda L., Williams, Jr John W.., Burke, James R.et al. **NIH Conferences**: Systematic Review: Factors Associated With **Risk for and Possible Prevention of Cognitive Decline in Later Life**. *Ann Intern Med* August 3, 2010 153:182-193.

Poels MM, Ikram MA, van der Lugt A et al. **Cerebral microbleeds** are associated with worse cognitive function: The **Rotterdam** Scan Study. Neurology. 2012 Jan 31;78(5):326-33.

Pollock BG, Mulsant BH, et al. Double-blind comparison of **citalopram and risperidone** for the treatment of behavioural and psychotics symptoms associated with dementia. *Am J Geriatr Psychiatry* 2007; 15: 942-952.

Pollock, Bruce G., Mulsant, Benoit H. Between Scylla and Charybdis: **antipsychotic and other psychotropic medications** in older nursing home residents CMAJ 2011 183: 778-779.

Pouryamout L, Dams J, Wasem J, Dodel R, Neumann A. Economic Evaluation of Treatment Options in Patients with Alzheimer's Disease: A **Systematic Review of Cost-Effectiveness** Analyses. Drugs. 2012 Apr 5.

Powell MR, et al. Cognitive measures predict pathologic Alzheimer disease. Arch Neurol. 2006 Jun;63(6):865-8. (InfoPOEMs: Baseline scores on the Mayo Cognitive Factor Scales (MCFS) are somewhat predictive of developing Alzheimer disease after 6 years. (LOE = 2b))

Prince M, Acosta D, Ferri CP, et al. Dementia incidence and mortality in middle-income countries, and associations with **indicators of cognitive reserve**: a 10/66 Dementia Research Group population-based cohort study. Lancet 2012; online May 23.

Pruss H, Höltje M, Maier N, et al. **IgA NMDA receptor antibodies** are markers of synaptic immunity in slow cognitive impairment. Neurology 2012;78:1743–1753.

Purandare N, Burns A, Morris J, et al. Association of **cerebral emboli with accelerated cognitive deterioration** in Alzheimer's disease and vascular dementia. Am J Psychiatry. 2012 Mar;169(3):300-8.

Qaseem A, Snow V, Cross JT Jr, et al. **American College of Physicians/American Academy of Family Physicians Panel on Dementia**. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2008 Mar 4;148(5):370-8.

Querfurth HW, LaFerla FM. **Alzheimer's** Disease-**Mechanism of Disease**. N Engl J Med 2010 362: 329-344

Quinn JF.; Raman R,Thomas RG.; et al. **Docosahexaenoic Acid (DHA) Supplementation** and Cognitive Decline in Alzheimer Disease: A Randomized Trial. JAMA. 2010;304(17):1903-1911.

Rabins PV et al. Practice Guideline for the Treatment of patients with **Alzheimer's Disease and other Dementias. APA American 2007** http://www.psych.org/psych_pract/treatg/pg/AlzPG101007.pdf

Raffaitin C, Féart C, Le Goff M, et al. **Metabolic syndrome** and cognitive decline in French elders: The Three-City Study. Neurology. 2011 Feb 8;76(6):518-25.

Rafii MS, Walsh S, Little JT, et al. Alzheimer's Disease Cooperative Study. A phase II trial of **huperzine A** in mild to moderate Alzheimer disease. Neurology. 2011 Apr 19;76(16):1389-94. (not benefit)

Raina P, Santaguida P, Ismaila A, et al. Effectiveness of **cholinesterase inhibitors and memantine** for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008 Mar 4;148(5):379-97.

Rait G., Walters K., Bottomley C., Petersen I., Iliffe S., Nazareth I. **Survival** of people with clinical diagnosis of dementia in primary care: cohort study. BMJ 2010;341:c3584, doi: 10.1136/bmj.c3584 (Published 5 August 2010)

TOP

Raivio MM, Laurila JV, Strandberg TE, et al. **Neither atypical nor conventional antipsychotics increase mortality** or hospital admissions among elderly patients with dementia: a two-year prospective study. Am J Geriatr Psychiatry. 2007 May;15(5):416-24.

Rappaport SA, Marcus RN, Manos G, McQuade RD, Oren DA. A randomized, double-blind, placebo-controlled tolerability study of **intramuscular aripiprazole** in acutely agitated patients with Alzheimer's, vascular, or mixed dementia. J Am Med Dir Assoc. 2009 Jan;10(1):21-7.

Rapoport MJ, Herrmann N, Molnar FJ, et al. Sharing the responsibility for assessing the risk of the **driver** with dementia. CMAJ. 2007 Sep 11;177(6):599-601.

Raschetti R, Albanese E, Vanacore N, Maggini M. Cholinesterase inhibitors in **mild cognitive impairment**: a systematic review of randomised trials. PLoS Med. 2007 Nov 27;4(11):e338. The use of ChEIs in MCI was not associated with any delay in the onset of AD or dementia. Moreover, the safety profile showed that the risks associated with ChEIs are not negligible.

Redelmeier DA, Thiruchelvam D, Daneman N. **Delirium** after elective surgery among elderly patients **taking statins**. CMAJ. 2008 Sep 23;179(7):645-52.

Rabinovici GD, Rosen HJ, Alkalay A, et al. **Amyloid vs FDG-PET** in the differential diagnosis of AD and FTLD. Neurology. 2011 Nov 30.

Reynolds CF 3rd, Butters MA, Lopez O, et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of **donepezil** combined with antidepressant pharmacotherapy. Arch Gen Psychiatry. 2011 Jan;68(1):51-60. (no clear benefit)

Ringman John M. Setting the stage for **prevention of familial Alzheimer's disease**, The Lancet Neurology, Volume 10, Issue 3, March 2011, Pages 200-201, ISSN 1474-4422, DOI: 10.1016/S1474-4422(10)70328-8.

Rinne JO, et al. 11C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with **bapineuzumab**: a phase 2, double-blind, placebo-controlled, ascending-dose study. Lancet Neurol 2010; 9: 363–72.

Ritchie K., Carrière I., Ritchie C. Wet al. **Designing prevention programmes** to reduce incidence of dementia: prospective cohort study of modifiable risk factors. BMJ 2010;341:c3885, doi: 10.1136/bmj.c3885 (Published 5 August 2010)

Rizzo Matthew. **Impaired Driving From Medical Conditions**: A 70-Year-Old Man Trying to Decide if He Should Continue Driving. JAMA. 2011;305(10):1018-1026.

Roberts RO, Geda YE, Knopman DS, et al. The incidence of **MCI differs by subtype and is higher in men**: the Mayo Clinic Study of Aging. Neurology 2012;78:342–351.

Robinson DM, Keating GM. **Memantine**: a review of its use in Alzheimer's disease. Drugs. 2006;66(11):1515-34.

Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007 Sep 11;69(11):1074-83. Epub 2007 Aug 29. Both unilateral and bilateral **oophorectomy** preceding the onset of menopause are associated with an increased risk of cognitive impairment or dementia. The effect is age-dependent and suggests a critical age window for neuroprotection.

Rodda J, Carter J. **Cholinesterase inhibitors and memantine** for symptomatic treatment of dementia. BMJ. 2012 May 1;344:e2986.

Rodrigue KM, Kennedy KM, Devous MD Sr, et al. **β-Amyloid burden in healthy aging**: Regional distribution and cognitive consequences. Neurology. 2012 Feb 7;78(6):387-95.

Roe CM, Fagan AM, Williams MM, et al. Improving **CSF biomarker** accuracy in predicting prevalent and incident Alzheimer disease. Neurology. 2011 Feb 8;76(6):501-10.

Roe CM, Fagan AM, Grant EA, et al. **Cerebrospinal fluid biomarkers**, **education**, **brain volume**, and future cognition. Arch Neurol. 2011 Sep;68(9):1145-51.

Rolland Y, et al. **Exercise program** for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc. 2007 Feb;55(2):158-65. A simple exercise program, 1 hour twice a week, led to significantly slower decline in ADL score in patients with AD living in a nursing home than routine medical care.

Roman GC, Salloway S, Black SE, et al. Randomized, placebo-controlled, clinical trial of **donepezil in vascular dementia**: differential effects by **hippocampal size**. Stroke. 2010 Jun;41(6):1213-21. Epub 2010 Apr 15.

Rosenberg PB, Drye LT, Martin BK, et al. DIADS-2 Research Group. **Sertraline** for the treatment of **depression in Alzheimer disease**. Am J Geriatr Psychiatry. 2010 Feb;18(2):136-45. CONCLUSIONS: Sertraline not effective.

Rosenberg RN. Treat Alzheimer disease **before it is symptomatic**. Arch Neurol. 2011 Oct;68(10):1237-8.

Rosenheck RA, Leslie DL, Sindelar JL, et al. Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease (**CATIE-AD**) investigators. **Cost-benefit analysis** of second-generation antipsychotics and placebo in a randomized trial of the treatment of psychosis and aggression in Alzheimer disease. Arch Gen Psychiatry. 2007 Nov;64(11):1259-68. There were no differences in measures of effectiveness between initiation of active treatments or placebo (which represented watchful waiting) but the placebo group had significantly lower health care costs. Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, Rosenheck RA, Hsiao JK, Lieberman JA, Schneider LS; CATIE-AD Study Group. Clinical Symptom Responses to Atypical Antipsychotic Medications in Alzheimer's Disease: Phase 1 Outcomes From the CATIE-AD Effectiveness Trial. Am J Psychiatry. 2008 Jun 2. [Epub ahead of print] In this descriptive analysis of outpatients with Alzheimer's disease in usual care settings, some clinical symptoms improved with atypical antipsychotics. Antipsychotics may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas. They do not appear to improve functioning, care needs, or quality of life.

Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. **Normative data for the Montreal Cognitive Assessment (MoCA)** in a population-based sample. Neurology. 2011 Sep 27;77(13):1272-5.

Rossom RC, Rector TS, Lederle FA, et al. Are All Commonly Prescribed Antipsychotics Associated with Greater **Mortality** in Elderly Male Veterans with Dementia? J Am Geriatr Soc. 2010 May 7. Commonly prescribed doses of haloperidol, olanzapine, and risperidone, but not quetiapine, were associated with a short-term increase in mortality.

Rusanen Minna; Kivipelto Miia; Quesenberry Charles P. Jr; et al. Heavy **Smoking in Midlife** and Long-term Risk of Alzheimer Disease and Vascular Dementia. Arch Intern Med. 2011;171(4):333-339.

Sacchetti E, Turrina C, Valsecchi P. **Cerebrovascular accidents in elderly people treated with antipsychotic** drugs: a systematic review. Drug Saf. 2010 Apr 1;33(4):273-88. doi: 10.2165/11319120-000000000-00000.

Sachs GA, Carter R, Holtz LR, et al. **Cognitive impairment**: an independent predictor of **excess mortality**: a cohort study. Ann Intern Med. 2011 Sep 6;155(5):300-8.

Saczynski, J.S., Beiser, A., Seshadri, S., et al. **Depressive symptoms** and risk of dementia: The Framingham Heart Study. Neurology 2010 75: 35-41.

Sanders Robert D, Pandharipande Pratik P, Davidson Andrew J, et al. Anticipating and managing **postoperative delirium** and cognitive decline in adults. BMJ 2011;343:doi:10.1136/bmj.d4331 (Published 20 July 2011)

Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of **simvastatin to treat Alzheimer disease**. Neurology. 2011 Aug 9;77(6):556-63. (no benefit)

Saposnik G, Cote R, Rochon PA, et al. On behalf of the Investigators of the Registry of the Canadian Stroke Network and the Stroke Outcome Research Canada (SORCan) Working Group. Care and outcomes in patients with **ischemic stroke** with and without preexisting dementia. Neurology. 2011 Nov 1;77(18):1664-1673.

Scarmeas N, et al. **Physical activity, diet**, and risk of Alzheimer disease. JAMA. 2009 Aug 12;302(6):627-37. In this study, both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD.

Scarmeas N, Honig LS, Choi H, et al. **Seizures** in Alzheimer disease: who, when, and how common? Arch Neurol. 2009 Aug;66(8):992-7.

Schafer JH, et al. **Homocysteine** and cognitive function in a population-based study of older adults. J Am Geriatr Soc. 2005 Mar;53(3):381-8.

Schmidt C, Wolff M, Weitz M, et al. **Rapidly progressive Alzheimer disease**. Arch Neurol. 2011 Sep;68(9):1124-30.

Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of **atypical antipsychotics** for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006 Mar;14(3):191-210.

Schneider LS, Dagerman KS, Higgins JP, McShane R. Lack of Evidence for the Efficacy of **Memantine in Mild Alzheimer** Disease. Arch Neurol. 2011 Apr 11.

Schoonenboom NS, Reesink FE, Verwey NA, et al. **Cerebrospinal fluid markers** for differential dementia diagnosis in a large memory clinic cohort. Neurology. 2012 Jan 3;78(1):47-54.

Schrijvers Elisabeth M. C., Koudstaal Peter J., Hofman Albert, et al. **Plasma Clusterin** and the Risk of Alzheimer Disease. JAMA. 2011;305(13):1322-1326.doi:10.1001/jama.2011.381.

Schrijvers EMC, Verhaaren BFJ, Koudstaal PJ, Hofman A, Ikram MA, Breteler MMB. Is **dementia incidence declining**? Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology 2012;78:1456 –1463.

Schott JM, Warren JD, Barkhof F, Rossor MN, Fox NC. Suspected early dementia. BMJ. 2011 Sep 20;343:d5568. doi: 10.1136/bmj.d5568.

Seitz DP, Adunuri N, Gill SS, et al. **Antidepressants for agitation and psychosis** in dementia. Cochrane Database Syst Rev. 2011 Feb 16;2:CD008191. Currently there are relatively few studies of antidepressants for the treatment of agitation and psychosis in dementia. The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies. Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics.

Sessums LL, Zembrzuska H, Jackson JL. Does this patient have **medical decision-making capacity**?. JAMA. 2011 Jul 27;306(4):420-7.

Seshadri Sudha; Fitzpatrick Annette L.; Ikram M. Arfan et al; for the CHARGE, GERAD1, and EADI1 Consortia Genome-wide Analysis of **Genetic Loci Associated With Alzheimer Disease**. *JAMA*. 2010;303(18):1832-1840.

Shah RC, Buchman AS, Wilson RS, et al. **Hemoglobin level** in older persons and incident Alzheimer disease: Prospective cohort analysis. Neurology. 2011 Jul 19;77(3):219-26.

Sheldon Tony. Study of **rivastigmine for delirium** in intensive care is stopped after **deaths.** BMJ 2010;340:c2895, doi: 10.1136/bmj.c2895 (Published 28 May 2010)

Simmons BB, Hartmann B, Dejoseph D. **Evaluation of Suspected Dementia**. Am Fam Physician. 2011 Oct 15;84(8):895-902.

Singh J, Kour K, Jayaram MB. **Acetylcholinesterase inhibitors for schizophrenia**. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD007967. DOI: 10.1002/14651858.CD007967.pub2. The results seem to favour the use of acetylcholinesterase inhibitors in combination with antipsychotics on a few domains of mental state and cognition, but because of the various limitations in the studies as mentioned in the main text, the evidence is weak.

Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of **onset of cognitive decline**: results from **Whitehall II** prospective cohort study. BMJ 2012;344:d7622. Evident in **middle age** (age 45-49).

Sink KM, Thomas J 3rd, Xu H, Craig B, et al. Dual Use of Bladder **Anticholinergics and Cholinesterase Inhibitors**: Long-Term Functional and Cognitive Outcomes. J Am Geriatr Soc. 2008 Apr 1. [Epub ahead of print] In higher-functioning NH residents, dual use of ChIs and bladder anticholinergics may result in greater rates of functional decline than use of ChIs alone. The MDS-COGS may not be sensitive enough to detect differences in cognition due to dual use.

TOP

Small GW, Siddarth P, Kepe V, et al. Prediction of cognitive decline by **positron emission tomography** of brain amyloid and tau. Arch Neurol. 2012 Feb;69(2):215-22.

Snowden M, Steinman L, Mochan K, et al. Effect of **Exercise on Cognitive Performance** in Community-Dwelling Older Adults: Review of Intervention Trials and Recommendations for Public Health Practice and Research. J Am Geriatr Soc. 2011 Apr;59(4):704-716.

Snowden JS et al. The **clinical diagnosis of early-onset dementias**: Diagnostic accuracy and clinicopathological relationships. Brain 2011 Aug 11

Soininen H, West C, Robbins J, Niculescu L. Long-Term Efficacy and Safety of **Celecoxib** in Alzheimer's Disease. Dement Geriatr Cogn Disord. 2006 Oct 26;23(1):8-21 [Epub ahead of print] Celecoxib 200 mg bid did not slow the progression of AD in this study, and the occurrence of adverse events was as expected for an elderly population with a complex chronic medical condition.

Sojkova J, Zhou Y, An Y, et al. Longitudinal Patterns of {beta}-**Amyloid Deposition in Nondemented Older Adults**. Arch Neurol. 2011 May;68(5):644-9.

Solomon PR, Murphy CA. Should we **screen for Alzheimer's** disease? A review of the evidence for and against screening Alzheimer's disease in primary care practice. Geriatrics. 2005 Nov;60(11):26-31.

Song X, Mitnitski A, Rockwood K. **Nontraditional risk factors** combine to predict Alzheimer disease and dementia. Neurology. 2011 Jul 19;77(3):227-34.

Streim JE, Porsteinsson AP, Breder CD, Swanink R, Marcus R, McQuade R, Carson WH. A randomized, double-blind, placebo-controlled study of **aripiprazole** (~9mg/d) for the treatment of psychosis in nursing home patients with Alzheimer disease. Am J Geriatr Psychiatry. 2008 Jul;16(7):537-50. n=256 10weeks. In nursing home residents with AD and psychosis, aripiprazole did not confer specific benefits for the treatment of psychotic symptoms; but psychological and behavioral symptoms, including agitation, anxiety, and depression, were improved with aripiprazole, with a low risk of AEs.

Sudeep S Gill, Paula A Rochon, Nathan Herrmann, et al. Atypical antipsychotic drugs and **risk of ischaemic stroke**: population based retrospective cohort study BMJ, doi:10.1136/bmj.38330.470486.8F (published 24 January 2005) CONCLUSION: Older adults with dementia who take atypical antipsychotics have a similar risk of ischaemic stroke to those taking typical antipsychotics.

Suh GH, Shah A. Effect of **antipsychotics on mortality** in elderly patients with dementia: a 1-year prospective study in a nursing home. Int Psychogeriatr. 2005 Sep;17(3):429-41.

Sultzer DL, Davis SM, Tariot PN, et al. **CATIE-AD** Group. Clinical **symptom responses** to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry. 2008 Jul;165(7):844-54.

Takeda A, Loveman E, Clegg A, et al. A systematic review of the clinical effectiveness of **donepezil, rivastigmine and galantamine** on cognition, quality of life and adverse events in Alzheimer's disease. Int J Geriatr Psychiatry. 2005 Dec 2;21(1):17-28

Tangney CC, Aggarwal NT, Li H, et al. **Vitamin B12**, cognition, and brain MRI measures: A cross-sectional examination. Neurology. 2011 Sep 27;77(13):1276-82.

Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. **Memantine** treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004;291:317-24.

Tariot PN, Schneider L, Katz IR, et al. Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. Am J Geriatr Psychiatry. 2006 Sep;14(9):767-76. Epub 2006 Aug 11. Erratum in: Am J Geriatr Psychiatry. 2006 Nov;14(11):988. n=284 All treatment groups showed improvement in measures of psychosis without significant differences between them when planned comparisons were performed. Participants treated with quetiapine or haloperidol showed inconsistent evidence of improvement in agitation. Tolerability was better with quetiapine compared with haloperidol.

Teramura-Grönblad M, Muurinen S, Soini H, et al. Use of **anticholinergic drugs and cholinesterase inhibitors** and their association with psychological well-being among frail older adults in residential care facilities. Ann Pharmacother. 2011 May;45(5):596-602.

Teri L, Gibbons LE, McCurry SM, et al. **Exercise plus behavioral management** in patients with Alzheimer disease: a randomized controlled trial. JAMA. 2003 Oct 15;290(15):2015-22.

The American Geriatrics Society **2012 Beers Criteria Update** Expert Panel. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2012 Feb 29.

Thoonsen H, Richard E, Bentham P, Gray R, et al. **Aspirin in Alzheimer's disease: increased risk of intracerebral hemorrhage**: cause for concern? Stroke. 2010 Nov;41(11):2690-2.

Tilly J, Reed P, editor(s). Dementia care practice recommendations for assisted living residences and nursing homes. Washington (DC): Alzheimer's Association; 2006 Sep. 28 p. http://www.alz.org/documents/national/DementiaCarePracticeRecommendations.pdf

Tsivgoulis G, Alexandrov AV, Wadley VG, et al. Association of higher **diastolic blood pressure** levels with cognitive impairment. Neurology 2009; 73:589-595.

Unverzagt FW, McClure LA, Wadley VG, et al. **Vascular risk factors** and cognitive impairment in a stroke-free cohort. Neurology. 2011 Nov 8;77(19):1729-36.

Van den Boogaard M, Pickkers P, Slooter AJC, et al. Development and validation of **PRE-DELIRIC** (PREdiction of DELIRium in ICu patients) **delirium prediction model** for intensive care patients: observational multicentre study. BMJ 2012;344:e420.

van der Flier WM, Pijnenburg YA, Fox NC, et al. **Early-onset versus late-onset Alzheimer's disease**: the case of the missing APOE E4 allele. Lancet Neurol. 2010 Dec 22.

van Eijk MM, Roes KC, Honing ML, et al. Effect of **rivastigmine** as an adjunct to usual care with **haloperidol** on duration of **delirium** and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial.Lancet.2010Nov4.

van Himbergen TM, Beiser AS, Ai M, et al. **Biomarkers for Insulin Resistance and Inflammation** and the Risk for All-Cause Dementia and Alzheimer Disease: Results From the Framingham Heart Study. Arch Neurol. 2012 Jan 2.

Varsaldi F, et al. Impact of the **CYP2D6** polymorphism on steady-state plasma concentrations and clinical outcome of **donepezil** in Alzheimer's disease patients. Eur J Clin Pharmacol. 2006 Jul 15; [Epub ahead of print]

Vercambre MN, Grodstein F, Manson JE, et al. **Physical activity** and cognition in women with vascular conditions. (**WACS**) Arch Intern Med. 2011 Jul 25;171(14):1244-50.

Verghese PB, Castellano JM, Holtzman DM. **Apolipoprotein E** in Alzheimer's disease and other neurological disorders. Lancet Neurol. 2011 Mar;10(3):241-52.

Verhey FR, Verkaaik M, Lousberg R. **Olanzapine versus Haloperidol** in the Treatment of Agitation in Elderly Patients with Dementia: Results of a Randomized Controlled Double-Blind Trial. Dement Geriatr Cogn Disord. 2005 Oct 21;21(1):1-8

Vernooij-Dassen M, Draskovic I, McCleery J, Downs M. **Cognitive reframing** for carers of people with dementia. Cochrane Database of Systematic Reviews 2011, Issue 11. Art. No.: CD005318. DOI: 10.1002/14651858.CD005318.pub2. Cognitive reframing for family carers of people with dementia seems to reduce psychological morbidity and subjective stress but without altering appraisals of coping or burden. The results suggest that it may be an effective component of individualised, multi-component interventions for carers.

Vickrey BG, et al. The effect of a **disease management intervention** on quality and outcomes of dementia care: a randomized, controlled trial. Ann Intern Med. 2006 Nov 21;145(10):713-26.

Vidoni ED, Townley RA, Honea RA, Burns JM; For the Alzheimer's Disease Neuroimaging Initiative. **Alzheimer disease biomarkers** are associated with body mass index. Neurology. 2011 Nov 22;77(21):1913-1920.

Vigen CL, Mack WJ, Keefe RS, et al. **Cognitive Effects of Atypical Antipsychotic** Medications in Patients With Alzheimer's Disease: Outcomes From **CATIE-AD**. Am J Psychiatry. 2011 May 15.

Villemagne VL, Pike KE, Chételat G, et al. **Longitudinal assessment of Aβ** and cognition in aging and Alzheimer disease. Ann Neurol. 2011 Jan;69(1):181-92. doi: 10.1002/ana.22248.

Villemagne VL, Okamura N, Pejoska S, et al. In vivo assessment of **vesicular monoamine transporter** type 2 in dementia with lewy bodies and Alzheimer disease. Arch Neurol. 2011 Jul;68(7):905-12.

Voisin T, Vellas B. Diagnosis and treatment of patients with **severe Alzheimer's disease**. Drugs Aging. 2009;26(2):135-44. doi: 10.2165/0002512-200926020-00005.

Waldemar G, Dubois B, Emre M, Georges J, McKeith IG, et al. **EFNS**. Recommendations for the **diagnosis and management** of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol 2007 Jan;14(1):e1-26.

Wallin AK, Blennow K, Zetterberg H, Londos E, Minthon L, Hansson O. **CSF biomarkers** predict a more malignant outcome in Alzheimer disease. Neurology. 2010 May 11;74(19):1531-7.

Wang CZ, Du GJ, Zhen Z, Calway T, Yuan CS. Significant dose **differences in donepezil purchased from the United States and Canada**. Ann Intern Med. 2011 Aug 16;155(4):279-80.

Wang W, Li HL, Wang DX, et al. **Haloperidol prophylaxis decreases delirium** incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. Crit Care Med. 2012 Mar;40(3):731-9. For elderly patients who are admitted to the intensive care unit (ICU) after noncardiac surgery, the use of prophylactic continuous intravenous (0.5mg x 1 then 0.1mg/hr) haloperidol during the first 12 hours decreases the incidence of delirium.

Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The **Confusion Assessment Method (CAM)** : a systematic review of current usage. J Am Geriatr Soc [Internet]. 2008 May [cited 2011 Oct 4];56(5):823-30.

Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to **particulate air pollution** and cognitive decline in older women. Arch Intern Med. 2012;172(3):219-227.

Whitmer RA, Karter AJ, Yaffe K, et al. **Hypoglycemic episodes** and risk of dementia in older patients with type 2 diabetes mellitus.JAMA. 2009 Apr 15;301(15):1565-72.

Widera Eric, Steenpass Veronika, Marson Daniel, et al. **Finances in the Older Patient** With Cognitive Impairment: "He Didn't Want Me to Take Over." JAMA. 2011;305(7):698-706.doi:10.1001/jama.2011.164

Williams JW, Plassman BL, Burke J, et al. **Preventing Alzheimer's disease** and cognitive decline. Evid Rep Technol Assess (Summ). 2010 April;193:1-727.

Wilson RS, Hebert LE, Scherr PA, Barnes LL, Mendes de Leon CF, et al. **Educational attainment** and cognitive decline in old age. Neurology. 2009 Feb 3;72(5):460-5. The results suggest that education is robustly associated with level of cognitive function but not with rate of cognitive decline and that the former association primarily accounts for education's correlation with risk of dementia in old age.

Wilson RS, Hebert LE, Scherr PA, et al. **Cognitive decline after hospitalization** in a community population of older persons. Neurology 2012; 78:950 –956

Wilson RS, Segawa E, Boyle PA, Bennett DA. Influence of **late-life cognitive activity** on cognitive health. Neurology. 2012 Apr 10;78(15):1123-9.

Winblad B, et al. 3-Year Study of Donepezil Therapy in Alzheimer's Disease: Effects of **Early and Continuous** Therapy. Dement Geriatr Cogn Disord. 2006 Feb 27;21(5-6):353-363 [Epub ahead of print]

Winblad B, Kilander L, Eriksson S, et al. **Severe Alzheimer's** Disease Study Group. **Donepezil** in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1;367(9516):1057-65.

Winblad, B, Andreasen N, et al. Safety, tolerability, and antibody response of active **Aβ immunotherapy with CAD106** in patients with Alzheimer's disease: randomised, double-blind, placebo-controlled, fi rst-in-human study. Lancet Neurol 2012

TOP

Winslow BT, Onysko MK, Stob CM. **Treatment of Alzheimer Disease**. Am Fam Physician. 2011;83(12):1403-1412.
Witlox J, Eurelings LS, de Jonghe JF, et al.. **Delirium** in elderly patients and the risk of **postdischarge mortality**, institutionalization, and dementia: a meta-analysis. JAMA. 2010 Jul 28;304(4):443-51.

Wong Camilla L.; Holroyd-Leduc Jayna; Simel DL.; Straus SE. **Does This Patient Have Delirium**?: Value of Bedside Instruments. JAMA. 2010;304(7):779-786. The **Confusion Assessment Method** is the most accurate tool for diagnosing delirium in adults that can be performed in less than 5 minutes. The Mini-Mental State Examination (MMSE) was the least useful diagnostic tool for delirium. (LOE = 3a)
Woods DL, Craven RF, Whitney J. The effect of therapeutic **touch** on behavioral symptoms of persons with dementia. Altern Ther Health Med 2005; 11:66-74. (InfoPOEMs: Short-duration therapeutic touch, a specific treatment modality often practiced by nurses, decreases behavioral symptoms in patients with dementia, especially vocalizing and manual manipulation of hands or objects. This simple intervention was administered twice daily for 5 minutes to 7 minutes by a trained practitioner. (LOE = 1b-))

Woods B, Aguirre E, Spector AE,OrrellM. **Cognitive stimulation to** improve cognitive functioning in people with dementia. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD005562. DOI: 10.1002/14651858.CD005562.pub2. There was consistent evidence from multiple trials that cognitive stimulation programmes benefit cognition in people with mild to moderate dementia over and above any medication effects.
Whitwell JL, Shiung MM, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr. **MRI** patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. Neurology. 2007 Sep 26; [Epub ahead of print]
Woods SW, Morgenstern H, Saksa JR, et al. Incidence of **tardive dyskinesia with atypical versus conventional antipsychotic** medications: a prospective cohort study. J Clin Psychiatry. 2010 Feb 9.
Xie J, Brayne C, Matthews FE; Medical Research Council Cognitive Function and Ageing Study collaborators. **Survival times** in people with dementia: analysis from population based cohort study with 14 year follow-up. BMJ. 2008 Feb 2;336(7638):258-62. Epub 2008 Jan 10. **Men will live a median 4.1 years and women a median of 4.6 years beyond a diagnosis of dementia**. Survival time is shorter in older people and in patients with disability. (LOE = 1b)
Xiong C, Roe CM, Buckles V, et al. Role of family history for Alzheimer **biomarker abnormalities** in the adult children study. Arch Neurol. 2011 Oct;68(10):1313-9.
Yaffe Kristine, Weston Andrea, Graff-Radford Neill R., et al. Original Contribution Association of **Plasma β-Amyloid Level and Cognitive Reserve** With Subsequent Cognitive Decline. *JAMA*. 2011;305(3):261- 266.doi:10.1001/jama.2010.1995.
Yaffe K, Middleton LE, Lui LY, et al. **Mild cognitive impairment, dementia**, and their subtypes in **oldest old women**. Arch Neurol. 2011 May;68(5):631-6
Yaffe K, Laffan AM, Harrison SL, et al. **Sleep-disordered breathing**, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011; 306(6):613-619.
Yaffe K, Lindquist K, Schwartz AV, et al. **Advanced glycation end product level**, diabetes, and accelerated cognitive aging. Neurology. 2011 Oct 4;77(14):1351-6.
Young J, Inouye SK. **Delirium in older people**. BMJ. 2007 Apr 21;334(7598):842-6.
Young John, Meagher David, MacLullich Alasdair. **Cognitive assessment of older people**. BMJ 2011;343:d5042 doi: 10.1136/bmj.d5042.
Zekry D, Gold G. Management of **mixed dementia**. Drugs Aging. 2010 Sep 1;27(9):715-28. doi: 10.2165/11538250-000000000-00000.
Zhan C, et al. Potentially **inappropriate** medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey.JAMA. 2001 Dec 12;286(22):2823-9.
Zhong KX, Tariot PN, Mintzer J, et al. **Quetiapine** to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. Curr Alzheimer Res. 2007 Feb;4(1):81-93. n=333. The results of this study suggest that quetiapine 200mg/day was effective and well-tolerated for treating agitation associated with dementia. However, caution should be exercised given the concerns regarding increased mortality with atypical antipsychotics in this vulnerable patient population.

Useful Web sites:

Alzheimer Society Canada www.alzheimer.ca
Alzheimer Association USA www.alz.org
Alzheimer Society UK www.alzheimers.org.uk

TOP

LTC-Elderly-Pearls Chart: References

[1] Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing. 2008 Nov;37(6):673-9.

[2] The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2012 Apr;60(4):616-631.

[3] Bell AD, Roussin A, Cartier R, Chan WS, Douketis JD, Gupta A, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society Guidelines Executive Summary. Can J Cardiol. 2011 Mar-Apr;27(2):208-21.

[4] Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):7S-47S.

[5] RxFiles. Reference List of Drugs with Anticholinergic Effects. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/members/Psyc-anticholinergic-Ref%20List%20SPDP-complete.pdf

[6] Bareham J, Regier L, Jensen B. Behaviour Management in Dementia – RxFiles Newsletter. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-BPSD-Newsletter.pdf

[7] Regier L, Bareham J. Individualizing Glycemic Targets in the Frail Elderly - RxFiles Q&A. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/members/Diabetes-Glucose-Targets-in-Elderly-LTC.pdf {Also see article in CFP jounal: Diabetes in the frail elderly; Individualization of glycemic management http://www.cfp.ca/content/58/5/543.full }

[8] Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med. 2011 Apr 19;154(8):554-9.

[9] Breault R, Regier L, Jensen B. Metformin: Precautions with Renal Impairment, Hepatic Disease and Heart Failure. RxFiles Q&A, Oct 2008. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Metformin-LacticAcidosis-QandA.pdf

[10] Dumont Z. The Gout – RxFiles Q&A & Chart. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Gout.pdf

[11] Jin M. Heart Failure Treatment – RxFiles Chart. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Heart-Failure.pdf

[12] RxFiles Weight Chart and Furosemide Sliding Scale – RxFiles Q&A. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/HF-FurosemideSlidingScale.pdf

[13] RxFiles ACCORD Lipid & BP Trial Overview. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/ACCORD-BP-Lipid-Trial-Overview.pdf

[14] Rakugi H, Ogihara T, Goto Y, Ishii M; JATOS Study Group. Comparison of strict- and mild-blood pressure control in elderly hypertensive patients: a per-protocol analysis of JATOS. Hypertens Res. 2010 Nov;33(11):1124-8.

[15] RxFiles Lipid Trials. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents-major%20trials.pdf

[16] RxFiles Lipid Agents. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents.pdf

[17] Regier L, Jensen B. Statins in the Media. RxFiles Q&A. May 2012. Accessed 08 May 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-statins-heart-risk-media.pdf

[18] RxFiles Osteoporosis Tx Chart. http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-osteoporosis.pdf

[19] FRAX Canada – Online Calculator: Accessed 04 Apr 2012 at http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19

[20] Stone S. Vitamin D – RxFiles Q&A Summary. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/Vitamin-D-Overview-QandA.pdf

[21] Stone S, Regier L. Opioids for Chronic Non-Cancer Pain (CNCP) Management in the Elderly – RxFiles Q&A. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/Opioids-Pain-ELDERLY-QandA.pdf

[22] Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics inolder people with insomnia: meta-analysis of risks and benefits. BMJ. 2005 Nov 19;331(7526):1169.

[23] Herpes Zoster Vaccine – RxFiles Q&A. Accessed 04 Apr 2012 at http://www.rxfiles.ca/rxfiles/uploads/documents/Zostavax-QandA.pdf

[24] Hutchison, L.C., & Sleeper, R.B. (2010). Biomedical Principles of Aging. In *Fundamentals of Geriatric Pharmacotherapy: An Evidence-Based Approach* (pp. 56). Bethesda, MD: American Society of Health-System Pharmacists.

TOP

References :

Anticholinergic Cognitive Burden Scale http://www.indydiscoverynetwork.org/AnticholinergicCognitiveBurdenScale.html
Campbell NL, Boustani MA, Lane KA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. Neurology. 2010 Jul 13;75(2):152-9.
Carrière I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009 Jul 27;169(14):1317-24.
Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc. 2008 Dec;56(12):2203-10. Cumulative anticholinergic exposure across multiple medications over 1 year may negatively affect verbal memory and executive function in older men. Prescription of drugs with anticholinergic effects in older persons deserves continued attention to avoid deleterious adverse effects.
Kennedy J, Deberdt W, Siegal A, et al. **Olanzapine does not enhance cognition** in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. Int J Geriatr Psychiatry. 2005 Nov;20(11):1020-7.
Lackner TE, Wyman JF, McCarthy TC, Monigold M, Davey C. Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin 5mg/day in cognitively impaired nursing home residents with urge urinary incontinence. J Am Geriatr Soc. 2008 May;56(5):862-70. n=50. 4 weeks. Short-term treatment using oral extended-release oxybutynin 5 mg once daily was safe and well tolerated, with no delirium, in older female nursing home participants with mild to severe dementia. Future research should investigate different dosages and long-term treatment.
Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008 Mar 10;168(5):508-13.
Sink KM, Thomas J 3rd, Xu H, Craig B, et al. Dual Use of Bladder Anticholinergics and Cholinesterase Inhibitors: Long-Term Functional and Cognitive Outcomes. J Am Geriatr Soc. 2008 Apr 1. [Epub ahead of print] In higher-functioning NH residents, dual use of ChIs and bladder anticholinergics may result in greater rates of functional decline than use of ChIs alone. The MDS-COGS may not be sensitive enough to detect differences in cognition due to dual use.
Teramura-Grönblad M, Muurinen S, Soini H, et al. Use of anticholinergic drugs and cholinesterase inhibitors and their association with psychological well-being among frail older adults in residential care facilities. Ann Pharmacother. 2011 May;45(5):596-602.
The American Geriatrics Society **2012 Beers Criteria Update** Expert Panel. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2012 Feb 29.
Torjesen I. Anticholinergic effects of common drugs are associated with increased **mortality** in over 65s. BMJ. 2011 Jun 28;342:d4037.

References:

[1] Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol. 2006 Dec;46(12):1481-6.
[2] National Prescribing Service. Examples of medications with anticholinergic activity. January 2009. Available: http://www.brisbanesouth.com.au/content/Document/Resources/NPS/NPS%20Anticholinergic%20Medications%20200902.pdf
[3] Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008 Jul;56(7):1333-41.
[4] Drugs with Anticholinergic Activity. Canadian Pharmacist's Letter 2011; 27(12):271206.
[5] Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psyc. 2001.
[6] Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med. 2000 Sep;93(9):457-62.
[7] Feinberg M. The problems of anticholinergic adverse effects in older patients. Drugs Aging. 1993 Jul-Aug;3(4):335-48.
[8] Treatment of Dry Mouth. Canadian Pharmacist's Letter 2010; 26(10):261006.

TOP

RxFiles Academic Detailing

Essential Tremor (ET) & Restless Legs Syndrome (RLS) - Treatment Options

Additional References:
AAN Essential Tremor Guideline, Neurology Oct 2011. http://www.neurology.org/content/early/2011/10/18/WNL.0b013e3182360f0d.full.pdf
Abboud H, Ahmed A, Fernandez HH. Essential tremor: Choosing the right management plan for your patient. Cleve Clin J Med. 2011 Dec;78(12):821-8.
Baker WL, White CM, Coleman CI. Effect of nonergot dopamine agonists on symptoms of restless legs syndrome. Ann Fam Med. 2008 May-Jun;6(3):253-62.
Batool-Anwar S, Malhotra A, Forman J, Winkelman J, Li Y, Gao X. Restless legs syndrome and hypertension in middle-aged women. Hypertension. 2011;58:791–796.
Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. Am Fam Physician. 2008 Jul 15;78(2):235-40.
Bogan RK, et al.; TREAT RLS US Study Group. Ropinirole in the treatment of RLS: a US-based double-blind, placebo-controlled RCT. Mayo Clin Proc. 2006 Jan;81(1):17-27.(InfoPOEMs Apr/06).
Bushara KO, Malik T, Exconde RE. The effect of levetiracetam on essential tremor. Neurology. 2005 Mar 22;64(6):1078-80.
Canadian Adverse Reaction Newsletter. Quinine sulfate and serious adverse reactions. April 2011.
Cesnik E, Casetta I, Turri M, Govoni V, Granieri E, Strambi LF, Manconi M. Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. Neurology. 2010 Dec 7;75(23):2117-20.
Connor GS, Edwards K, Tarsy D. Topiramate in essential tremor: findings from double-blind, placebo-controlled, crossover trials. Clin Neuropharmacol. 2008 Mar-Apr;31(2):97-103.
Crawford P, Zimmerman EE. Differentiation and diagnosis of tremor. Am Fam Physician. 2011 Mar 15;83(6):697-702.
Deuschl G, Raethjen J, Hellriegel H, et al. Treatment of patients with essential tremor. Lancet Neurol. 2011 Feb;10(2):148-61
El-Tawil S, Al Musa T, Valli H, et al. Quinine for muscle cramps. Cochrane Database Syst Rev. 2010 Dec 8;12:CD005044. There is moderate quality evidence that quinine significantly reduces cramp frequency, intensity and cramp days in dosages between 200 and 500 mg/day. There is moderate quality evidence that with use up to 60 days, the incidence of serious adverse events is not significantly greater than for placebo in the identified trials. Further research is required on the optimal dose and duration of use, and also on alternative treatments.
Gao X, Schwarzschild MA, Wang H, Ascherio A. Obesity and restless legs syndrome in men and women. Neurology. 2009 Apr 7;72(14):1255-61. Both overall and abdominal adiposity are associated with increased likelihoods of having restless legs syndrome (RLS).
Garcia-Borreguero D, Larrosa O, Williams AM, Albares J, et al. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. Neurology. 2010 Jun 8;74(23):1897-904.
Garrison SR, Dormuth CR, Morrow RL, et al. Nocturnal leg cramps and prescription use that precedes them: a sequence symmetry analysis. Arch Intern Med. 2012 Jan 23;172(2):120-6.
Gjerstad MD, Tysnes OB, Larsen JP. Increased risk of leg motor restlessness but not RLS in early Parkinson disease. Neurology 2011;77:1941–1946.
Gironell A, Kulisevsky J, Barbanoj M, et al. A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. Arch Neurol. 1999 Apr;56(4):475-80.
Hallegraeff JM, van der Schans CP, et al. Stretching before sleep reduces the frequency and severity of nocturnal leg cramps in older adults: a randomised trial. J Physiother. 2012;58(1):17-22.
Hay WJ, Lemon MD, Farver DK. Gabapentin Enacarbil for Treatment of Restless Legs Syndrome in Adults (February). Ann Pharmacother. 2012 Jan 31.
Health Canada Aug/07: Eli Lilly Canada advises Healthcare Professionals that they will cease sale of Permax August 30, 2007 due to risk of cardiac valvulopathy.
Hoque R, Chesson AL Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med. 2010 Feb 15;6(1):79-83.
Katzberg, Hans D., Khan, Ahmir H., So, Yuen T. Assessment: Symptomatic treatment for muscle cramps (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2010 74: 691-696
Koller WC. Propranolol therapy for essential tremor of the head. Neurology. 1984;34(8):1077-9.
Koller W, Biary N, Cone S. Disability in essential tremor: effect of treatment. Neurology. 1986 Jul;36(7):1001-4.
Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S; for the Osteoporotic Fractures in Men (MrOS) Study Group. Association of Incident Cardiovascular Disease With Periodic Limb Movements During Sleep in Older Men: Outcomes of Sleep Disorders in Older Men (MrOS) Study. Circulation. 2011 Sep 13;124(11):1223-1231.
Kumar H, Jog M. A patient with tremor, part 1: making the diagnosis. CMAJ. 2011 Aug 2.
Kumar H, Jog M. A patient with tremor, part 2: from diagnosis to treatment. CMAJ. 2011 Aug 15.
Leschziner G, Gringras P. Restless legs syndrome. BMJ. 2012 May 23;344:e3056.
Lettieri CJ, Eliasson AH. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. Chest. 2009 Jan;135(1):74-80. Epub 2008 Nov 18. PCDs resulted in clinically significant improvements in symptoms of RLS in comparison to the use of sham devices & may be an effective adjunctive or alternative therapy for RLS.
Li Y, Munger KL, Batool-Anwar S, et al. Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. Neurology. 2012 May 8;78(19):1500-6.
Louis ED. Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. Lancet Neurol. 2010 May 5. [Epub ahead of print]
Machado A, Fernandez HH, Deogaonkar M. Deep brain stimulation: What can patients expect from it? (Essential tremor) Cleveland Clinic Journal of Medicine 2012; 79(2):113-120.
Manconi M, Ferri R, Zucconi M, et al. Preferential D2 (bromocriptine) or preferential D3 (pramipexole) dopamine agonists in restless legs syndrome. Neurology. 2011 Jul 12;77(2):110-7.
Medcalf P, Bhatia KP. Restless legs syndrome. BMJ. 2006 Sep 2;333(7566):457-8.
Molnar MZ, Novak M, Mucsi I. Management of restless legs syndrome in patients on dialysis.Drugs. 2006;66(5):607-24.
Monderer RS, Wu WP, Thorpy MJ. Nocturnal leg cramps. Curr Neurol Neurosci Rep. 2010 Jan;10(1):53-9.
Ondo WG, et al.; Topiramate Essential Tremor Study Investigators. Topiramate in essential tremor: a double-blind, placebo-controlled trial. Neurology. 2006 Mar 14;66(5):672-7. Epub 2006 Jan 25. (InfoPOEMs: Topiramate (Topamax) is slightly better than placebo in improving tremor and function in patients with essential tremor. In this study, the differences do not appear to be clinically significant. Given the expense and the significant drop-out rate due to side effects, topiramate should not be used as a first-line treatment. (LOE = 1b))
Ondo W, Hunter C, Vuong KD, Schwartz K, Jankovic J. Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. Mov Disord. 2000 Jul;15(4):678-82.
Oertel Wolfgang, Trenkwalder Claudia, Benes Heike, et al. and on behalf of the SP710 study group. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. The Lancet Neurology, In Press, Corrected Proof, Available online 24 June 2011
Pahwa R, Lyons K, Hubble JP, Busenbark K, Rienerth JD, Pahwa A, Koller WC. Double-blind controlled trial of gabapentin in essential tremor. Mov Disord. 1998 May;13(3):465-7.
Pérez-Díaz H, Iranzo A, Rye DB, Santamaría J. Restless abdomen: a phenotypic variant of restless legs syndrome. Neurology. 2011 Sep 27;77(13):1283-6.
Pharmacist's Letter: Mirapex (Pramipexole) for RLS Nov/06.
Reccoppa L, Malcolm R, Ware M. Gabapentin abuse in inmates with prior history of cocaine dependence. Am J Addict. 2004 May-Jun;13(3):321-3.
Sasso E, Perucca E, Calzetti S. Double-blind comparison of primidone and phenobarbitone in essential tremor. *Neurology* 1988;38:808–810.
Sasso E, Perucca E, Fava R, Calzetti S. Quantitative comparison of barbiturates in essential hand and head tremor. Mov Disord. 1991;6(1):65-8.
Satija P, Ondo WG. Restless legs syndrome : pathophysiology, diagnosis and treatment. CNS Drugs. 2008;22(6):497-518
Scholz H, Trenkwalder C, Kohnen R, et al. Dopamine agonists for restless legs syndrome. Cochrane Database Syst Rev. 2011 Mar 16;3:CD006009. The meta-analyses show the superiority of dopamine agonists over placebo in RCTs up to seven months. Cabergoline and pramipexole showed larger efficacy compared to levodopa in some but not all outcomes.
Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 2011; 12: 440–44.
Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep.N Engl J Med. 2007 Aug 16;357(7):639-47. Epub 2007 Jul 18. We have discovered a variant associated with susceptibility to periodic limb movements in sleep. The inverse correlation of the variant with iron stores is consistent with the suspected involvement of iron depletion in the pathogenesis of the disease.
Trenkwalder C, et al. Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with restless legs syndrome. Mov Disord. 2006 Jun 5; [Epub ahead of print]
Trenkwalder C, et al; PEARLS Study Group. Cabergoline in treatment of restless legs syndrome: the PEARLS Study. Neurology. 2004 Apr 27;62(8):1391-7.
Trenkwalder C, et al.; Therapy with Ropinirole; Efficacy and Tolerability in RLS 1 Study Group. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry. 2004 Jan;75(1):92-7.
Trotti LM, Bhadriraju S, Becker LA. Iron for restless legs syndrome. Cochrane Database Syst Rev. 2012 May 16;5:CD007834. There is insufficient evidence to determine whether iron therapy is beneficial for the treatment of RLS.
Vignatelli L, Billiard M, Clarenbach P, et al; EFNS Task Force. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. Eur J Neurol. 2006 Oct;13(10):1049-65. The following level A recommendations can be offered: for primary RLS, cabergoline, gabapentin, pergolide, ropinirole, levodopa and rotigotine by transdermal delivery (the latter two for short-term use) are effective in relieving the symptoms. Transdermal oestradiol is ineffective for PLMD.
Webb AJS, Fischer U, Rothwell PM. Effects of beta-blocker selectivity on blood pressure variability and stroke: a systematic review. Neurology 2011;77:731–737.
Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol. 2010 Sep 2.
Winkelman JW, Allen RP, Tenzer P, Hening W. Restless legs syndrome: nonpharmacologic and pharmacologic treatments. Geriatrics. 2007 Oct;62(10):13-6.
Winkelman JW, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology. 2006 Sep 26;67(6):1034-9. Epub 2006 Aug 23.
Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology. 2008 Jan 1;70(1):35-42. Restless legs syndrome (RLS) is associated with prevalent coronary artery disease and cardiovascular disease. This association appears stronger in those with greater frequency or severity of RLS symptoms.
Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. Biol Psychiatry. 2005 Sep 15;58(6):510-4. Epub 2005 Jul 7.
Zesiewicz TA, Ward CL, Hauser RA, et al.. A pilot, double-blind, placebo-controlled trial of pregabalin (Lyrica) in the treatment of essential tremor. Mov Disord. 2007 Aug 15;22(11):1660-3.
Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. (AAN) Neurology. 2011 Nov 8;77(19):1752-5. http://www.neurology.org/content/early/2011/10/18/WNL.0b013e318236f0fd.full.pdf

RxFiles: *Q&A Summary*
© www.RxFiles.ca - Jun 2012
Loren Regier BSP BA, Brent Jensen BSP

Acknowledgement of Reviewers:

- Dr. Alex Rajput, Neurology, University of Saskatchewan, Saskatoon, SK; Dr. Carol Boyle, Neurology, Saskatoon, SK; RxFiles Advisory Committee

RxFiles provides objective comparisons for optimal drug therapy decision making via:

- Academic Detailing (to Saskatchewan physicians, pharmacists, & nurse practitioners)
- RxFiles Drug Comparison Charts book {8th Edition coming - Summer 2010; see http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx}
- RxFiles.ca Website – both free and subscriber only access areas; see http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx
- Newsletters, Q&As, Trial Summaries, Charts; participation in continued professional learning (http://www.usask.ca/cme/)
- Contributions to Canadian and international evidence informed drug therapy discussions and academic detailing developments.

[1] Zesiewicz TA, et al. Practice Parameter: Therapies for essential tremor. Report - American Academy of Neurology. Neurology. 2005 Jun 22 http://www.neurology.org/cgi/reprint/64/12/2008.pdf?ck=nck
[2] Louis ED. Essential tremor. Lancet Neurol. 2005 Feb;4(2):100-110.
[3] Smaga S. Tremor. Am Fam Physician. 2003 Oct 15;68(8):1545-52.
[4] Lyons KE, Pahwa R, Comella CL, et al. Benefits and risks of pharmacological treatments for essential tremor. Drug Saf. 2003;26(7):461-81.
[5] Sullivan KL, Hauser RA, Zesiewicz TA. Essential tremor. Epidemiology, diagnosis, and treatment. Neurologist. 2004 Sep;10(5):250-8.
[6] Micromedix 2010.
[7] Lyons KE, Pahwa R. Pharmacotherapy of essential tremor : an overview of existing and upcoming agents. CNS Drugs. 2008;22(12):1037-45.
[8] Elble RJ. Tremor: clinical features, pathophysiology, and treatment. Neurol Clin. 2009 Aug;27(3):679-95, v-vi.
[9] Jensen B. RxFiles Anticonvulsants Drug Chart. http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-psyc-seizure.pdf (Subscription required)
[10] Serrano-Dueñas M. Use of primidone in low doses (250 mg/day) versus high doses (750 mg/day) in the management of essential tremor. Double-blind comparative study with one-year follow-up. Parkinsonism Relat Disord. 2003 Oct;10(1):29-33.
[11] Connor GS. A double-blind placebo-controlled trial of topiramate (Mean dose 333mg/d) treatment for essential tremor. Neurology. 2002 Jul 9;59(1):132-4.
[12] Jensen B. RxFiles Benzodiazepine Drug Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-Psyc-Benzodiazepines.pdf
[13] Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, Jankovic J, Karp B, Ludlow CL, Miyasaki JM, Naumann M, So Y; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 May 6;70(19):1699-706.
[14] Bushara KO, Malik T, Exconde RE. The effect of levetiracetam on essential tremor. Neurology. 2005 Mar 22;64(6):1078-80.
[15] Thorpy MJ. New paradigms in the treatment of restless legs syndrome. Neurology. 2005 Jun 28;64(12_suppl_3):S28-S33.
[16] Allen RP, Picchietti D, Hening WA, et al; Restless Legs Syndrome Diagnosis and Epidemiology workshop at the NIH. Sleep Med. 2003 Mar;4:101-19.
[17] Chaudhuri KR, Forbes A, Grosset D, et al.. Diagnosing restless legs syndrome (RLS) in primary care. Curr Med Res Opin. 2004 Nov;20(11):1785-95.
[18] 2004 Restless Legs Syndrome Foundation Bulletin. Accessed June 02, 2005 @ http://www.rls.org/literature/bulletin.html
[19] Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc. 2004 Jul;79(7):916-22.
[20] Micromedix 2009; and Micromedix Drug Consults – Restless Legs Syndrome – Drugs of Choice Dec 2002.
[21] Happe S, Trenkwalder C. Role of dopamine receptor agonists in the treatment of restless legs syndrome. CNS Drugs. 2004;18(1):27-36.
[22] Pharmacists Letter June 2005 – Treatment of Restless Legs Syndrome.
[23] Hening WA, Allen RP, Earley CJ, et al. Restless Legs Syndrome Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep. 2004May 1;27(3):560-83.
[24] Earley CJ. Clinical practice. Restless legs syndrome. N Engl J Med. 2003 May 22;348(21):2103-9.
[25] Manconi M, Govoni V, De Vito A, Economou NT, et al. Restless legs syndrome and pregnancy. Neurology. 2004 Sep 28;63(6):1065-9.
[26] Jensen B. RxFiles Parkinson's Drug Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-Parkinson.pdf (Subscription required.)
[27] Regier L. RxFiles Opioid Drug Chart. http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Opioid.pdf (Subscription required.);
Newsletter: http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-Chronic-NonCa-NEWSLETTER-Header.pdf ;
Opioid Sample Treatment Agreement: http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.doc

TOP

References: Multiple Sclerosis Agents Comparison Chart – www.RxFiles.ca

[1] Micromedex 2011

[2] Calabresi PA. Diagnosis and management of multiple sclerosis. Am Fam Physician. 2004 Nov 15;70(10):1935-44.

[3] Rizvi SA, Agius MA. Current approved options for treating patients with multiple sclerosis. Neurology. 2004 Dec 28;63(12 Suppl 6):S8-14.

[4] Goodin DS, Frohman EM, Garmany GP Jr, et al.; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. 2002 Jan 22;58(2):169-78. (Goodin DS, Frohman EM, Hurwitz B, O'Connor PW, Oger JJ, Reder AT, Stevens JC. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. **2007** Mar 27;68(13):977-84.)
Deisenhammer F. Neutralizing Antibodies to Interferon-beta and other Immunological Treatments for Multiple Sclerosis: Prevalence and Impact on Outcomes. CNS Drugs. 2009;23(5):379-96. doi: 10.2165/00023210-200923050-00003.
Pachner AR, Cadavid D, Wolansky L, Skurnick J. Effect of anti-IFN{beta} antibodies on MRI lesions of MS patients in the BECOME study. Neurology. 2009 Nov 3;73(18):1485-92. PubMed PMID: 19884576. High levels of anti-interferon beta (IFNbeta) antibodies, which result in diminished bioactivity, are correlated with reduced therapeutic efficacy of IFNbeta.
Pachner AR, Warth JD, Pace A, Goelz S; INSIGHT investigators. Effect of neutralizing antibodies on biomarker responses to interferon beta: the INSIGHT study. Neurology. 2009 Nov 3;73(18):1493-500. These data provide evidence that high titers of neutralizing antibodies abolish the in vivo response to interferon beta.
Polman Chris H, Bertolotto A, Deisenhammer F et al; Recommendations for clinical use of data on neutralising antibodies to interferon-beta therapy in multiple sclerosis, The Lancet Neurology, Vol 9, Issue 7, July 2010, P 740-50.

[5] Briggs GG, Freeman RK, Sumner JY. Drugs in **Pregnancy** and Lactation **9th Edition**. Williams & Wilkins, Baltimore, 2011.

[6] Filippi M, Rovaris M, Inglese M, et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet. 2004 Oct 23;364(9444):1489-96.

[7] Andersen O, Elovaara I, Farkkila M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2004 May;75(5):706-10.

[8] **PRISMS** Study Group and the University of British Columbia MS/MRI Analysis Group.. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology. 2001 Jun 26;56(12):1628-36. Erratum in: Neurology 2001 Sep 25;57(6):1146.

[9] Li DK, Zhao GJ, Paty DW; University of British Columbia MS/MRI Analysis Research Group. The **SPECTRIMS** Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: **MRI** results. Neurology. 2001 Jun 12;56(11):1505-13.

[10] Secondary Progressinv Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (**SPECTRIMS**) Study Group.. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: **Clinical** results. Neurology. 2001 Jun 12;56(11):1496-504.

[11] Comi G, Filippi M, Barkhof F, et al.; Early Treatment of Multiple Sclerosis Study Group. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study (**ETOMS**). Lancet. 2001 May 19;357(9268):1576-82.

[12] Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998 Nov 7;352(9139):1498-504. Erratum in: Lancet 1999 Feb 20;353(9153):678.

[13] Medscape Medical News. www.medscape.com/viewarticle/501540. Last acccessed 17 Mar 2005

[14] Clanet M, Kappos L, Hartung HP, Hohlfeld R; European IFNbeta-1a Dose-Comparison Study Investigators. Interferon beta-1a in relapsing multiple sclerosis: four-year extension of the European IFNbeta-1a Dose-Comparison Study. Mult Scler. 2004 Apr;10(2):139-44.

[15] Galetta SL. The controlled high risk Avonex multiple sclerosis trial (**CHAMPS** Study). J Neuroophthalmol. 2001 Dec;21(4):292-5. Erratum in: J Neuroophthalmol 2002 Mar;22(1):67.

[16] **CHAMPS** Study Group. Interferon beta-1a for optic neuritis patients at high risk for multiple sclerosis. Am J Ophthalmol. 2001 Oct;132(4):463-71.

[17] Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. **CHAMPS** Study Group. N Engl J Med. 2000 Sep 28;343(13):898-904.

[18] : Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. Ann Neurol. 1998 Jan;43(1):79-87.

[19] Important Drug Warning. http://www.fda.gov/medwatch/SAFETY/2005/avonex_DHCP.pdf. Last accessed 17 Mar 2005.

[20] Molyneux PD, Barker GJ, Barkhof F, et al.; European Study Group on Interferon Beta-1b in Secondary Progressive MS. Clinical-MRI correlations in a European trial of interferon beta-1b in secondary progressive MS. Neurology. 2001 Dec 26;57(12):2191-7.

[21] Kappos L, Polman C, Pozzilli C, et al.; European Study Group in Interferon beta-1b in Secondary-Progressive MS. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. Neurology. 2001 Dec 11;57(11):1969-75.

[22] Koch-Henriksen N, Sorensen PS. The Danish National Project of interferon-beta treatment in relapsing-remitting multiple sclerosis. The Danish Multiple Sclerosis Group. Mult Scler. 2000 Jun;6(3):172-5.

[23] Miller DH, Molyneux PD, Barker GJ, et al. Effect of interferon-beta1b on magnetic resonance imaging outcomes in secondary progressive multiple sclerosis: results of a European multicenter, randomized, double-blind, placebo-controlled trial. European Study Group on Interferon-beta1b in secondary progressive multiple sclerosis. Ann Neurol. 1999 Dec;46(6):850-9.
Ebers GC, Reder AT, Traboulsee A, et al.; Investigators of the **16-Year Long-Term Follow-Up** Study. Long-term follow-up of the original interferon-beta1b trial in multiple sclerosis: design and lessons from a 16-year observational study. Clin Ther. 2009 Aug;31(8):1724-36.

[24] Filippini G, Munari L, Incorvaia B, et al. Interferons in relapsing remitting multiple sclerosis: a **systematic review. Lancet**. 2003 Feb 15;361(9357):545-52.

[25] MS Therapy Consensus Group J Neurol 2004;251:1329-39

[26] Reess J, Haas J, Gabriel K, Fuhlrott A, Fiola M. Both paracetamol and ibuprofen are equally effective in managing flu-like symptoms in relapsing-remitting multiple sclerosis patients during interferon beta-1a (AVONEX) therapy. Mult Scler. 2002 Feb;8(1):15-8.

[27] Panitch H, Goodin DS, Francis G, et al.; **EVIDENCE** Study Group. Evidence of Interferon Dose-response: European North American Compartative Efficacy; University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002 Nov 26;59(10):1496-506. (Panitch H, Goodin D, Francis G. For the **EVIDENCE** (Evidence of Interferon Dose-response: European North American Comparative Efficacy) Study Group and the University of British Columbia MS/MRI Research Group. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: Final comparative results of the EVIDENCE trial. J Neurol Sci. 2005 Sep 16; [Epub ahead of print])

[28] Durelli L, Verdun E, Barbero P, et al.; Independent Comparison of Interferon (INCOMIN) Trial Study Group. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (**INCOMIN**). Lancet. 2002 Apr 27;359(9316):1453-60.

[29] Leary S, Miller D, Stevenson V, Brex P, Chard D, Thompson A. Interferon Beta 1a in PPMS. Neurology 2003;60:44-51

[30] Johnson KP, Brooks BR, Ford CC, et al. Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial. Mult Scler. 2003 Dec;9(6):585-91.

[31] Wolinsky JS, Comi G, Filippi M, et al. European/Canadian Glatiramer Acetate Study Group. Copaxone's effect on MRI-monitored disease in relapsing MS is reproducible and sustained. Neurology. 2002Oct 22;59(8):1284-6.

[32] Wolinsky JS, Narayana PA, Johnson KP; Multiple Sclerosis Study Group and the MRI Analysis Center. United States open-label glatiramer acetate extension trial for relapsing multiple sclerosis: MRI and clinical correlates. Multiple Sclerosis Study Group and the MRI Analysis Center. Mult Scler. 2001 Feb;7(1):33-41.

[33] Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol. 2001 Mar;49(3):290-7.

[34] Johnson KP, Brooks BR, Ford CC, et al. Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Copolymer 1 Multiple Sclerosis Study Group. Mult Scler. 2000 Aug;6(4):255-66.

[35] Munari L, Lovati R, Boiko A. Therapy with glatiramer acetate for multiple sclerosis. Cochrane Database Syst Rev. 2004;(1):CD004678. (Rovaris M, et al. Effect of glatiramer acetate on MS lesions enhancing at different ga

TOP

doses. Neurology. 2002 Nov 12;59(9):1429-32.) & (Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol. 2001 Mar;49(3):290-7.)

[36] Brenner T, Arnon R, Sela M et al. Humoral and cellular immune responses to Co-polymer 1 in MS patients treated with Copaxone. J Neuroimmunol 2001;115:152-160. (Namaka M, Pollitt-Smith M, Gupta A, et al. The clinical importance of neutralizing antibodies in relapsing-remitting multiple sclerosis. Curr Med Res Opin. 2006 Feb;22(2):223-39.The induction of NAbs in IFN-beta treated patients reduce clinical effect and accelerate disease progression.), (Ure DR, Rodriguez M. Polyreactive antibodies to glatiramer acetate promote myelin repair in murine model of demyelinating disease. FASEB J. 2002 Aug;16(10):1260-2. Epub 2002 Jun 7.) (Goodin DS, Frohman EM, Hurwitz B, O'Connor PW, Oger JJ, Reder AT, Stevens JC. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2007 Mar 27;68(13):977-84.)
van der Voort Laura F.; Gilli Francesca; Bertolotto Antonio; et al. Clinical Effect of Neutralizing Antibodies to Interferon Beta That Persist Long After Cessation of Therapy for Multiple Sclerosis. Arch Neurol. 2010;0(2010):2010.21.

[37] Cohen BA, Khan O, Jeffery DR, Bashir K, et al. Identifying and treating patients with suboptimal responses. Neurology. 2004 Dec 28;63(12 Suppl 6):S33-40.

[38] Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. Neurology. 2004 Dec 28;63(12 Suppl 6):S28-32.

[39] Cohen BA, Jeffery DR. Identification of suboptimal responders to immune modulating agents and the role of mitoxantrone in worsening multiple sclerosis. Neurology. 2004 Dec 28;63(12 Suppl 6):S1-2.

[40] Rizvi SA, Zwibel H, Fox EJ. Mitoxantrone for multiple sclerosis in clinical practice. Neurology. 2004 Dec 28;63(12 Suppl 6):S25-7.

[41] Hartung HP, Gonsette R, Konig N, et al.; Mitoxantrone in Multiple Sclerosis Study Group (**MIMS**). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet. 2002 Dec 21-28;360(9350):2018-25.

[42] van de Wyngaert FA, Beguin C, D'Hooghe MB, et al. A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. Acta Neurol Belg. 2001 Dec;101(4):210-6.

[43] Millefiorini E, Gasperini C, Pozzilli C, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. J Neurol. 1997 Mar;244(3):153-9.

[44] Edan G, Miller D, Clanet M, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatry. 1997 Feb;62(2):112-8.

[45] Bastianello S, Pozzilli C, D'Andrea F, et al. A controlled trial of mitoxantrone in multiple sclerosis: serial MRI evaluation at one year. Can J Neurol Sci. 1994 Aug;21(3):266-70.

[46] Goodin DS, Arnason BG, Coyle PK, et al.; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003 Nov 25;61(10):1332-8.

[47] Scott LJ, Figgitt DP. Mitoxantrone: a review of its use in multiple sclerosis. CNS Drugs. 2004;18(6):379-96.

[48] Fox EJ. Management of worsening multiple sclerosis with mitoxantrone: a review. Clin Ther. 2006 Apr;28(4):461-74.
Le Page E, Leray E, Taurin G, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. J Neurol Neurosurg Psychiatry. 2008 Jan;79(1):52-6.
Le Page E, Leray E, Edan G. Longterm safety profile of mitoxantrone in a French cohort of 802 multiple sclerosis patients: a 5-year prospective study. Mult Scler 2011;17:867-75.

[49] O'Connor PW, Goodman A, Willmer-Hulme AJ, et al.; Natalizumab Multiple Sclerosis Trial Group. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2004 Jun 8;62(11):2038-43.

[50] Miller DH, Khan OA, Sheremata WA, et al.; International Natalizumab Multiple Sclerosis Trial Group. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003 Jan 2;348(1):15-23.

[51] Tubridy N, Behan PO, Capildeo R, et al. The effect of anti-alpha4 integrin antibody on brain lesion activity in MS. The UK Antegren Study Group. Neurology. 1999 Aug 11;53(3):466-72.

[52] FDA Alert for Healthcare Professionals. Natalizuma (marketed as Tysabri) 02/28/2005; http://www.fda.gov/cder/drug/InfoSheets/HCP/natalizumabHCP.pdf. Last accessed 15 Mar 2005.

[53] Polman CH, O'Connor PW, Havrdova E, et al. AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910. (InfoPOEMs: Natalizumab reduces the likelihood of relapse and progression of disability in patients with relapsing multiple sclerosis (RMS). Although no cases of progressive multifocal leukoencephalopathy (PML) were seen in this study, and the drug was well tolerated, a meta-analysis estimates the risk at approximately 1 per 1000 patients treated for 18 months. (LOE = 1b))

[54] Rudick RA, Stuart WH, Calabresi PA, et al. **SENTINEL** Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):911-23. (Ransohoff RM. Natalizumab for multiple sclerosis. N Engl J Med. 2007 Jun 21;356(25):2622-9.)
Pucci E, Giuliani G, Solari A, Simi S, Minozzi S, Di Pietrantonj C, Galea I. **Natalizumab** for relapsing remitting multiple sclerosis. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD007621. DOI: 10.1002/14651858.CD007621.pub2. Although one trial did not contribute to efficacy results due to its duration, we found robust evidence in favour of a reduction in relapses and disability at 2 years in RRMS patients treated with NTZ. The drug was well tolerated. There are current significant safety concerns due to reporting of an increasing number of PML cases in patients treated with NTZ. This review was unable to provide an up-to-date systematic assessment of the risk due to the maximum 2 year-duration of the trials included. An independent systematic review of the safety profile of NTZ is warranted. NTZ should be used only by skilled neurologists in MS centres under surveillance programs.

[55] Kleinschmidt-Demasters BK, Tyler KL. Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis. N Engl J Med. 2005 Jun 9; [Epub ahead of print]
(Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006 Mar 2;354(9):924-33.) (May 3, 2007 - Biogen Idec (NASDAQ: BIIB) and Elan Corporation, plc (NYSE: ELN) announced today that new data from the TOUCH Prescribing Programä and TYGRIS safety study confirm the safety profile from previous clinical studies of TYSABRI® (natalizumab). Also presented at the 59th annual meeting of the American Academy of Neurology in Boston, MA were extension study data that showed that TYSABRI has a sustained treatment effect on clinical relapses and the risk of disability progression in multiple sclerosis (MS) patients treated for up to three years. The companies recently reported that as of mid-April 2007 approximately 12,500 patients have been prescribed TYSABRI worldwide. The companies estimate that in both commercial use and clinical trials, there are currently over 10,000 patients on TYSABRI therapy worldwide. No New PML Cases 10 Months After Tysabri Allowed Back on Market. The drug is currently being used by more than 10,00 patients worldwide -- including roughly 6600 in the U.S. -- the manufacturer said.) July 31/08 Biogen, Elan Report Brain Infections in Patients Shares of Biogen Idec Inc. and Elan Corp. fell sharply in late trading Thursday, after the companies said their multiple sclerosis drug Tysabri has been linked to **two new cases** of a rare and often fatal brain inflammation.
Goodin DS, Cohen BA, O'Connor P, Kappos L, Stevens JC; Therapeutics and Technology Assessment Subcommittee of the **American Academy of Neurology**. Assessment: the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 Sep 2;71(10):766-73. The **PML** risk in a pooled clinical trial cohort has been estimated to be 1 person for every 1,000 patients treated for an average of 17.9 months, although this figure could change in either direction with more experience with the drug.
December 17, 2008 — Biogen Idec and Élan reported to the United States Securities and Exchange Commission (SEC) that "relevant regulatory agencies" had been informed of another case of progressive multifocal leukoencephalopathy (PML) with natalizumab (Tysabri) monotherapy in a patient with multiple sclerosis (MS). The case was found through surveillance, the companies note, and the patient is stable. The male patient is from Germany and had been on natalizumab monotherapy for 26 months. He is reported to be stable and under the care of his physician. The companies released information on their December 11 Form 8-K report to the SEC December 15.
Health Canada Feb/09 New Safety Information Regarding Progressive Multifocal Leukoencephalopathy (PML) Associated with Tysabri (natalizumab) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-_avis/prof/_2009/tysabri_2_hpc-cps-eng.php
Biogen http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9ODc0MXxDaGlsZElEPS0xfFR5cGU9Mw==&t=1
Chen, Yiping, Bord, Evelyn, Tompkins, Troy, et al. Asymptomatic Reactivation of **JC Virus** in Patients Treated with Natalizumab. N Engl J Med 2009 361: 1067-1074.
Wenning, Werner, Haghikia, Aiden, Laubenberger, Jorg, et al. **Treatment of Progressive Multifocal Leukoencephalopathy** Associated with Natalizumab. N Engl J Med 2009 361: 1075-1080.
Linda, Hans, von Heijne, Anders, Major, Eugene O., et al. **Progressive Multifocal Leukoencephalopathy** after **Natalizumab Monotherapy**. N Engl J Med 2009 361: 1081-1087.
Major, Eugene O.Reemergence of PML in Natalizumab-Treated Patients -- New Cases (=14), Same Concerns. N Engl J Med 2009 361: 1041-1043.
FDA Sep/09 documents 13 PML cases http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107198.htm
October 27, 2009 — The European Medicines Agency (EMEA) disclosed October 23 that it has begun a review of the risk–benefit balance for use of natalizumab (*Tysabri*, Biogen Idec/Elan) in relapsing-remitting multiple sclerosis in light of new cases of progressive multifocal leukoencephalopathy (PML) with treatment. The EMEA notes it started a review of the benefits and risks of natalizumab because reports of PML cases worldwide have climbed now to 23 since the drug was reinstated in the market in 2006. "This review is initiated to discuss any additional measures necessary to ensure the safe use of Tysabri and how to balance the risks to the patients against the benefits of the treatment," a press release from EMEA notes. The release was a round-up of EMEA activities as of October 2009. Natalizumab was taken off the market in February 2005 after the first 3 cases of PML were reported. On September 23, 2009, th

Drug Administration (FDA) reported that the count for confirmed cases of PML worldwide in patients treated with natalizumab as monotherapy had reached 13. They have now confirmed the new total case count at 23.
Jan 21,2010 (Dow Jones)--As of Wednesday, there have been 31 cases of a rare brain infection in multiple sclerosis patients on Tysabri, sold by Biogen Idec Inc. (BIIB) and Elan Corp. (ELN), according to a review by a European regulatory panel. The European Medicines Agency's Committee for Medicinal Products for Human Use, known as CHMP, reported the cases of progressive multifocal leukoencephalopathy, or PML, in a review of the drug that concluded its rewards outweigh its risks and the drug should stay on the market. Of the **31 cases**, 23 of the patients were on the drug for more than two years, which puts the infection rate at about 1 in 1,000 patients for those exceeding that duration. This assertion is the same held by the company and implied by the drug's label.
FDA Feb/10 notified healthcare professionals and patients that the risk of developing progressive multifocal leukoencephalopathy (PML) increases with the number of Tysabri infusions received. This new safety information, based on reports of 31 confirmed cases of PML received by the FDA as of January 21, 2010, will now be included in the Tysabri drug label and patient *Medication Guide*.
March 18, 2010 9:22 AM EDT Biogen Idec (Nasdaq: BIIB) disclosed that the number of PML cases involving those taking its Tysabri drug has increased to 42 patients with 9 who have died.
May/10 Biogen Idec Canada Inc., has updated the Tysabri product information with new information on Progressive Multifocal Leukoencephalopathy (PML). The risk of PML increases with increasing duration of treatment with Tysabri. After 24 infusions, physicians are to review with their patients, the benefits and risk of continuing Tysabri treatment.
Schröder A, Lee DH, Hellwig K, Lukas C, Linker RA, Gold R. **Successful Management of Natalizumab**-Associated Progressive Multifocal Leukoencephalopathy and Immune Reconstitution Syndrome in a Patient With Multiple Sclerosis. Arch Neurol. 2010 Jul 12.
Oct 22/10 - Two more patients taking Biogen Idec Inc's multiple sclerosis drug Tysabri (natalizumab) have developed progressive multifocal leukoencephalopathy (PML), the company said on Wednesday. The Cambridge, Massachusetts-based biotechnology company said in its latest monthly update that as of Oct. 1, there have been **70 confirmed cases of PML**, up from 68 as of Sept. 2. Of those, 14 have died and 56 are alive with varying degrees of disability ranging from mild to severe. There were no additional deaths in October. As of June 30, about 71,400 patients had received Tysabri since it was launched.
Vermersch P, Kappos L, Gold R, et al. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. Neurology. 2011 May 17;76(20):1697-704.
FDA Jan/12 JC virus is common and usually harmless, the agency said, but its presence — along with either of the other two PML risk factors — can be dangerous in patients taking immunomodulating drugs like natalizumab. The other risk factors are treatment with natalizumab for longer than 2 years, and previous treatment with immunosuppressant drugs such as methotrexate or cyclophosphamide. The FDA estimates that patients with all three risk factors face about a 1% risk for PML (11 cases per 1000 patients treated).
Bloomgren G, Richman S, Hotermans C, et al. **Risk** of natalizumab-associated **progressive multifocal leukoencephalopathy**. N Engl J Med 2012;366:1870-80.

[56] Pozzilli C, Antonini G, Bagnato F, et al. Monthly corticosteroids decrease neutralizing antibodies to IFNbeta1 b: a randomized trial in multiple sclerosis. J Neurol. 2002 Jan;249(1):50-6.
[57] Rio J, Nos C, Marzo ME, Tintore M, Montalban X. Low-dose steroids reduce flu-like symptoms at the initiation of IFNbeta-1b in relapsing-remitting MS. Neurology. 1998 Jun;50(6):1910-2.
[58] Visser LH, Beekman R, Tijssen CC, et al. A randomized, double-blind, placebo-controlled pilot study of i.v. immune globulins in combination with i.v. methylprednisolone in the treatment of relapses in patients with MS. Mult Scler. 2004 Feb;10(1):89-91.
[59] Craig J, Young CA, Ennis M, et al. A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. J Neurol Neurosurg Psychiatry. 2003 Sep;74(9):1225-30.
[60] Beck RW, Trobe JD, Moke PS, et al. Optic Neuritis Study Group. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. Arch Ophthalmol. 2003 Jul;121(7):944-9.
[61] van de Wyngaert FA, Beguin C, D'Hooghe MB, et al. A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. Acta Neurol Belg. 2001 Dec;101(4):210-6.
[62] Edan G, Miller D, Clanet M, et al.. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatry. 1997 Feb;62(2):112-8.
[63] Cazzato G, Mesiano T, Antonello R, et al. Double-blind, placebo-controlled, randomized, crossover trial of high-dose methylprednisolone in patients with chronic progressive form of multiple sclerosis. Eur Neurol. 1995;35(4):193-8.
[64] Beck RW, Cleary PA, Anderson MM Jr, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med. 1992 Feb 27;326(9):581-8.
[65] Filippini G, Brusaferri F, Sibley WA, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database Syst Rev. 2000;(4):CD001331.
Martinelli V, Rocca MA, Annovazzi P, et al. A short-term randomized MRI study of high-dose **oral** vs intravenous methylprednisolone in MS. Neurology. 2009 Dec 1;73(22):1842-8.
[66] Sharrack B, Hughes RA, Morris RW, et al. The effect of oral and intravenous methylprednisolone treatment on subsequent relapse rate in multiple sclerosis. J Neurol Sci. 2000 Feb 1;173(1):73-7.
[67] Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J. [Randomized controlled trial of high-dose peroral methylprednisolone in attacks of multiple sclerosis] Ugeskr Laeger. 1999 Nov 29;161(48):6625-9.
[68] Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J. Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. Neurology. 1998 Aug;51(2):529-34.
[69] Barnes D, Hughes RA, Morris RW, et al. Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. Lancet. 1997 Mar 29;349(9056):902-6.
[70] Filipini G, Brusaferri F, Sibley WA et al. Corticosteroids or ACTH for acute exacerbations in MS. Cochrane DataBase Syst Rev 2000;CD001331.
[71] Wenning GK, Wietholter H, Schnauder G et al. Recovery of the HTPA axis from suppression by short-term, high dose IV prednisolone therapy in patients with MS. Acta Neurol Scand 1994;89:270-273.
[72] Morrow SA, Stoian CA, Dmitrovic J, Chan SC, Metz LM. The bioavailability of IV methylprednisolone and oral prednisone in multiple sclerosis. Neurology. 2004 Sep 28;63(6):1079-80.
[73] Rizvi SA, Bashir K. Other therapy options and future strategies for treating patients with multiple sclerosis. Neurology. 2004 Dec 28;63(12 Suppl 6):S47-54.
[74] Patti F, Amato MP, Filippi M, et al. A double blind, placebo-controlled, phase II, add-on study of cyclophosphamide (CTX) for 24 months in patients affected by multiple sclerosis on a background therapy with interferon-beta study denomination: CYCLIN. J Neurol Sci. 2004 Aug 15;223(1):69-71.
La Mantia L, Milanese C, Mascoli N, et al. Cyclophosphamide for multiple sclerosis. Cochrane Database Syst Rev. 2002;(4):CD002819.
Patti F, Reggio E, Palermo F, et al. A. Stabilization of rapidly worsening multiple sclerosis for 36 months in patients treated with interferon beta plus cyclophosphamide followed by interferon beta. J Neurol. 2004 Dec;251(12):1502-6.
Jeffery DR. The argument against the use of cyclophosphamide and mitoxantrone in the treatment of multiple sclerosis. J Neurol Sci. 2004 Aug 15;223(1):41-6.
Krishnan C, Kaplin AI, Brodsky RA, et al. Reduction of Disease Activity and Disability With High-Dose Cyclophosphamide in Patients With Aggressive Multiple Sclerosis. Arch Neurol. 2008 Jun 9. [Epub ahead of print] Treatment with HiCy (50 mg/kg/d for 4 consecutive days) was safe and well tolerated in our patients with MS. Patients experienced (n=9) a pronounced reduction in disease activity and disability after HiCy treatment. This immunoablative regimen of cyclophosphamide for patients with aggressive MS is worthy of further study and may be an alternative to bone marrow transplantation.
Makhani N, Gorman MP, Branson HM, et al. **Cyclophosphamide** therapy in pediatric multiple sclerosis. Neurology. 2009 May 13. Cyclophosphamide is an option for the treatment of children with aggressive multiple sclerosis refractory to first-line therapies. Recommendations regarding patient selection, treatment administration, and monitoring are discussed.
[75] Casetta I ; Iuliano G ; Filippini G. **Azathioprine** for multiple sclerosis. **Cochrane** Database Syst Rev. 2007; (4):CD003982 (ISSN: 1469-493X) {Azathioprine is an appropriate maintenance treatment for patients with multiple sclerosis who frequently relapse and require steroids. Cumulative doses of 600 g should not be exceeded in relation to a possible increased risk of malignancy. Considering the trade off between the benefits and harms, azathioprine is a fair alternative to interferon beta for treating multiple sclerosis. A logical next step for future trials would seem the direct comparison of azathioprine and interferon beta. In fact the direct comparison between these two widely used treatments in multiple sclerosis has not been made.}
[76] Giovannoni G, Comi G, Cook S, et al. the **CLARITY** Study Group, A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. N Engl J Med 2010 0: NEJMoa0902533. (n=1326, 96 weeks, 3.5 or 5.25mg/kg)
For cladribine versus placebo, the relative risk reduction in the annualized relapse rate was 57.6% for the group receiving 3.5 mg per kilogram of body weight and 54.5% for those receiving 5.25 mg per kilogram. Adverse effects were similar in all three trials of cladribine and fingolimod, and rates of events leading to discontinuation of a study drug were low but still at least twice as frequent with high-dose cladribine (7.9% for the 5.25-mg dose) and fingolimod (10% and 14% for the 1.25-mg dose). Side effects: herpetic infections, ?cancer & lymphocytopenia.
Giovannoni G, Cook S, Rammohan K, et al; on behalf of the **CLARITY** study group. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with **cladribine** tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol. 2011 Mar 10.
June 22/11, Merck Serono announced that, in light of feedback from regulatory authorities, the company would **no longer pursue a global approval process for cladribine tablets (Movectro)** for the treatment of relapsing-remitting MS & indeed would withdraw the drug from Australia and Russia, where it already had achieved approval.
[77] Gray O, McDonnell GV, Forbes RB. Intravenous immunoglobulins for multiple sclerosis. Cochrane Database Syst Rev. 2003;(4):CD002936.

TOP

Dudesek A and Zettl U. Intravenous immunoglobulins as therapeutic option in the treatment of MS. J Neurol 2006; 253 (suppl 5):v50-58.
Schwarz S, Meinck HM, Storch-Hagenlocher B. [Intravenous immunoglobulins in multiple sclerosis. An update]. Nervenarzt. 2009 Aug;80(8):918-28. German.
[78] Gray O, McDonnell GV, Forbes RB. Methotrexate for multiple sclerosis. Cochrane Database Syst Rev. 2004;(2):CD003208.
[79] Keegan M, Konig F, McClelland R et al. Relation between humoral pathological changes in multiple sclerosis and response to therapeutic plasma exchange. Lancet. 2005 Aug 13-19;366(9485):579-82.
[80] Muraro PA, Bielekova B. Emerging therapies for multiple sclerosis. Neurotherapeutics. 2007 Oct;4(4):676-92.
Hauser SL, Waubant E, Arnold DL, et al. HERMES Trial Group. B-cell depletion with **rituximab** in relapsing-remitting multiple sclerosis. N Engl J Med. 2008 Feb 14;358(7):676-88. A single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks.
Hawker K, O'Connor P, Freedman MS, et al. OLYMPUS trial group. Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009 Oct;66(4):460-71.
Naismith RT, Piccio L, Lyons JA, et al. **Rituximab** add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. Neurology. 2010 Jun 8;74(23):1860-7.
[81] O'Connor Paul, Wolinsky Jerry S., Confavreux Christian. Randomized Trial of Oral **Teriflunomide** for Relapsing Multiple Sclerosis (**TEMSO**). N Engl J Med 2011;365:1293-303.
[82] Cohen, JA., Barkhof F, Comi G, et al., **TRANSFORMS** Study, Oral **Fingolimod** or Intramuscular Interferon for Relapsing Multiple Sclerosis. N Engl J Med 2010 0: NEJMoa0907839 (n=1292, 1yr, 1.25 or 0.5mg po od vs 30ug IM/wk)
Kappos L, Radue EW, O'Connor P et al. **FREEDOMS** Study, A Placebo-Controlled Trial of Oral **Fingolimod** in Relapsing Multiple Sclerosis. N Engl J Med 2010 0: NEJMoa0909494.. (n=1272, 2yr, 1.25 or 0.5mg po od vs placebo)
For fingolimod versus placebo, the relative risk reduction was 54% for the 0.5-mg dose and 60% for the 1.25-mg dose. For fingolimod versus interferon beta-1a, the relative risk reduction was 52% for the 0.5-mg dose and 39% for the 1.25-mg dose. Adverse effects were similar in all three trials of cladribine and fingolimod, and rates of events leading to discontinuation of a study drug were low but still at least twice as frequent with high-dose cladribine (7.9% for the 5.25-mg dose) and fingolimod (10% and 14% for the 1.25-mg dose). Side effects: herpetic infections, ?cancer, macular edema, bradycardia & lymphocytopenia.
Medical Letter. Oral Fingolimod (Gilenya) for Multiple Sclerosis. Dec 13/27, 2010.
Khatri B, Barkhof F, Comi G, et al; Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised **extension of the TRANSFORMS** study. Lancet Neurol. 2011 May 13.
Pelletier Daniel, Hafler David A. **Fingolimod** for Multiple Sclerosis. N Engl J Med 2012; 366:339-347.
Jain N, Bhatti MT. Fingolimod-associated **macular edema**: Incidence, detection, and management. Neurology. 2012 Feb 28;78(9):672-80.
[83] Frohman EM, Goodin DS, Calabresi PA, et al.; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003 Sep 9;61(5):602-11. (Whiting P, et al. Accuracy of magnetic resonance imaging for the diagnosis of multiple sclerosis: systematic review. BMJ. 2006 Mar 24; [Epub ahead of print] (InfoPOEMs: Magnetic resonance imaging (MRI) is not particularly useful in either ruling in or ruling out multiple sclerosis (MS). Relying on it to make the diagnosis will result in overdiagnosis of patients, and using it to rule out MS will cause you to miss approximately half the patients who will eventually be given a clinical diagnosis. (LOE = 1a))
Thompson Alan J, Toosy Ahmed T, Ciccarelli Olga, Pharmacological management of **symptoms in multiple sclerosis**: current approaches and future directions, The Lancet Neurology, Volume 9,Issue 12, Dec 2010, Pages 1182-1199.
Polman C, Reingold S, Banwell B, et al. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the "McDonald Criteria."Annals of Neurology.2011 Jan 11; 3-76.
[84] Crayton H, Heyman RA, Rossman HS. A multimodal approach to managing the symptoms of multiple sclerosis. Neurology. 2004 Dec 14;63(11 Suppl 5):S12-8.
[85]Taus C, Giuliani G, Pucci E, D'Amico R, Solari A. Amantadine for fatigue in multiple sclerosis. Cochrane Database Syst Rev. 2003;(2):CD002818. (Pucci E, Branas P, D'Amico R, Giuliani G, Solari A, Taus C. Amantadine for fatigue in multiple sclerosis. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD002818. The efficacy of amantadine in reducing fatigue in people with MS is poorly documented, as well as its tolerability.)
[86] Stankoff B, Waubant E, Confavreux C, et al.; French Modafinil Study Group. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology. 2005 Apr 12;64(7):1139-43.
Brousil JA, Roberts RJ, Schlein AL. Cladribine: an investigational immunomodulatory agent for multiple sclerosis. Ann Pharmacother. 2006 Oct;40(10):1814-21. Epub 2006 Sep 19.
[87] Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database Syst Rev. 2003;(4):CD001332. (Gallien P, Reymann JM, Amarenco G, Nicolas B, de Seze M, Bellissant E. Placebo controlled, randomised, double blind study of the effects of botulinum A toxin on detrusor sphincter dyssynergia in multiple sclerosis patients. J Neurol Neurosurg Psychiatry. 2005 Dec;76(12):1670-6.)
[88] Goodman AD, Brown TR, Edwards KR, et al. MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol. 2010 Oct;68(4):494-502.
[89] Bennett M, Heard R. Hyperbaric oxygen therapy for multiple sclerosis. Cochrane Database Syst Rev. 2004;(1):CD003057.
[90] Krupp LB, Christodoulou C, Melville P, Scherl WF, MacAllister WS, Elkins LE. Donepezil improved memory in multiple sclerosis in a randomized clinical trial. Neurology. 2004 Nov 9;63(9):1579-85.
[91] Brown SJ. The Role of Vitamin D in Multiple Sclerosis (June). Ann Pharmacother. 2006 May 9; [Epub ahead of print]
Munger KL, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006 Dec 20;296(23):2832-8.
Ascherio A, Munger KL, Simon KC. Vitamin D and multiple sclerosis. Lancet Neurol. 2010 Jun;9(6):599-612.
Bentzen J, Flachs EM, Stenager E, Brønnum-Hansen H, Koch-Henriksen N. Prevalence of multiple sclerosis in Denmark 1950-2005. Mult Scler. 2010 Mar 9.
Stein MS, Liu Y, Gray OM, et al. A randomized trial of high-dose **vitamin D2** in relapsing-remitting multiple sclerosis. Neurology 2011;77:1611–1618.
[92] Steultjens EM, Dekker J, Bouter LM, et al. Occupational therapy for multiple sclerosis. Cochrane Database Syst Rev. 2003;(3):CD003608.

Additional references:

Abbas M, Lalive PH, Chofflon M, Simon HU, Chizzolini C, Ribi C. **Hypereosinophilia** in patients with multiple sclerosis treated with **natalizumab**. Neurology. 2011 Oct 18;77(16):1561-4.
Ascherio A, Munger KL, Simon KC. **Vitamin D** and multiple sclerosis. Lancet Neurol. 2010 Jun;9(6):599-612.
Axtell RC, de Jong BA, Boniface K, et al. **T helper type 1 and 17 cells** determine effi cacy of interferon-beta in multiple sclerosis and experimental encephalomyelitis. Nat Med 2010; 16: 406–12.
Bagert BA, Marder E, Stüve O. Chronic Cerebrospinal Venous Insufficiency (**CCSVI**) and Multiple Sclerosis. Arch Neurol. 2011 Jul 11.
Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in **children**: clinical diagnosis, therapeutic strategies, and future directions. Lancet Neurol. 2007 Oct;6(10):887-902.
Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in **children with acute demyelination**: a prospective national cohort study. Lancet Neurol. 2011 Mar 31.
Baracchini C, Perini P, Calabrese M, et al. No evidence of chronic cerebrospinal venous insufficiency (**CCSVI**) at multiple sclerosis onset. Ann Neurol. 2011 Jan;69(1):90-9. doi: 10.1002/ana.22228.
Baracchini C, Perini P, Calabrese M, et al. Normal Cerebrospinal Venous Drainage (**CCSVI**) in MS at Onset. Ann Neurol. 2011 March 7.
Baracchini C, Perini P, Causin F, et al. Progressive multiple sclerosis is not associated with chronic cerebrospinal venous insufficiency (**CCSVI**). Neurology. 2011 Aug 17.
Bazelier MT, van Staa T-P, Uitdehaag BMJ, et al. Risk of **fractures** in patients with multiple sclerosis: a population based cohort study. Neurology 2012;78:1967–1973.
Bejaoui K, Rolak LA. What is the **risk of permanent disability** from a multiple sclerosis relapse? Neurology. 2010 Mar 16;74(11):900-2.
Bermel R, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick R. Intramuscular **interferon beta-1a** therapy in patients with relapsing-remitting multiple sclerosis: a **15-year follow-up** study. Mult Scler. 2010 Feb 18.
Bermel Robert A, Cohen Jeffrey A, Multiple sclerosis: advances in understanding pathogenesis and emergence of **oral treatment** options, The Lancet Neurology, Volume 10, Issue 1, January 2011, Pages 4-5, ISSN 1474-4422, DOI: 10.1016/S1474-4422(10)70282-9.

TOP

Bielekova B, Becker BL. **Monoclonal antibodies** in MS: mechanisms of action. Neurology. 2010 Jan 5;74 Suppl 1:S31-40.
Bielekova B, Richert N, Herman ML, et al. Intrathecal effects of **daclizumab** treatment of multiple sclerosis. Neurology 2011;77:1877–1886.
Birnbaum G, Cree B, Altafullah I, Zinser M, Reder AT. Combining beta interferon and **atorvastatin may increase disease** activity in multiple sclerosis. Neurology. 2008 Jun 4. [Epub ahead of print]
Bourre B, Marignier R, Zéphir H, et al. **Neuromyelitis optica and pregnancy**. Neurology 2012;78:875– 879.
Brioschi A, Gramigna S, et al. Effect of Modafinil on Subjective Fatigue in Multiple Sclerosis and Stroke Patients. Eur Neurol. 2009 Aug 7;62(4):243-249. [Epub ahead of print]
Brousil JA, Roberts RJ, Schlein AL. Cladribine: an investigational immunomodulatory agent for multiple sclerosis. Ann Pharmacother. 2006 Oct;40(10):1814-21. Epub 2006 Sep 19.
Buck D, Cepok S, Hoffmann S, et al. Influence of the **HLA-DRB1 Genotype on Antibody Development to Interferon Beta** in Multiple Sclerosis. Arch Neurol. 2011 Apr;68(4):480-7.
Calabresi PA, Giovannoni G, Confavreux C, et al.for the AFFIRM and SENTINEL Investigators. The incidence and significance of **anti-natalizumab antibodies**. Results from AFFIRM and SENTINEL. Neurology. 2007 Aug 29; [Epub ahead of print] The incidence of persistent antibody positivity associated with natalizumab is 6%. Reduced clinical efficacy is apparent in persistently positive patients. Patients with a suboptimal clinical response or persistent infusion-related adverse events should be considered for antibody testing.
Calabrese M, Rinaldi F, Mattisi I, et al. The predictive value of **gray matter** atrophy in clinically isolated syndromes. Neurology. 2011 Jul 19;77(3):257-63.
Caloyeras JP, Zhang B, et al. **Cost-Effectiveness Analysis of Interferon Beta-1b** for the Treatment of Patients With a First Clinical Event Suggestive of Multiple Sclerosis. Clin Ther. 2012 Apr 26.
CAMMS223 Trial Investigators, Coles AJ, Compston DA, et al. **Alemtuzumab** vs. Interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008 Oct 23;359(17):1786-801. In patients with early, relapsing-remitting multiple sclerosis, alemtuzumab was more effective than interferon beta-1a but was associated with autoimmunity, most seriously manifesting as immune thrombocytopenic purpura. The study was not powered to identify uncommon adverse events.
Carrá A, Onaha P, Luetic G, et al. Therapeutic outcome 3 years after **switching of immunomodulatory** therapies in patients with relapsing-remitting multiple sclerosis in Argentina. Eur J Neurol. 2008 Apr;15(4):386-93. In conclusion, patients who fail first-line immunomodulatory therapy generally benefit from switching to another class of immunomodulatory therapy.
Castela E, Lebrun-Frenay C, Laffon M, et al. Evolution of **Nevi** During Treatment With **Natalizumab**: A Prospective Follow-up of Patients Treated With Natalizumab for Multiple Sclerosis. Arch Dermatol. 2010 Sep 20.
Castrop F, Kowarik MC, Albrecht H, et al. Severe **multiple sclerosis relapse under fingolimod** therapy: Incident or coincidence? Neurology. 2012 Mar 20;78(12):928-30.
Chard DT, Geurts JJ. Predicting the development of multiple sclerosis: Is **gray matter** a missing piece of the puzzle? Neurology. 2011 Jul 19;77(3):210-1.
Chilcott J, McCabe C, Tappenden P, et al. Cost Effectiveness of Multiple Sclerosis Therapies Study Group. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. Commentary: evaluating disease modifying treatments in multiple sclerosis. BMJ. 2003 Mar 8;326(7388):522; discussion 522.
Ciccone A, Beretta S, Brusaferri F, et al. **Corticosteroids** for the long-term treatment in multiple sclerosis. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006264. There is no enough evidence that long-term corticosteroid treatment delays progression of long term disability in patients with MS. Since one study at high risk of bias showed that the administration of pulsed high dose i. v. MP is associated with a significant reduction in the risk of long term disability progression in patients with RR MS, an adequately powered, a quality RCT is needed to investigate this finding.
Clerico M, Faggiano F, Palace J, Rice G, Tintorè M, Durelli L. Recombinant **interferon beta** or glatiramer acetate for delaying conversion of the **first demyelinating event to multiple sclerosis**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005278. The efficacy of IFN beta treatment on preventing the conversion from CIS to CDMS was confirmed over two years of follow-up. Since patients had some clinical heterogeneity (length of follow-up, clinical findings of initial attack), it could be useful for the clinical practice to further analyse the efficacy of IFN beta treatment in different patient subgroups.
Clifford DB. Lessons from the clinic: A case of **natalizumab-associated PML**. Neurology. 2011 Feb 8;76(6):574.
Cohen JA, Imrey PB, Calabresi PA, et al.; **ACT** Investigators. Results of the Avonex Combination Trial (ACT) in relapsing-remitting MS. Neurology. 2009 Feb 10;72(6):535-41. This trial did not demonstrate benefit of adding low-dose oral methotrexate or every other month IV methylprednisolone to interferon beta-1a in relapsing-remitting multiple sclerosis.
Cohen, JA., Barkhof F, Comi G, et al., **TRANSFORMS** Study Group, Oral **Fingolimod** or Intramuscular **Interferon** for Relapsing Multiple Sclerosis. N Engl J Med 2010 0: NEJMoa0907839
Cohen JA, Chun J. Mechanisms of **Fingolimod's** Efficacy and Adverse Effects in Multiple Sclerosis. Annals of Neurology. Accepted manuscript online: 21 MAR 2011: 1-59.
Coles A. The fragile benefit of BENEFIT [editorial]. Lancet Neurol. 2007;6:753-4.
Coles AJ, Fox E, Vladic A, et al. **Alemtuzumab versus interferon beta-1a** in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. **CAMMS223**. Lancet Neurol. 2011 Mar 10.
Coles AJ, Fox E, Vladic A, et al. **Alemtuzumab more effective than interferon β-1a** at 5-year follow-up of **CAMMS223** Clinical Trial. Neurology. 2012 Apr 3;78(14):1069-78.
Comabella M. Risk of multiple sclerosis in **children with acute demyelination**. Lancet Neurol. 2011 Mar 31.
Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol 2001;49:290-7.
Comi G, Filippi M, Barkhof F, et al. Effect of **early interferon treatment** on conversion to definite multiple sclerosis: a randomised study. Lancet. 2001;357:1576−82.
Comi G, Martinelli V, Rodegher M, et al. for the PreCISe study group. Effect of glatiramer acetate on conversion to **clinically definite** multiple sclerosis in patients with clinically isolated syndrome (**PreCISe study**): a randomised, double-blind, placebo-controlled trial. Lancet. 2009 Oct 6. [Epub ahead of print]
Comi G, De Stefano N, Freedman M, et al. Comparison of **two dosing frequencies of subcutaneous interferon beta-1a** in patients with a first clinical demyelinating event suggestive of multiple sclerosis (**REFLEX**): a phase 3 randomised controlled trial. Lancet Neurol 2011; published online Dec 5. (Rebif 44ug sc three times a week or once a week x 2 years)
Comi G et al. Placebo-controlled trial of oral **laquinimod** for multiple sclerosis. (**ALLEGRO**) N Engl J Med 2012 Mar 15; 366:1000. (n=1106, 2yrs, ↑ALT 5 vs 2%)
Confavreux C, Vukusic S, Moreau T, Adeleine P. **Relapses and progression of disability** in multiple sclerosis. N Engl J Med. 2000 Nov 16;343(20):1430-8.
Connick P, Kolappan M, Crawley C, et al. **Autologous mesenchymal stem cells** for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol 2012
Conway D, Cohen JA. **Combination therapy** in multiple sclerosis. Lancet Neurol. 2010 Mar;9(3):299-308.
Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ. 2012 May 14.
Cossburn M, Pace AA, Jones J, et al. Autoimmune disease after **alemtuzumab** treatment for multiple sclerosis in a multicenter cohort. Neurology. 2011 Aug 9;77(6):573-9.

TOP

Coyle PK. **Pediatric multiple sclerosis**: just like their elders? Arch Neurol. 2011 Apr;68(4):419-21.
Cree BA, Stuart WH, Tornatore CS, et al. Efficacy of **Natalizumab** Therapy in Patients of **African Descent** With Relapsing Multiple Sclerosis: Analysis of AFFIRM and SENTINEL Data. Arch Neurol. 2011 Apr;68(4):464-8.
Deisenhammer F. **Neutralizing Antibodies** to Interferon-beta and other Immunological Treatments for Multiple Sclerosis: Prevalence and Impact on Outcomes. CNS Drugs. 2009;23(5):379-96. doi: 10.2165/00023210-200923050-00003.
DeLorenze GN, et al. Epstein-Barr virus and multiple sclerosis: evidence of association from a prospective study with long-term follow-up. Arch Neurol. 2006 Jun;63(6):839-44.
Devonshire V, Havrdova E, Radu EW, et al. **Relapse and disability** outcomes in patients with multiple sclerosis treated with **fingolimod**: subgroup analyses of the double-blind, randomised, placebo-controlled **FREEDOMS** study. Lancet Neurol 2012
D'haeseleer Miguel, Cambron Melissa, Vanopdenbosch Ludo, et al. **Vascular aspects** of multiple sclerosis. The Lancet Neurology 1 July 2011 (Volume 10 Issue 7 Pages 657-666.
Doepp F, Würfel JT, Pfueller CF, et al. **Venous drainage** in multiple sclerosis: A combined MRI and ultrasound study. Neurology. 2011 Nov 8;77(19):1745-51.
EMA Jan/12 European and U.S. regulators are reviewing Novartis AG's (NOVN) **Gilenya** pill for multiple sclerosis after reports of **11 deaths** among patients who took the drug.
Farez MF, Correale J. Yellow Fever Vaccination and Increased Relapse Rate in Travelers With Multiple Sclerosis. Arch Neurol. 2011 Jun 13.
Fassas A et al. Long-term results of **stem cell transplantation** for MS: A single-center experience. Neurology 2011 Mar 22; 76:1066.
Fazekas F, et al. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. Austrian Immunoglobulin in Multiple Sclerosis Study Group. Lancet. 1997 Mar 1;349(9052):589-93.
FDA Dec/11 has received a report of a patient with multiple sclerosis (MS) who **died** within 24 hours of taking the first dose of **Gilenya (fingolimod).** At this time, FDA cannot conclude whether the drug resulted in the patient's death.
FDA May/12 warned clinicians on Thursday that "**liberation therapy**," an experimental procedure that uses angioplasty balloons or stents to open narrowed veins in the chest and neck, has not been approved to treat chronic cerebrospinal venous insufficiency (**CCSVI**) and could be dangerous. Liberation therapy has been associated with one death due to a brain hemorrhage and one stroke, says the FDA. Other possible risks include blood clots, cranial nerve damage, and migrating stents.
Filippi M, Wolinsky JS, Comi G; CORAL Study Group. Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing multiple sclerosis: a multicentre, double-blind, randomised, placebo-controlled study. Lancet Neurol. 2006 Mar;5(3):213-20. Erratum in: Lancet Neurol. 2006 May;5(5):383.
Filippi M, Rocca MA, Camesasca F, et al. **Interferon {beta}-1b and glatiramer** acetate effects on permanent **black hole evolution**. Neurology. 2011 Apr 5;76(14):1222-8.
Filippi M, Rocca MA, Barkhof W et al. Association between **pathological and MRI findings** in multiple sclerosis. Lancet Neurol. 2012 Apr;11(4):349-360.
Fox RJ, Rae-Grant A. Chronic cerebrospinal venous insufficiency (**CCSVI**): Have we found the cause and cure of MS? Neurology. 2011 Jul 12;77(2):98-100.
Fragoso YD, Finkelsztejn A, Kaimen-Maciel DR, et al. Long-Term Use of **Glatiramer Acetate by 11 Pregnant** Women with Multiple Sclerosis: A Retrospective, Multicentre Case Series. CNS Drugs. 2010 Aug 31. doi: 10.2165/11538960-000000000-00000. [Epub ahead of print]
Freedman MS, Bar-Or A, Oger J, et al. On behalf of the MAESTRO-01 Investigators. A phase III study evaluating the efficacy and safety of **MBP8298** in secondary progressive MS. Neurology. 2011 Oct 18;77(16):1551-1560. (not provide a clinical benefit)
Freedman MS, Wolinsky JS, Wamil B, et al; For the **Teriflunomide** Multiple Sclerosis Trial Group and the MRI Analysis Center. Teriflunomide added to interferon-β in relapsing multiple sclerosis: A randomized phase II trial. Neurology. 2012 Jun 5;78(23):1877-1885.
Frohman EM, Havrdova E, Lublin F, et al. Most patients with multiple sclerosis or a clinically isolated demyelinating syndrome should be treated at the time of diagnosis. Arch Neurol. 2006 Apr;63(4):614-9.
Frohman EM, Racke MK, Raine CS. **Multiple sclerosis**--the plaque and its pathogenesis. N Engl J Med. 2006 Mar 2;354(9):942-55.
Gelfand JM, Cree BA, McElroy J, et al. **Vitamin D** in African Americans with multiple sclerosis. Neurology. 2011 May 24;76(21):1824-30.
Gheuens S, Smith DR, Wang X, Alsop DC, et al. Simultaneous **PML-IRIS after discontinuation of natalizumab** in a patient with MS. Neurology. 2012 May 1;78(18):1390-3.
Ghezzi A, Banwell B, Boyko A, et al. The management of multiple sclerosis in children: a European view. Mult Scler. 2010;16(10):1258-1267.
Gholipour T, Healy B, Baruch NF, et al. Demographic and clinical characteristics of **malignant** multiple sclerosis. Neurology. 2011 Jun 7;76(23):1996-2001.
Giampiero A. Chronic cerebrospinal venous insufficiency (**CCSVI**) and susceptibility to multiple sclerosis. Ann Neurol. 2011 Apr 12. doi: 10.1002/ana.22451.
Gilli F, Navone ND, Perga S, et al. **Loss of Braking Signals** During Inflammation: A Factor Affecting the Development and Disease Course of Multiple Sclerosis. Arch Neurol. 2011 Mar 14.
Giovannoni G, Comi G, Cook S, et al. the **CLARITY** Study Group, A Placebo-Controlled Trial of Oral **Cladribine** for Relapsing Multiple Sclerosis. N Engl J Med 2010 0: NEJMoa0902533.
Giovannoni G, Cook S, Rammohan K, et al; on behalf of the **CLARITY** study group. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with **cladribine** tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol. 2011 Mar 10.
Gladstone DE, et al. High-dose cyclophosphamide (200mg/kg over 4 days) for moderate to severe refractory multiple sclerosis. Arch Neurol. 2006 Oct;63(10):1388-93. Epub 2006 Aug 14.
Goodin DS, Reder AT, Ebers GC, et al. **Survival in MS**: A randomized cohort study **21 years** after the start of the pivotal **IFNβ-1b** trial. Neurology. 2012 Apr 24;78(17):1315-22.
Goodman AD, Brown TR, Edwards KR, et al. A phase 3 trial of extended release oral **dalfampridine** in multiple sclerosis. Ann Neurol 2010; 68: 494–502.
Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in **pediatric-onset** compared with adult-onset multiple sclerosis. Arch Neurol. 2009 Jan;66(1):54-9.
Gorman MP, Tillema JM, Ciliax AM, Guttmann CR, Chitnis T. **Daclizumab** use in patients with pediatric multiple sclerosis. Arch Neurol. 2012 Jan;69(1):78-81.
Gray OM, McDonnell GV, Forbes RB. A systematic review of oral **methotrexate** for multiple sclerosis. Mult Scler. 2006 Aug;12(4):507-10.
Green AJ, McQuaid S, Hauser SL, Allen IV, Lyness R. **Ocular pathology in multiple sclerosis**: retinal atrophy and infl ammation irrespective of disease duration. Brain 2010; 133: 1591–601.
Hader WJ, Yee IM. **Incidence and prevalence** of multiple sclerosis in Saskatoon, Saskatchewan. Neurology. 2007 Sep 18;69(12):1224-9.
Hartung HP, Freedman MS, et al. For the BENEFIT Study Group. **Interferon {beta}-1b-neutralizing antibodies 5 years** (**BENEFIT**) after clinically isolated syndrome. Neurology. 2011 Aug 17.
Hasan SK, Buttari F, Ottone T, et al. Risk of **acute promyelocytic leukemia** in multiple sclerosis: Coding variants of DNA repair genes. Neurology. 2011 Mar 22;76(12):1059-65.
Havla JB, Pellkofer HL, Meinl I, et al. Rebound of disease activity after **withdrawal of fingolimod** (FTY720) treatment. Arch Neurol. 2012 Feb;69(2):262-4.

TOP

Hawker K, O'Connor P, Freedman MS, et al. OLYMPUS trial group. **Rituximab** in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009 Oct;66(4):460-71.

Health Canada June/08 There have been rare reports of serious liver injury in patients receiving Tysabri, occurring as early as 6 days after first dose. Tysabri product label has been updated for liver injury, hypersensitivity reactions and herpes infections.

Health Canada Feb/12 is informing Canadians of an ongoing safety review of the multiple sclerosis (MS) drug **Gilenya** (the brand name for **fingolimod**). The review was initiated following reports of serious adverse events, including 11 deaths reported internationally. No deaths have been reported in Canada.

Hedström AK, Akerstedt T, Hillert J, et al. **Shift work** at young age is associated with increased risk for multiple sclerosis. Ann Neurol. 2011 Oct 17.

Hellwig K, Schimrigk S, Fischer M, et al. Allergic and nonallergic delayed infusion reactions during **natalizumab** therapy. Arch Neurol. 2008 May;65(5):656-8. **Delayed infusion reactions** occurred in 4 of 40 relapse-remitting multiple sclerosis patients treated with natalizumab. Our cases illustrate that some of these infusion reactions may be treated effectively with steroids and reduction of the infusion rate. In cases of antibody-mediated reactions, treatment should be stopped immediately.

Hellwig K, Gold R, Marousi S, et al. **Immune reconstitution inflammatory syndrome** after withdrawal of **natalizumab**? Neurology. 2011 Apr 12;76(15):1362-3.

Hernan MA, Alonso A, Hernandez-Diaz S. Tetanus vaccination and risk of multiple sclerosis: a systematic review. Neurology. 2006 Jul 25;67(2):212-5. Tetanus vaccination is associated with a lower risk of multiple sclerosis.

Hesse D, Frederiksen JL, Koch-Henriksen N, et al. **Methylprednisolone does not** restore biological response in multiple sclerosis patients with **neutralizing antibodies** against interferon-beta. Eur J Neurol. 2009 Jan;16(1):43-7. Monthly pulsed MP treatment in NAb positive patients has no beneficial effect on NAb status or IFN-beta bioactivity.

Hommes OR, et al. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. Lancet. 2004 Sep 25-Oct 1;364(9440):1149-56.

Huppke P, Stark W, Zürcher C, Huppke B, Brück W, Gärtner J. **Natalizumab use in pediatric** multiple sclerosis. Arch Neurol. 2008 Dec;65(12):1655-8. Natalizumab treatment was effective and well tolerated in our pediatric patients with RRMS who did not respond to initial immunomodulatory treatments. Therefore, it is a promising second-line therapy for pediatric patients with RRMS.

Jacobs LD, Beck RW, Simon JH, et al. Intramuscular **interferon beta-1a** therapy initiated during a **first demyelinating** event in multiple sclerosis. N Engl J Med. 2000;343:898−904.

Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;45:1268-76.

Johnson KP, Brooks BR, Cohen JA, et al.; Copolymer 1 Multiple Sclerosis Study Group. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. 1995. Neurology. 2001 Dec;57(12 Suppl 5):S16-24.

Johnson KP, Brooks BR, Ford CC, Goodman AD, et al. Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial. Mult Scler. 2003 Dec;9(6):585-91.

Kapoor Raju, Furby Julian, Hayton Thomas et al; **Lamotrigine for neuroprotection** in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial, The Lancet Neurology, Available online 8 June 2010. (not successful)

Kappos L, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. (PRISMS) study Neurology. 2006 Sep 26;67(6):944-53. Despite the limitations inherent in any long-term study (for example, potential differences between returning and nonreturning patients), these results indicate that patients with relapsing-remitting multiple sclerosis can experience sustained benefit over many years from early interferon beta-1a subcutaneous therapy three times weekly compared with patients whose treatment is delayed. This effect was more apparent in the patients receiving the higher dose.

Kappos L, et al.; FTY720 D2201 Study Group. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med. 2006 Sep 14;355(11):1124-40.

Kappos L, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006 Aug 16; [Epub ahead of print] Betaseron **BENEFIT**

Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Radu EW, Bauer L, Dahms S, Lanius V, Pohl C, Sandbrink R; **BENEFIT** Study Group. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet. 2007 Aug 4;370(9585):389-97. Our data suggest that early initiation of treatment with interferon beta-1b prevents the development of confirmed disability, supporting its use after the first manifestation of relapsing-remitting MS.

Kappos L, Freedman MS, Polman CH, et al.; for the **BENEFIT** Study Group. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. Lancet Neurol. 2009 Sep 10. Effects on the rate of conversion to CDMS and the favourable long-term safety and tolerability profile support early initiation of treatment with interferon beta-1b, although a delay in treatment by up to 2 years did not affect long-term disability outcomes.

Kappos, Ludwig, Radue, EW, O'Connor, P, et al. **FREEDOMS** Study Group, A Placebo-Controlled Trial of Oral **Fingolimod** in Relapsing Multiple Sclerosis. N Engl J Med 2010 0: NEJMoa0909494.

Kappos L, Li D, Calabresi PA, et al. **Ocrelizumab** in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011; published online Nov 1. D

Kappos L, Bates D, Edan G, et al. **Natalizumab** treatment for multiple sclerosis: updated recommendations for patient **selection and monitoring**. Lancet Neurol. 2011 Aug;10(8):745-58.

Kelly VM, Nelson LM, Chakravarty EF. **Obstetric outcomes** (pregnancy) in women with multiple sclerosis and epilepsy. Neurology. 2009 Nov 18. [Epub ahead of print]

Khalil M, Langkammer C, Ropele S, et al. Determinants of **brain iron** in multiple sclerosis: a quantitative 3T MRI study. Neurology 2011;77:1691–1697.

Khoury SJ.; Healy BC.; Kivisakk P; et al. A Randomized Controlled Double-Masked Trial of **Albuterol** Add-on Therapy in Patients With Multiple Sclerosis. Arch Neurol. 2010;67(9):1055-1061.

Kieseier BC and Hartung HP. Current Disease Modifying Therapies in MS. Semin Neurol 2003; 23(2): 133-145.

Kieseier BC, Wiendl H. Transforming multiple sclerosis trials into practical reality. Lancet Neurol. 2011 May 13.

Kinkel RP, Kollman C, O'Connor P, et al. **IM interferon beta-1a** delays definite multiple sclerosis **5 years after a first demyelinating event**. Neurology 2006; 66: 678–84.

Kinkel RP, Dontchev M, Kollman C, et al; for the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance Investigators. Association Between Immediate Initiation of Intramuscular Interferon Beta-1a at the Time of a Clinically Isolated Syndrome and Long-term Outcomes: A **10-Year Follow-up** of the Controlled High-Risk **Avonex** Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. (**CHAMPS**) Arch Neurol. 2012 Feb;69(2):183-190.

Kleiter I, Hellwig K, Berthele A, et al. for the Neuromyelitis Optica Study Group. Failure of **Natalizumab** to Prevent Relapses in Neuromyelitis Optica. Arch Neurol. 2012 Feb;69(2):239-245

TOP

Koch-Henriksen N, et al. Danish Multiple Sclerosis Group. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006 Apr 11;66(7):1056-60. Epub 2006 Mar 1. In this study, 250 microg interferon-beta-1b (Betaseron) administered every other day did not prove clinically superior to once-a-week 22 microg interferon-beta-1a.(Rebif)

Kolber Michael, Makus Ken, Allan G. Michael, et al. **Vascular intervention** for multiple sclerosis (CCSVI). Can Fam Physician June 2011 57: 676.

Kotzamani D, Panou T, Mastorodemos V, et al. Rising incidence of multiple sclerosis in **females associated with urbanization**. Neurology. 2012 May 29;78(22):1728-35.Krumbholz M, Pellkofer H,

Gold R, Hoffmann LA, Hohlfeld R, Kumpfel T. **Delayed Allergic Reaction to Natalizumab** Associated With Early Formation of Neutralizing Antibodies. Arch Neurol. 2007 Sep;64(9):1331-1333. Clinicians and patients should be alert not only to immediate but also to significantly delayed substantial allergic reactions to natalizumab.

Krupp LB, Christodoulou C, Melville P, et al. Multicenter randomized clinical trial of **donepezil** for memory impairment in multiple sclerosis. Neurology. 2011 Apr 26;76(17):1500-7. (**not work**)

Kuhle J, Pohl C, Mehling M, et al. Lack of association between antimyelin antibodies and progression to multiple sclerosis. N Engl J Med. 2007 Jan 25;356(4):371-8. Presence of anti-MOG or anti-MBP or both was not significantly associated with conversion to CDMS in our CIS cohort. However, patients with anti-myelin oligodendrocyte glycoprotein (anti-MOG) and anti-myelin basic protein antibodies (anti-MBP) had higher lesion load & more disseminated lesions in cranial MRI as well as higher values for CSF leucocytes and intrathecal IgG production. Our data support a correlation of anti-MOG & anti-MBP to inflammatory signs in MRI & CSF. The prognostic value of these antibodies for CDMS, seems to be less pronounced than previously reported.

Kuhle J, Gosert R, B¨uhler R, et al. Management and outcome of **CSF-JC virus PCR-negative PML** in a natalizumab-treated patient with MS. Neurology 2011; 77:2010 –2016.

Langer-Gould A, Huang S, Van Den Eeden SK, et al. **Vitamin d**, pregnancy, breastfeeding, and postpartum multiple sclerosis relapses. Arch Neurol. 2011 Mar;68(3):310-3.

Langer-Gould A, Zhang JL, Chung J, Yeung Y, Waubant E, Yao J. Incidence of acquired **CNS demyelinating syndromes** in a multiethnic cohort of **children**. Neurology 2011;77:1143–1148.

Lanzillo R, Orefice G, Quarantelli M, et al. **Atorvastatin** Combined To Interferon to Verify the Efficacy (**ACTIVE**) in relapsing-remitting active multiple sclerosis patients: a longitudinal controlled trial of combination therapy. Mult Scler. 2010 Feb 11.

Laupacis A, Lillie E, Dueck A, et al. Association between chronic cerebrospinal venous insufficiency (**CCSVI**) and multiple sclerosis: a meta-analysis. CMAJ. 2011 Oct 3.

Leavitt VM, Sumowski JF, Chiaravalloti N, DeLuca J. **Warmer outdoor temperature** is associated with worse **cognitive** status in multiple sclerosis. Neurology 2012;78: 964 –968.

Li DK, Paty DW. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis. Ann Neurol 1999;46:197-206.

Li Y, Munger KL, Batool-Anwar S, et al. Association of multiple sclerosis with **restless legs syndrome** and other sleep disorders in women. Neurology. 2012 May 8;78(19):1500-6.

Løken-Amsrud KI, Holmøy T, Bakke SJ, et al. **Vitamin D** and disease activity in multiple sclerosis before and during interferon-β treatment. Neurology. 2012 Jun 13.

Lucas RM et al. Sun exposure and **vitamin D** are independent risk factors for CNS demyelination. *Neurology* 2011 Feb 8; 76:540.

Lucchinetti CF, Popescu BFG, Bunyan RF, et al. Inf **lammatory cortical demyelination** in early multiple sclerosis. N Engl J Med 2011;365:2188-97.

Makhani N, Gorman MP, Branson HM, et al. **Cyclophosphamide** therapy in pediatric multiple sclerosis. Neurology. 2009 May 13. Cyclophosphamide is an option for the treatment of children with aggressive multiple sclerosis refractory to first-line therapies. Recommendations regarding patient selection, treatment administration, and monitoring are discussed.

Marder E, Gupta P, Greenberg BM, et al. No Cerebral or Cervical Venous Insufficiency (**CCSVI**) in US Veterans With Multiple Sclerosis. Arch Neurol. 2011 Aug 8.

Marriott JJ, Miyasaki JM, Gronseth G, O'Connor PW. Evidence Report: The efficacy and safety of **mitoxantrone** (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) . Neurology. 2010 May 4;74(18):1463-70. http://www.neurology.org/cgi/reprint/74/18/1463

The accumulated Class III and IV evidence suggests an increased incidence of systolic dysfunction and therapy-related acute leukemia (TRAL) with mitoxantrone therapy. Systolic dysfunction occurs in approximately 12% of patients with MS treated with mitoxantrone, congestive heart failure occurs in approximately 0.4%, and leukemia occurs in approximately 0.8%. The number needed to harm is 8 for systolic dysfunction and 123 for TRAL.

Martinelli Boneschi F, Rovaris M, et al. Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled clinical trials. Mult Scler. 2003 Aug;9(4):349-55.

Martinelli V et al. The Italian Mitoxantrone Group. **Acute myeloid leukemia** in Italian patients with multiple sclerosis treated with **mitoxantrone**. Neurology. 2011 Nov 22;77(21):1887-1895.

Marcus JF, Shalev SM, Harris CA, et al. **Severe hypercalcemia following vitamin d supplementation** in a patient with multiple sclerosis: a note of caution. Arch Neurol. 2012 Jan;69(1):129-32.

Massacesi L, Parigi A, Barilaro A, et al. Efficacy of azathioprine on multiple sclerosis new brain lesions evaluated using magnetic resonance imaging. Arch Neurol. 2005 Dec;62(12):1843-7.

Mayo Clinic tools for healthier lives www.mayoclinic.com/health/multiple-sclerosis/ds00188

Medical Letter. **Dalfampridine** (Ampyra) for MS. Sept 20, 2010.

Mikaeloff Y, et al **Hepatitis B vaccination** and the risk of childhood-onset multiple sclerosis. Arch Pediatr Adolesc Med. 2007 Dec;161(12):1176-82. Vaccination against HB does not seem to increase the risk of a first episode of MS in childhood.

Mikaeloff Y, Caridade G, Suissa S, Tardieu M. **Hepatitis B vaccine** and the risk of CNS inflammatory demyelination in childhood. Neurology. 2008 Oct 8. [Epub ahead of print] Hepatitis B vaccination does not generally increase the risk of CNS inflammatory demyelination in childhood. However, the Engerix B vaccine appears to increase this risk, particularly for confirmed multiple sclerosis, in the longer term. Our results require confirmation in future studies.

Mikol DD, Barkhof F, Chang P, et al. **REGARD** study group. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008 Oct;7(10):903-14.

Miller DH, Leary SM. **Primary-progressive** multiple sclerosis. Lancet Neurol. 2007 Oct;6(10):903-12.

Miller DH, Weber T, Grove R, et al. **Firategrast** for relapsing remitting multiple sclerosis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2012; publised online Jan 6.

Miller DH, Chard DT, Ciccarelli O. **Clinically isolated syndromes**. Lancet Neurol. 2012 Feb;11(2):157-69.

Miravalle A, Jensen R, et al. **Immune reconstitution inflammatory syndrome** in patients with multiple sclerosis following cessation of **natalizumab** therapy. Arch Neurol. 2011 Feb;68(2):186-91.

Moen SM, Celius EG, Sandvik L, et al. **Low bone mass** in newly diagnosed multiple sclerosis and clinically isolated syndrome. Neurology. 2011 Jul 12;77(2):151-7.

Mowry E, Waubant E, McCulloch C et al. **Vitamin D status** predicts new brain MRI activity in multiple sclerosis Ann Neurol. 2012 Mar 19.

Mullen JT, Vartanian TK, Atkins MB. **Melanoma** complicating treatment with **natalizumab** for multiple sclerosis. N Engl J Med. 2008 Feb 7;358(6):647-8.

Multiple Sclerosis Society for Professionals www.mssociety.org.uk/for_professionals/index.html

TOP

Munger KL, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006 Dec 20;296(23):2832-8. The results of our study suggest that high circulating levels of vitamin D are associated with a lower risk of multiple sclerosis.

Murray TJ. Diagnosis and treatment of multiple sclerosis. BMJ. 2006 Mar 4;332(7540):525-7.

Naismith RT, Bourdette D. **Interruption of natalizumab** therapy for multiple sclerosis: What are the risks? Neurology. 2011 May 31;76(22):1854-5.

Namaka M, Pollitt-Smith M, Gupta A, et al. The clinical importance of neutralizing antibodies in relapsing-remitting multiple sclerosis. Curr Med Res Opin. 2006 Feb;22(2):223-39.The induction of NAbs in IFN-beta treated patients reduce clinical effect and accelerate disease progression.

Namaka M, et al . Corticosteroids and Multiple Sclerosis: To Treat or Not to Treat: CPJ 2005;138 (6):54-59.

National Multiple Sclerosis Society. Disease Management Consensus Paper. (http://www.nationalmssociety.org/pdf/forpros/Exp_Consensus.pdf. Accessed April 2,2005.

NICE: National Institute for Health and Clinical Excellence**. Natalizumab** for the treatment of adults with highly active relapsing-remitting multiple sclerosis. London (UK): National Institute for Health & Clinical Excellence (NICE); 2007 Aug. 21 p. (Technology appraisal guidance; no. 127). Natalizumab is recommended as an option for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI. People currently receiving natalizumab, but for whom treatment would not have been recommended according to the above section of this guidance, should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

NICE: Cohen D. NICE rules out NHS prescription of fingolimod for multiple sclerosis. BMJ. 2011 Aug 10;343:d5117.

Nikfar Shekoufeh, Rahimi Roja, Abdollahi Mohammad, A meta-analysis of the efficacy and tolerability of **interferon-[beta]** in multiple sclerosis, overall and by drug and disease type, Clinical Therapeutics, Volume 32, Issue 11, October 2010, Pages 1871-1888, ISSN 0149-2918, DOI: 10.1016/j.clinthera.2010.10.006.

Noyes K, Bajorska A, Chappel A, et al. Cost-effectiveness of **disease-modifying therapy** for multiple sclerosis: A population-based study. Neurology July 20, 2011 WNL.0b013e3182270402.

Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis. The **radiologically isolated syndrome**. Neurology. 2008 Dec 10. [Epub ahead of print] Individuals with MRI anomalies highly suggestive of demyelinating pathology, not better accounted for by another disease process, are very likely to experience subsequent radiologic or clinical events related to multiple sclerosis.

O'Connor P, Comi G, Montalban X, Antel J, et al. ; FTY720 D2201 Study Group. Oral **fingolimod** (FTY720) in multiple sclerosis: two-year results of a phase II extension study. Neurology. 2009 Jan 6;72(1):73-9. Once-daily oral treatment with FTY720, 1.25 or 5.0 mg, for up to 2 years, was well tolerated and was associated with low relapse rates and lesion activity.

O'Connor P, Filippi M, Arnason B, et al. for the **BEYOND** Study Group. 250 mug or 500 mug interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009 Oct;8(10):889-897. Epub 2009 Sep 2.

O'Connor PW, Goodman A, Kappos L, et al. Disease activity return during **natalizumab treatment interruption** in patients with multiple sclerosis. Neurology. 2011 May 31;76(22):1858-65.

O'Connor Paul, Wolinsky Jerry S., Confavreux Christian. Randomized Trial of Oral **Teriflunomide** for Relapsing Multiple Sclerosis. (**TEMSO**) N Engl J Med 2011;365:1293-303.

Optic Neuritis Study Group. Multiple sclerosis risk after **optic neuritis**: final optic neuritis treatment trial follow-up. Arch Neurol 2008;65:727-732. {InfoPOEMS: After 15 years of follow up, 50% of patients with optic neuritis went on to develop multiple sclerosis (MS). Patients with 1 or more white matter lesions on magnetic resonance imaging (MRI) have the greatest risk of developing MS. (LOE = 1b-)}

Orton SM, Wald L, Confavreux C, et al. Association of **UV radiation** with multiple sclerosis prevalence and sex ratio in France. Neurology. 2011 Feb 1;76(5):425-31.

Otto C, Oltmann A, Stein A, et al. Intrathecal **EBV antibodies** (**Epstein-Barr virus**) are part of the polyspecific immune response in multiple sclerosis. Neurology. 2011 Apr 12;76(15):1316-21.

Pachner AR, Cadavid D, Wolansky L, Skurnick J. Effect of **anti-IFN{beta} antibodies on MRI lesions** of MS patients in the BECOME study. Neurology. 2009 Nov 3;73(18):1485-92. High levels of anti-interferon beta (IFNbeta) antibodies, which result in diminished bioactivity, are correlated with reduced therapeutic efficacy of IFNbeta.

Pachner AR, Warth JD, Pace A, Goelz S; INSIGHT investigators. Effect of **neutralizing antibodies** on biomarker responses to interferon beta: the INSIGHT study. Neurology. 2009 Nov

Pascual AM, Téllez N, Boscá I, Mallada J, et al. Revision of the risk of secondary **leukemia after mitoxantrone** in multiple sclerosis populations is required. Mult Scler. 2009 Oct 13.

Patsopoulos NA et al. **Genome-wide meta-analysis** identifies novel multiple sclerosis susceptibility loci. Ann Neurol. 2011 Dec;70(6):897-912.

Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Neurology 1993;43:662-7.

Pelletier Daniel, Hafler David A. **Fingolimod** for Multiple Sclerosis. N Engl J Med 2012; 366:339-347.

Pharmacist's Letter: Immunomodulators used in the Treatment of MS. Jan 2007.

Pharmacist's Letter. **Drugs Used to Treat Multiple Sclerosis Symptoms**. Mar, 2010.

Pittock SJ, Weinshenker BG, Noseworthy JH, Lucchinetti CF, Keegan M, Wingerchuk DM, Carter J, Shuster E, Rodriguez M. Not every patient with multiple sclerosis should be treated at time of diagnosis. Arch Neurol. 2006 Apr;63(4):611-4.

Polman CH, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005 Dec;58(6):840-6.

Polman CH et al. **Diagnostic criteria for multiple sclerosis: 2010 revisions to the "McDonald criteria**." *Ann Neurol* 2011 Jan 11; [e-pub ahead of print]. (http://dx.doi.org/10.1002/ana.22366)

Polman C, Reingold S, Banwell B, et al. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the "McDonald Criteria."Annals of Neurology.2011 Jan 11; 3-76.

Polman Chris H, Bertolotto Antonio, Deisenhammer Florian et al; Recommendations for clinical use of data on **neutralising antibodies** to **interferon-beta** therapy in multiple sclerosis, The Lancet Neurology, Volume 9, Issue 7, July 2010, Pages 740-750.

Pohl D, Waubant E, Banwell B, et al. Treatment of **pediatric** multiple sclerosis and variants. Neurology. 2007 Apr 17;68(16 Suppl 2):S54-65.

Ponsonby A-L, Lucas RM, van der Mei IA, et al. Offspring number, **pregnancy, and risk of a first clinical demyelinating event**: the **AusImmune** Study. Neurology 2012;78: 867– 874.

Portaccio E, Ghezzi A, Hakiki B, et al; For the MS Study Group of the Italian Neurological Society. **Breastfeeding** is not related to postpartum relapses in multiple sclerosis. Neurology. 2011 Jul 12;77(2):145-150.

Poulin F, Rico P, Côté J, Bégin LR. Interferon beta-induced **panniculitis** mimicking acute appendicitis. Arch Dermatol. 2009 Aug;145(8):916-7.
3;73(18):1493-500. These data provide evidence that high titers of neutralizing antibodies abolish the in vivo response to interferon beta.

PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: long-term efficacy of interferon-beta-1a in relapsing MS [published correction appears in

TOP

Neurology 2001;57:1146]. Neurology 2001;56:1628-36.
Pucci E, Giuliani G, Solari A, Simi S, Minozzi S, Di Pietrantonj C, Galea I. **Natalizumab** for relapsing remitting multiple sclerosis. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD007621. DOI: 10.1002/14651858.CD007621.pub2. Although one trial did not contribute to efficacy results due to its duration, we found robust evidence in favour of a reduction in relapses and disability at 2 years in RRMS patients treated with NTZ. The drug was well tolerated. There are current significant safety concerns due to reporting of an increasing number of PML cases in patients treated with NTZ. This review was unable to provide an up-to-date systematic assessment of the risk due to the maximum 2 year-duration of the trials included. An independent systematic review of the safety profile of NTZ is warranted. NTZ should be used only by skilled neurologists in MS centres under surveillance programs.
Racke MK, Lovett-Racke AE, Karandikar NJ. The **mechanism** of action of **glatiramer** acetate treatment in multiple sclerosis. Neurology. 2010 Jan 5;74 Suppl 1:S25-30.
Ramagopalan SV, Meier UC, Conacher M, et al. Role of the **HLA System** in the Association Between Multiple Sclerosis and **Infectious Mononucleosis**. Arch Neurol. 2011 Apr;68(4):469-72.
Ramagopalan SV, Handel AE, Giovannoni G, et al. Relationship of **UV exposure** to prevalence of multiple sclerosis in England. Neurology. 2011 Apr 19;76(16):1410-4. PubMed PMID: 21502600.
Ravnborg M, Sørensen PS, Andersson M, et al. **Methylprednisolone** in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (**MECOMBIN** study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. Lancet Neurol. 2010Jun 7. Interpretation Monthly pulses of methylprednisolone 500mg po od x 3 days per month for 3-4yrs in combination with interferon beta-1a do not seem to affect disability progression any more than interferon beta-1a treatment alone. More research is required to assess whether this treatment regimen might benefit particular pt subsets.
Renoux C, Vukusic S, et al. Adult Neurology Departments KIDMUS Study Group. Natural history of multiple sclerosis with childhood onset. N Engl J Med. 2007 Jun 21;356(25):2603-13. Patients with **childhood-onset** multiple sclerosis take longer to reach states of irreversible disability but do so at a younger age than patients with adult-onset multiple sclerosis.
Rigotti DJ, Inglese M, Kirov II, et al. Two-year serial whole-brain **N-acetyl-L-aspartate** in patients with relapsing-remitting multiple sclerosis. Neurology. 2012 May 1;78(18):1383-9.
Riise T, Mohr DC, Munger KL, Rich-Edwards JW, Kawachi I, Ascherio A. **Stress** and the risk of multiple sclerosis. Neurology. 2011 May 31;76(22):1866-71.
Rizzo Matthew. **Impaired Driving From Medical Conditions**: A 70-Year-Old Man Trying to Decide if He Should Continue Driving. JAMA. 2011;305(10):1018-1026.
Rudick RA, Lee JC, Cutter GR, et al. **Disability Progression** in a Clinical Trial of Relapsing-Remitting Multiple Sclerosis: Eight-Year Follow-up. Arch Neurol. 2010 Jul 12.
Sadaka Y et al. 2010 **McDonald criteria for diagnosing pediatric** multiple sclerosis. Ann Neurol 2012 Mar 4.
Saure C, Warnke C, Zohren F, et al. **Natalizumab** and Impedance of the Homing of CD34+ Hematopoietic Progenitors. Arch Neurol. 2011 Nov;68(11):1428-31.
Scalfari A, Neuhaus A, Daumer M, Ebers GC, Muraro PA. **Age and disability accumulation** in multiple sclerosis. Neurology. 2011 Sep 27;77(13):1246-52.
Schweikert A, Kremer M, Ringel F, et al. Primary central nervous system **lymphoma** in a patient treated with **natalizumab**. Ann Neurol. 2009 Sep;66(3):403-6.
Sellebjerg F, Barnes D, Filippini G, et al. EFNS Task Force on Treatment of Multiple Sclerosis Relapses. EFNS guideline on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis relapses. Eur J Neurol. 2005 Dec;12(12):939-46.
Sharac J, McCrone P, Sabes-Figuera R. **Pharmacoeconomic** considerations in the treatment of multiple sclerosis. Drugs. 2010 Sep 10;70(13):1677-91. doi: 10.2165/11538000-000000000-00000.
Shery T, et al. The effects of gabapentin and memantine in acquired and congenital nystagmus - A retrospective study. Br J Ophthalmol. 2006 Mar 23; [Epub ahead of print]
Simon JH, Jacobs LD, Campion M, Wende K, Simonian N, Cookfair DL, et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. Ann Neurol 1998;43:79-87.
Solomon AJ, Klein EP, Bourdette D. "**Undiagnosing**" multiple sclerosis: The challenge of misdiagnosis in MS. Neurology. 2012 Jun 12;78(24):1986-91.
Sorensen PS, Deisenhammer F, Duda P, et al. EFNS Task Force on Anti-IFN-beta Antibodies in Multiple Sclerosis. Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. Eur J Neurol. 2005 Nov;12(11):817-27.
Sorensen PS, Mellgren SI, Svenningsson A, et al. NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (**NORMIMS** study): a randomised, placebo-controlled trial. Lancet Neurol. 2009 Apr 29. [Epub ahead of print] Oral methylprednisolone given in pulses every 4 weeks as an add-on therapy to subcutaneous interferon beta-1a in patients with relapsing-remitting multiple sclerosis leads to a significant reduction in relapse rate. However, because of the small number of patients and the high dropout rate, these findings need to be corroborated in larger cohorts.
Sørensen PS, Koch-Henriksen N, Jensen PE. **Neutralizing antibodies** against interferon-{beta} do not predispose antibodies against natalizumab. Neurology. 2011 Feb 22;76(8):759-60.
Sorensen PS, Lycke J, Erälinna JP, et al; for the **SIMCOMBIN** study investigators. **Simvastatin** as add-on therapy to interferon beta-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN study): a placebo-controlled randomised phase 4 trial. Lancet Neurol. 2011 Jul 8. (We found no beneficial effect of simvastatin)
Sormani MP, Li DK, Bruzzi P, et al. **Combined MRI lesions and relapses** as a surrogate for disability in multiple sclerosis. Neurology 2011;77:1684 –1690.
Staples Judith, Ponsonby Anne-Louise, Lim Lynette. Low maternal exposure to **ultraviolet radiation** in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis. BMJ 2010;340:c1640, doi: 10.1136/bmj.c1640 (Published 29 April 2010)
Stein MS, Liu Y, Gray OM, et al. A randomized trial of high-dose **vitamin D2** in relapsing-remitting multiple sclerosis. Neurology 2011;77:1611–1618.
Stewart N, Simpson S Jr, van der Mei I, et al. **Interferon-β and serum 25-hydroxyvitamin D** interact to modulate relapse risk in MS. Neurology. 2012 Jun 13.
Strupp M, Kalla R, Claassen J, et al. A randomized trial of **4-aminopyridine** in EA2 and related familial episodic ataxias. Neurology. 2011 Jul 19;77(3):269-75.
Stüve O, Cravens PD, Frohman EM, et al. Immunologic and clinical status **14 months after cessation of natalizumab** therapy. Neurology. 2008 Nov 5. [Epub ahead of print] This is the first long-term follow-up of patients who discontinued natalizumab. We did not observe a clinical, radiographic, or immunologic rebound phenomenon after discontinuation of natalizumab therapy.
Seewann A, Kooi E-J, Roosendaal SD, et al. Postmortem verification of MS cortical lesion detection with **3D DIR**. Neurology 2012;78:302–308. (Double inversion recovery)
Tan CS, Koralnik IJ. **Progressive multifocal leukoencephalopathy** (PML) and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010 Apr;9(4):425-37.
Tan IL, McArthur JC, Clifford DB, Major EO, Nath A. Immune reconstitution inflammatory syndrome **(IRIS) in natalizumab-associated PML**. Neurology. 2011 Aug 10.
Thompson Alan J, Toosy Ahmed T, Ciccarelli Olga, Pharmacological management of **symptoms in multiple sclerosis**: current approaches and future directions, The Lancet Neurology, Volume 9, Issue 12, December 2010, Pages 1182-1199, ISSN 1474-4422, DOI: 10.1016/S1474-4422(10)70249-0.
Torkildsen O, Wergeland S, Bakke S, et al. **ω-3 Fatty Acid Treatment** in Multiple Sclerosis (**OFAMS** Study): A Randomized, Double-Blind, Placebo-Controlled Trial. Arch Neurol. 2012 Apr 16.
Trampe AK, Hemmelmann C, Stroet A, et al. **Anti-JC virus antibodies** in a large German natalizumab-treated multiple sclerosis cohort. Neurology. 2012 May 29;78(22):1736-42.

TOP

Tsivgoulis G, Mantatzis M, Bogiatzi C, et al. **Extracranial venous hemodynamics in multiple sclerosis**: A case-control study. Neurology. 2011 Sep 27;77(13):1241-5.
Tur C, Montalban X, Tintoré M, et al. **Interferon Beta-1b** for the Treatment of Primary Progressive Multiple Sclerosis: Five-Year Clinical Trial Follow-up. Arch Neurol. 2011 Nov;68(11):1421-7.
Tzartos JS, Khan G, Vossenkamper A, et al. Association of innate immune activation with latent **Epstein-Barr virus** in active MS lesions. Neurology 2012;78:15–23.
Uccelli A, Ginocchio F, Mancardi GL, et al. Primary varicella zoster infection associated with **fingolimod** treatment. Neurology. 2011 Mar 15;76(11):1023-4.
van der Kop ML, Pearce MS, Dahlgren L, et al. **Neonatal and delivery outcomes** in women with multiple sclerosis. Ann Neurol. 2011 Jun 27. doi: 10.1002/ana.22483.
van der Voort LF, Gilli F, Bertolotto A, Knol DL, Uitdehaag BM, Polman CH, Killestein J. Clinical Effect of Neutralizing Antibodies to Interferon Beta That Persist Long After Cessation of Therapy for Multiple Sclerosis. Arch Neurol. 2010 Feb 8.
van der Voort Laura F.; Gilli Francesca; Bertolotto Antonio; et al. Clinical Effect of **Neutralizing Antibodies to Interferon Beta** That Persist Long After Cessation of Therapy for Multiple Sclerosis. Arch Neurol. 2010;0(2010):2010.21.
Van Der Walt A, Sung S, Spelman T, et al. A double-blind, randomized, controlled study of **botulinum toxin type A** in MS-related tremor. Neurology. 2012 Jul 3;79(1):92-9.
Vellinga MM, Castelijns JA, Barkhof F, et al. **Postwithdrawal rebound increase in T2 lesional activity in natalizumab**-treated MS patients. Neurology. 2007 Sep 13; [Epub ahead of print] n=21
Vennegoor A, Wattjes MP, van Munster ET, et al. Indolent course of **progressive multifocal leukoencephalopathy** (PML) during natalizumab treatment in MS. Neurology. 2011 Feb 8;76(6):574-6.
Verhey LH, Branson HM, Shro MM, et al. **MRI parameters** for prediction of multiple sclerosis **diagnosis in children** with acute CNS demyelination: a prospective national cohort study. Lancet Neurol 2011; published online Nov 7, 2011. DOI:10.1016/S1474-4422(11)70250-2.
Villar LM, García-Sánchez MI, Costa-Frossard L, et al. Immunological markers of optimal response to **natalizumab** in multiple sclerosis. Arch Neurol. 2012 Feb;69(2):191-7.
Viscidi RP, Khanna N, Tan CS, et al. **JC virus antibody** and viremia as predictors of progressive multifocal leukoencephalopathy in human immunodeficiency virus-1-infected individuals. Clin Infect Dis. 2011 Oct;53(7):711-5.
Waubant E, Mowry EM, Krupp L, et al. For the US Pediatric MS Network. **Common viruses associated with lower pediatric** multiple sclerosis risk. Neurology. 2011 Jun 7;76(23):1989-1995.
Waubant E, Pelletier D, Mass M, et al. on the behalf of the **ITN STAyCIS** Study Group; ITN020AI Study Management Team. Randomized controlled trial of **atorvastatin** in clinically isolated syndrome: The STAyCIS study. Neurology. 2012 Apr 10;78(15):1171-1178.
Weber-Schoendorfer C, Schaefer C. Multiple sclerosis, immunomodulators, and **pregnancy** outcome: a prospective observational study. Mult Scler. 2009 Sep;15(9):1037-42. Our findings suggest that neither GA nor IFN constitutes a major risk for prenatal developmental toxicity.
West TW, Cree BA. **Natalizumab dosage suspension**: are we helping or hurting? Ann Neurol. 2010 Sep;68(3):395-9.
Whiting P, et al. Accuracy of magnetic resonance imaging for the diagnosis of multiple sclerosis: systematic review. BMJ. 2006 Mar 24; [Epub ahead of print] (InfoPOEMs: Magnetic resonance imaging (MRI) is not particularly useful in either ruling in or ruling out multiple sclerosis (MS). Relying on it to make the diagnosis will result in overdiagnosis of patients, and using it to rule out MS will cause you to miss approximately half the patients who will eventually be given a clinical diagnosis. (LOE = 1a))
Wynn D, Kaufman M, Montalban X, et al. for the **CHOICE** investigators. **Daclizumab** in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010 Feb 15.
Yeh EA, Waubant E, Krupp LB, et al.; for the National Network of Pediatric MS Centers of Excellence. Multiple Sclerosis Therapies in **Pediatric Patients With Refractory Multiple Sclerosis**. Arch Neurol. 2010 Dec 13.
Zajicek J. Diagnosis and disease modifying treatments in multiple sclerosis. Postgrad Med J. 2005 Sep;81(959):556-61.
Zivadinov R, Weinstock-Guttman B, Hashmi K, et al. **Smoking** is associated with increased lesion volumes and brain atrophy in multiple sclerosis. Neurology. 2009 Aug 18;73(7):504-10.
Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency (**CCSVI**) in MS. Neurology. 2011 Jul 12;77(2):138-44.

National Multiple Sclerosis Society. Disease Management Consensus Paper. (http://www.nationalmssociety.org/pdf/forpros/Exp_Consensus.pdf. Accessed April 2,2005.

TOP

Parkinsons's References: www.RxFiles.ca

[1] Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the **American** Academy of Neurology. Neurology. **2002** Jan 8;58(1):11-7.

[2] Therapeutic Choices 4rd Edition, 2003

[3] **Treatment Guidelines**: Drugs for Parkinson's Disease. **The Medical Letter**: June, 2004 (Vol 2, Issue 22) pp. 41-46. Updated Oct, 2007.
Medical Letter: Treatment Guidelines. Drugs for Parsinson's Disease. **Jan 2011.**

[4] Micromedex 2011

[5] Guttman M, Kish SJ, Furukawa Y. Current concepts in the **diagnosis and management** of **Parkinson's disease**. **CMAJ**. **2003** Feb 4;168(3):293-301.

[6] Rascol O, Goetz C, Koller W, Poewe W, Sampaio C. Treatment interventions for **Parkinson's** disease: an **evidence based** assessment. **Lancet**. **2002** May 4;359(9317):1589-98.

[7] Briggs GG, Freeman RK, Sumner JY. Drugs in **Pregnancy** and Lactation 9**th Edition**. Williams & Wilkins, Baltimore, 2011.

[8] Olanow CW, Agid Y, Mizuno Y, et al. **Levodopa** in the treatment of Parkinson's disease: current controversies. Mov Disord. 2004 Sep;19(9):997-1005.
Lewitt PA. Levodopa for the treatment of Parkinson's disease. N Engl J Med. 2008 Dec 4;359(23):2468-76.

[9] Nahata MC, Morosco RS, Leguire LE. Development of two stable oral suspensions of levodopa-carbidopa for children with amblyopia. J Pediatr Ophthalmol Strabismus. 2000 Nov-Dec;37(6):333-7.

[10] The Hospital for Sick Children -SickKids: oral suspension levodopa-carbidopa formula last revised March 2002 http://www.sickkids.ca/pharmacy/custom/levodopa.asp

[11] **Stalevo** for Parkinson's disease. Med Lett Drugs Ther. 2004 May 10;46(1182):39-40.

[12] **Parcopa** f: A **Rapid Dissolving** Formulation of Carbidopa/Levodopa. Med Lett Drugs Ther. 2005 Jan 31;47(1201):12-13.

[13] Nyholm D, Nilsson Remahl AI, et al. **Duodenal** levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology. 2005 Jan 25;64(2):216-23.

[14] Olanow CW, Watts RL, Koller WC. An **algorithm** (decision tree) for the management of Parkinson's disease (**2001**): treatment guidelines. Neurology. 2001 Jun;56(11 Suppl 5):S1-S88.

[15] Ahlskog JE, Muenter MD. Frequency of **levodopa**-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord. 2001 May;16(3):448-58.

[16] Koller WC, Hutton JT, Tolosa E, et al. Immediate-release & **controlled-release** carbidopa/levodopa in PD: a 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. Neurology. 1999 Sep 22;53(5):1012-9.

[17] Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, Olanow CW, et al. Parkinson Study Group. **Levodopa** and the progression of Parkinson's disease. N Engl J Med. 2004 Dec 9;351(24):2498-508.

[18] Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL. The "on-off" phenomenon in Parkinson's disease. Relation to **levodopa absorption** and transport. N Engl J Med. 1984 Feb 23;310(8):483-8.

[19] van Hilten JJ, Ramaker C, Van de Beek WJ, Finken MJ. Bromocriptine for **levodopa**-induced motor complications in Parkinson's disease. Cochrane Database Syst Rev. 2000;(2):CD001203.

[20] Ramaker C, Hilten JJ. **Bromocriptine/levodopa** combined versus levodopa alone for early Parkinson's disease. Cochrane Database Syst Rev. 2002;(2):CD003634.

[21] Lees AJ, Katzenschlager R, Head J, Ben-Shlomo Y. **Ten-year** follow-up of three different initial treatments in de-novo PD: a randomized trial (PDRGUK). Neurology. 2001 Nov 13;57(9):1687-94.

[22] Hely MA, Morris JG, Reid WG, Trafficante R. Sydney multicenter study of Parkinson's disease: Non-L-dopa-responsive problems dominate at **15 years**. Mov Disord. 2004 Nov 18

[23] Hely MA, Morris JG, Traficante R, et al. The sydney multicentre study of Parkinson's disease: progression and mortality at **10 years**. J Neurol Neurosurg Psychiatry. 1999 Sep;67(3):300-7.

[24] Bracco F, Battaglia A, Chouza C, et al. PKDS009 Study Group. The long-acting dopamine receptor agonist **cabergoline** in early Parkinson's disease: final results of a 5-year, double-blind, levodopa-controlled study. CNS Drugs. 2004;18(11):733-46.

[25] Rinne UK, Bracco F, Chouza C, et al. Early treatment of Parkinson's disease with **cabergoline** (**3-5yr trial)** delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. Drugs. 1998;55 Suppl 1:23-30.

[26] Pinero A, Marcos-Alberca P, Fortes J. **Cabergoline**-related severe restrictive mitral regurgitation. N Engl J Med. 2005 Nov 3;353(18):1976-7.

[27] Navan P, Findley LJ, Undy MB, et al. A randomly assigned double-blind cross-over study examining the relative anti-parkinsonian tremor effects of pramipexole and pergolide. Eur J Neurol. 2005 Jan;12(1):1-8.

[28] Tintner R, Manian P, Gauthier P, Jankovic J. Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist **pergolide** for Parkinson Disease. Arch Neurol. 2005 Aug;62(8):1290-5.

[29] Arnold G, Gasser T, Storch A, Lipp A, Kupsch A, Hundemer HP, Schwarz J. High doses of pergolide improve clinical global impression in advanced Parkinson's disease-A preliminary open label study. Arch Gerontol Geriatr. 2005 Jul 16; [Epub ahead of print]

[30] Muraki M, et al. Effects of low-dose **pergolide** therapy on cardiac valves in patients with Parkinson's disease. J Cardiol. 2005 Dec;46(6):221-7.

[31] Holloway RG, Shoulson I, Fahn S, et al. Parkinson Study Group. **Pramipexole vs levodopa** as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol. 2004 Jul;61(7):1044-53.

[32] Navan P, Findley LJ, Jeffs JA, Pearce RK, et al. Randomized, double-blind, 3-month parallel study of the effects of **pramipexole**, **pergolide**, and placebo on Parkinsonian tremor. Mov Disord. 2003 Nov;18(11):1324-31.

[33] Parkinson Study Group. **Pramipexole vs levodopa** as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group (CALM-PD). JAMA. 2000 Oct 18;284(15):1931-8.

[34] Guttman M. Double-blind comparison of **pramipexole & bromocriptine** treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. Neurology. 1997 Oct;49(4):1060-5.

[35] Moller JC, Oertel WH, Koster J, Pezzoli G, Provinciali L. Long-term efficacy and safety of **pramipexole** in advanced Parkinson's disease: results from a European multicenter trial. Mov Disord. 2005 May;20(5):602-10.

[36] Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of **pramipexole**, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum. 2005 Aug;52(8):2495-505.

[37] Whone AL, Watts RL, Stoessl AJ, et al.; **REAL-PET** Study Group. Slower progression of Parkinson's disease with **ropinirole versus levodopa**: The REAL-PET study. Ann Neurol. 2003 Jul;54(1):93-101.

[38] Korczyn AD, Brunt ER, Larsen JP, et al. A 3-year randomized trial of **ropinirole** and bromocriptine in early Parkinson's disease. The 053 Study Group. Neurology. 1999 Jul 22;53(2):364-70. Erratum in: Neurology 1999 Sep 22;53(5):1162.

[39] Rascol O, Brooks DJ, Korczyn AD, et al. A **five-year** study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with **ropinirole or levodopa**. 056 Study Group. N Engl J Med. 2000 May 18;342(20):1484-91.

[40] Cassano P, Lattanzi L, Fava M, Navari S, Battistini G, Abelli M, Cassano GB. **Ropinirole** in treatment-resistant depression: a 16-week pilot study. Can J Psychiatry. 2005 May;50(6):357-60.

[41] Inzelberg R, Schechtman E, Nisipeanu P. **Cabergoline**, **pramipexole** and **ropinirole** used as monotherapy in early Parkinson's disease: an evidence-based comparison. Drugs Aging. 2003;20(11):847-55.

[42] Albin RL, Frey KA. Initial agonist treatment of Parkinson disease: a critique. Neurology. 2003 Feb 11;60(3):390-4.
Stowe R, Ives Nj, Clarke C et al. **Dopamine agonist therapy in early Parkinson's disease. Cochrane** Database Syst Rev. 2008 Apr 16;(2):CD006564. This meta-analysis confirms that motor complications are reduced with dopamine agonists compared to levodopa, but also establishes that other important side-effects are increased and symptom control is poorer with agonists. Larger, long-term comparative trials assessing patient-rated quality of life are needed to assess more reliably the balance of benefits and risks of dopamine agonists compared to levodopa.
Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet Neurol. 2009 Aug 24. [Epub ahead of print]

[43] Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. **Falling asleep** at the wheel: motor vehicle mishaps in persons taking **pramipexole** and **ropinirole**. Neurology. 1999 Jun 10;52(9):1908-10.

[44] Hobson DE, Lang AE, Martin WR, et al. Excessive daytime sleepiness and sudden-onset **sleep** in Parkinson disease: a survey by the Canadian Movement Disorders Group. JAMA. 2002 Jan 23-30;287(4):455-63.

[45] Paus S, Brecht HM, Koster J, Seeger G, Klockgether T, Wullner U. **Sleep attacks**, daytime sleepiness, and dopamine agonists in Parkinson's disease. Mov Disord. 2003 Jun;18(6):659-67.

[46] Driver-Dunckley E, Samanta J, Stacy M. Pathological **gambling** associated with dopamine agonist therapy in Parkinson's disease. Neurology. 2003 Aug 12;61(3):422-3.

[47] Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE. Pathological **Gambling** Caused by Drugs Used to Treat Parkinson Disease. Arch Neurol. 2005 Jul 11; [Epub ahead of print]

[48] April,2003 Health Canada warning **Permax** and **cardiac valvulopathy** http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/permax_dhpl_e.pdf

[49] Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with **pergolide** and relation to restrictive **valvular** heart disease. Lancet. 2004 Apr 10;363(9416):1179-83.

[50] Van Camp G, Flamez A, Cosyns B, Goldstein J, Perdaens C, Schoors D. Heart **valvular** disease in patients with Parkinson's disease treated with high-dose **pergolide**. Neurology. 2003 Sep 23;61(6):859-61.

[51] Pinero A, Marcos-Alberca P, Fortes J. **Cabergoline**-related severe restrictive mitral regurgitation. N Engl J Med. 2005 Nov 3;353(18):1976-7. (Concern because reports of drug being abused: may prolong orgasms in men) (Yamamoto M, Uesugi T, Nakayama T. Dopamine agonists and cardiac **valvulopathy** in Parkinson disease: a case-control study. Neurology. 2006 Oct 10;67(7):1225-9. The frequency of valvulopathy was significantly increased in the cabergoline group. Our results indicate that high cumulative dose and long-term treatment with cabergoline are risk factors for valvulopathy in patients with Parkinson disease. & Junghanns S, Fuhrmann JT, et al. **Valvular heart disease** in Parkinson's disease patients treated with dopamine agonists: A reader-blinded monocenter echocardiography study. Mov Disord. 2006 Nov 8; [Epub ahead of print] Our data suggest that ergot DAs are associated with higher prevalence of VHD compared to non-ergot DAs and controls. Standard echocardiography seems sufficient to detect VHD in PD patients treated with DAs.) (Schade R, Andersohn F, Suissa S, et al. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med 2007; 356:29-38. (InfoPOEMs: The risk of cardiac valve damage is elevated in patients taking pergolide (Permax) or cabergoline (Dostinex), especially if the dose is higher than 3 mg per day and the drug is taken for more than 6 months. The absolute risk is modest: approximately 2.5 additional cases of valve damage for every 1000 patients who take one of the drugs for 1 year. (LOE = 3b)) Zanettini R, Antonini A, Gatto G, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 2007; 356:39-46. Roth BL. Drugs and valvular heart disease. N Engl J Med 2007; 356:6-9. According to a Perspective accompanying the two studies, the new findings support prior clinical and mechanistic evidence for a link between a histologically distinct fibrotic valvulopathy and treatment with drugs that block the serotonin receptor 5-hydroxytryptamine 2B (5-HT2B). Pergolide and cabergoline have that biochemical action in common, while the other studied dopamine antagonists don't have significant effects on **5-HT2B**.)
Colao A, Galderisi M, Di Sarno A, et al. Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. J Clin Endocrinol Metab. 2008 Oct;93(10):3777-84. Epub 2008 Aug 5.

[52] Clarke CE, Guttman M. **Dopamine agonist** monotherapy in Parkinson's disease. Lancet. 2002 Nov 30;360(9347):1767-9.
Katzenschlager R, Head J, Schrag A, Ben-Shlomo Y, Evans A, Lees AJ; On behalf of the Parkinson's Disease Research Group of the United Kingdom. Fourteen-year final report of the randomized **PDRG-UK** trial comparing three initial treatments in PD. Neurology. 2008 Jun 25. [Epub ahead of print] Initial treatment with the dopamine agonist bromocriptine did not reduce mortality or motor disability and the initially reduced frequency in motor complications was not sustained. We found no evidence of a long-term benefit or clinically relevant disease-modifying effect with initial dopamine agonist treatment.

[53] Ancelin ML, et al. Non-degenerative mild **cognitive impairment** in elderly people and use of **anticholinergic** drugs: longitudinal cohort study. BMJ. 2006 Feb 25;332(7539):455-9. Epub 2006 Feb 1.

[54] Katzenschlager R, Sampaio C, Costa J, Lees A. **Anticholinergics** for symptomatic management of Parkinson's disease. Cochrane Database Syst Rev. 2003;(2):CD003735.

[55] Uitti RJ, Rajput AH, Ahlskog JE, Offord KP, Schroeder DR, Ho MM, et al. **Amantadine** treatment is an independent predictor of improved survival in Parkinson's disease. Neurology. 1996 Jun;46(6):1551-6.

[56] Inzelberg R, Bonuccelli U, Schechtman E, Miniowich A, Strugatsky R, CeravoloR, Logi C, Rossi C, Klein C, Rabey JM. Association between amantadine and the onset of dementia in Parkinson's disease. Mov Disord. 2006 May 16; [Epub ahead of print]

[57] Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of **amantadine** benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004 Jan;75(1):141-3.

[58] Crosby NJ, Deane KH, Clarke CE. **Amantadine** for dyskinesia in Parkinson's disease. Cochrane Database Syst Rev. 2003;(2):CD003467.
Elahi B, Phielipp N, Chen R. **N-methyl-d-aspartate antagonists (amantadine)** in levodopa induced dyskinesia: a meta-analysis. Can J Neurol Sci. 2012 Jul;39(4):465-72.
Gottwald MD, Aminoff MJ. Emerging Therapies for **Dopaminergic-induced Dyskineasias** in Parkinson's Disease. Annals of Neurology. Accepted manuscript online: 16 MAR 2011; 1-17.

[59] Brooks DJ, Sagar H; UK-Irish Entacapone Study Group. **Entacapone** is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. J Neurol Neurosurg Psychiatry. 2003 Aug;74(8):1071-9.

[60] Myllyla VV, Kultalahti ER, Haapaniemi H, Leinonen M; FILOMEN Study Group. Twelve-month safety of **entacapone** in patients with Parkinson's disease. Eur J Neurol. 2001 Jan;8(1):53-60.

[61] **Entacapone** improves motor fluctuations in levodopa-treated Parkinson's disease patients. Parkinson Study Group. Ann Neurol. 1997 Nov;42(5):747-55.

[62] Larsen JP, Worm-Petersen J, Siden A, Gordin A, et al.; NOMESAFE Study Group. The tolerability and efficacy of entacapone over **3 years** in patients with Parkinson's disease. Eur J Neurol. 2003 Mar;10(2):137-46.

[63] Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M; Celomen Study Group. Efficacy and safety of **entacapone** in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). Acta Neurol Scand. 2002 Apr;105(4):245-55.

[64] Deane K, Spieker S, Clarke C. **Catechol-O-methyltransferase** inhibitors for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004554.

TOP

[65] Olanow CW, Kieburtz K, Stern M, et al.; US01 Study Team. Double-blind, placebo-controlled study of **entacapone** in **levodopa**-treated patients with stable Parkinson disease. Arch Neurol. 2004 Oct;61(10):1563-8.
[66] Mortality in **DATATOP**: a multicenter trial in early Parkinson's disease. Parkinson Study Group. Ann Neurol. 1998 Mar;43(3):318-25.
[67] Impact of **deprenyl** and **tocopherol** treatment on Parkinson's disease in DATATOP patients requiring levodopa. Parkinson Study Group. Ann Neurol. 1996 Jan;39(1):37-45.
[68] Impact of deprenyl and **tocopherol** treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. Parkinson Study Group. Ann Neurol. 1996 Jan;39(1):29-36.
[69] Waters CH, Sethi KD, Hauser RA, et al.; Zydis **Selegiline** Study Group. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. Mov Disord. 2004 Apr;19(4):426-32.
[70] Olanow CW, Myllyla VV, Sotaniemi KA, et al. Effect of **selegiline** on mortality in patients with Parkinson's disease: a meta-analysis. Neurology. 1998 Sep;51(3):825-30.
[71] Mortality in **DATATOP**: a multicenter trial in early Parkinson's disease. Parkinson Study Group. Ann Neurol. 1998 Mar;43(3):318-25.
[72] Macleod A, Counsell C, Ives N, Stowe R. Monoamine oxidase B inhibitors for early Parkinson's disease. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004898.
[73] Ives NJ, Stowe RL, Marro J, et al. **Monoamine oxidase type** B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. BMJ. 2004 Sep 11;329(7466):593.
[74] Palhagen S, Heinonen E, Hagglund J, Kaugesaar T, Maki-Ikola O, Palm R; Swedish Parkinson Study Group. **Selegiline** slows the progression of the symptoms of Parkinson disease. Neurology. 2006 Apr 25;66(8):1200-6. Epub 2006 Mar 15.
[75] Van Gerpen JA. **Drug-induced** parkinsonism. Neurologist. 2002 Nov;8(6):363-70. (Cersosimo MG, Koller WC. The diagnosis of manganese-induced parkinsonism. Neurotoxicology. 2005 Nov 30; [Epub ahead of print])
Esper CD, Factor SA. Failure of recognition of drug-induced parkinsonism in the elderly. Mov Disord. 2007 Dec 7; [Epub ahead of print]
[76] Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Cherif AA. **Nonmotor fluctuations** in Parkinson's disease: frequent and disabling. Neurology. 2002 Aug 13;59(3):408-13.
Zesiewicz, T. A., Sullivan, K. L., Arnulf, I., et al. AAN Practice Parameter: Treatment of nonmotor symptoms of Parkinson disease: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010 74: 924-931.
Leentjens AF. The role of dopamine agonists in the treatment of depression in patients with Parkinson's disease: a systematic review. Drugs. 2011 Feb 12;71(3):273-86. doi: 10.2165/11585380-000000000-00000.
[77] Pollak P, Tison F, Rascol O, et al. **Clozapine** in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry. 2004 May;75(5):689-95.
Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. Lancet. 1999 Jun 12;353(9169):2041-2.
Low-dose **clozapine** for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. N Engl J Med. 1999 Mar 11;340(10):757-63.
[78] Morgante L, Epifanio A, Spina E, et al. **Quetiapine** and **clozapine** in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004 Jul-Aug;27(4):153-6.
Morgante L, Epifanio A, Spina E, Zappia M, Di Rosa AE, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004 Jul-Aug;27(4):153-6.
Ondo WG, Tintner R, Dat Voung K, Lai D, Ringholz G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Mov Disord. 2005 Mar 30.
[79] Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of **botulinum toxin B** for sialorrhea in Parkinson's disease. Neurology. 2004 Jan 13;62(1):37-40. (Wieler M, Camicioli R, Jones CA, Martin WR. **Botulinum** toxin injections do not improve **freezing of gait** in Parkinson disease.Neurology. 2005 Aug 23;65(4):626-8.)(Lagalla G, et al. Botulinum toxin type A for drooling in Parkinson's disease: A double-blind, randomized, placebo-controlled study. Mov Disord. 2006 Jan 26; [Epub ahead of print])
[80] Leroi I, Brandt J, Reich SG, Lyketsos CG, Grill S, Thompson R, Marsh L. Randomized placebo-controlled trial of **donepezil** in cognitive impairment in Parkinson's disease. Int J Geriatr Psychiatry. 2004 Jan;19(1):1-8.
Emre M, et al. **Rivastigmine** for dementia associated with Parkinson's disease. (Express) N Engl J Med. 2004 Dec 9;351(24):2509-18. (Wesnes KA, et al. Benefits of rivastigmine on attention in dementia associated with Parkinson disease. Neurology. 2005 Nov 22;65(10):1654-6.)
McKeith I, Del Ser T, Spano P, et al. Efficacy of **rivastigmine** in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. Lancet 2000;356:2031-2036.
Maidment I, Fox C, Boustani M. Cholinesterase inhibitors for Parkinson's disease dementia. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004747.
Almaraz AC, Driver-Dunckley ED, Woodruff BK, et al. Efficacy of **rivastigmine** for cognitive symptoms in Parkinson disease with **dementia**. Neurologist. 2009 Jul;15(4):234-7. Rivastigmine therapy for PDD is associated with significant tradeoffs in efficacy and adverse effects.
Carefully monitored trials of rivastigmine may provide meaningful benefits for a minority of PDD patients.
[81] Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of **modafinil** for treating subjective daytime sleepiness in patients with Parkinson's disease. Mov Disord. 2003 Mar;18(3):287-93. & Ondo WG, Fayle R, Atassi F, Jankovic J. **Modafinil** for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry. 2005 Dec;76(12):1636-9.
Zesiewicz, T. A., Sullivan, K. L., Arnulf, I., et al. AAN Practice Parameter: Treatment of nonmotor symptoms of Parkinson disease: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010 74: 924-931.
[82] Crosby NJ, Deane KH, Clarke CE. **Beta-blocker** therapy for tremor in Parkinson's disease. Cochrane Database Syst Rev. 2003;(1):CD003361.
[83] Dewey RB Jr, Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected **apomorphine** for parkinsonian off-state events. Arch Neurol. 2001 Sep;58(9):1385-92.
Stacy M. Apomorphine: North American clinical experience. Neurology. 2004 Mar 23;62(6 Suppl 4):S18-21.
Apomorphine for Advanced Parkinson's disease. Med Lett Drugs Ther. **2005** Jan 17;47(1200):7-8.
Haq IU, Lewitt PA, Fernandez HH. Apomorphine therapy in Parkinson's disease: a review. Expert Opin Pharmacother. 2007 Nov;8(16):2799-809.
[84] Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. Parkinson Study Group. Ann Neurol. 1996 Jan;39(1):37-45. (Etminan M, Gill SS, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. Lancet Neurol. 2005 Jun;4(6):362-5.) (Pham DQ, Plakogiannis R. Vitamin e supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: part 2. Ann Pharmacother. 2005 Dec;39(12):2065-71. Epub 2005 Nov 15.)
[85] Walter BL, Vitek JL. **Surgical** treatment for Parkinson's disease. Lancet Neurol. 2004 Dec;3(12):719-28.
[86] Valerie C. Anderson; Kim J. Burchiel; Penelope Hogarth; et al. **Pallidal vs Subthalamic** Nucleus Deep Brain Stimulation in Parkinson Disease. Arch Neurol. 2005;62:554-560.
Williams A, Gill S, Varma T, et al. on behalf of the **PD SURG** Collaborative Group. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol. 2010 Apr 28.
Follett, Kenneth A., Weaver, Frances M., Stern, Matthew, et al. the CSP 468 Study Group, **Pallidal versus Subthalamic** Deep-Brain Stimulation for Parkinson's Disease. N Engl J Med 2010 362: 2077-2091.
Brennan KA, Genever RW. Managing **Parkinson's disease during surgery**. BMJ. 2010 Nov 1;341:c5718. doi: 10.1136/bmj.c5718.
Bronstein JM, Tagliati M, Alterman RL, et al. **Deep brain stimulation** for Parkinson disease: an expert consensus and review of key issues. Arch Neurol. 2011 Feb;68(2):165.
Savica R, Matsumoto JY, Josephs KA, et al. **Deep brain stimulation** in benign tremulous parkinsonism. Arch Neurol. 2011 Aug;68(8):1033-6.
Castrioto A, Lozano AM, Poon YY, et al.Ten-Year Outcome of **Subthalamic Stimulation** in Parkinson Disease: A Blinded Evaluation. Arch Neurol. 2011 Aug 8.
Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. New Engl J Med 2006; 355: 896–908.
Moro E, Lozano AM, Pollak P, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord 2010; 25: 578–86.
Okun MS, Gallo BV, Mandybur G, et al, for the SJM DBS Study Group. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol 2012; published online Jan 11.
Machado A, Fernandez HH, Deogaonkar M. **Deep brain stimulation**: What can patients expect from it? Cleveland Clinic Journal of Medicine 2012; 79(2):113-120;doi:10.3949/ccjm.78gr.11006. (generally appendicular symptoms such as limb tremor & rigidity more responsive)
Sharma A, Szeto K, Desilets AR. Efficacy and Safety of **Deep Brain Stimulation** as an Adjunct to Pharmacotherapy for the Treatment of Parkinson Disease (February). Ann Pharmacother. 2012 Jan 10.
Tarsy D. Treatment of Parkinson disease: a 64-year-old man with **motor complications** of advanced Parkinson disease. JAMA. 2012 Jun 6;307(21):2305-14.
Weaver FM, Follett KA, Stern M, et al; For the CSP 468 Study Group. Randomized trial of **deep brain stimulation** for Parkinson disease: Thirty-six-month outcomes. Neurology. 2012 Jul 3;79(1):55-65.

Additional articles:

Aasly JO, Shi M, Sossi V et al. Cerebrospinal fluid amyloid β and tau in **LRRK2 mutation carriers**. Neurology. 2012 Jan 3;78(1):55-61.
Alcalay RN, Caccappolo E, Mejia-Santana H, et al. **Cognitive performance of GBA mutation carriers** with early onset PD: the CORE-PD study. Neurology 2012;78:1434–1440.
Almaraz AC, Driver-Dunckley ED, Woodruff BK, et al. Efficacy of **rivastigmine** for cognitive symptoms in Parkinson disease with **dementia**. Neurologist. 2009 Jul;15(4):234-7. Rivastigmine therapy for PDD is associated with significant tradeoffs in efficacy and adverse effects.
Carefully monitored trials of rivastigmine may provide meaningful benefits for a minority of PDD patients.
Antonini A, Cilia R. **Behavioural adverse effects of dopaminergic** treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. Drug Saf. 2009;32(6):475-88. doi: 10.2165/00002018-200932060-00004.
Antonini A. The conundrum of **neuroprotection** in Parkinson's disease. Lancet Neurol. 2011 Apr 7.
Arbouw ME, Movig KL, Koopmann M, Poels PJ, Guchelaar HJ, Egberts TC, Neef C, et al. **Glycopyrrolate for sialorrhea** in Parkinson disease: a randomized, double-blind, crossover trial. Neurology. 2010 Apr 13;74(15):1203-7. Oral glycopyrrolate 1 mg 3 times daily is an effective and safe therapy for sialorrhea in Parkinson disease. Classification of evidence: This study provides Class I evidence that glycopyrrolate 1 mg 3 times daily is more effective than placebo in reducing sialorrhea in patients with Parkinson disease during a 4-week study.
Barber Thomas M., Kenkre Julia, Garnett Catherine, et al. **Recurrence of hyperprolactinaemia following discontinuation of dopamine agonist** therapy in patients with prolactinoma occurs commonly especially in **macroprolactinoma**. Article first published online: 9 NOV 2011.
Barone P, et al. and the Depression/Parkinson Italian Study Group. **Pramipexole versus sertraline** in the treatment of **depression** in Parkinson's disease : A national multicenter parallel-group randomized study. J Neurol. 2006 Apr 20; [Epub ahead of print]
Barone P, Poewe W, Albrecht S et al. **Pramipexole** for the treatment of **depressive** symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010 May 7.
Becker C, Jick SS, Meier CR. Use of antihypertensives and the risk of Parkinson disease. Neurology. 2008 Feb 6; [Epub ahead of print] Current long-term use of **calcium channel blockers** was associated with a significantly reduced risk of a Parkinson disease diagnosis, while the risk was not materially altered for users of angiotensin converting enzyme inhibitors or beta-blockers and, with less statistical precision, for users of angiotensin II antagonists.
Bender A, et al. **Creatine** supplementation in Parkinson disease: a placebo-controlled randomized pilot trial. Neurology. 2006 Oct 10;67(7):1262-4. Cr improved patient mood and led to a smaller dose increase of dopaminergic therapy but had no effect over 2yrs on overall Unified Parkinson's Disease Rating Scale scores or dopamine transporter SPECT.
Benninger DH, Berman BD, Houdayer E, et al. **Intermittent theta-burst transcranial magnetic stimulation** for treatment of Parkinson disease. Neurology. 2011 Feb 15;76(7):601-9.
Berg D, Seppi K, Behnke S, et al. **Enlarged substantia nigra hyperechogenicity** and risk for Parkinson disease: a 37-month 3-center study of 1847 older persons. Arch Neurol. 2011 Jul;68(7):932-7.
Bonakdar RA, Guarneri E. **Coenzyme Q10**. Am Fam Physician. 2005 Sep 15;72(6):1065-70.
Bonnici André, Ruiner Carola-Ellen, St-Laurent Lyne, et al. An Interaction Between **Levodopa and Enteral Nutrition** Resulting in Neuroleptic Malignant–Like Syndrome and Prolonged ICU Stay. Ann Pharmacother .44:1504-1507.
Brandt-Christensen M, Kvist et al. Treatment with **antidepressants and lithium is associated** with increased risk of treatment with antiparkinson drugs: a pharmacoepidemiological study. J Neurol Neurosurg Psychiatry. 2006 Jun;77(6):781-3.
Brennan KA, Genever RW. Managing **Parkinson's disease during surgery**. BMJ. 2010 Nov 1;341:c5718. doi: 10.1136/bmj.c5718.

TOP

Bronstein JM, Tagliati M, Alterman RL, et al. **Deep Brain Stimulation** for Parkinson Disease: An Expert Consensus and Review of Key Issues. Arch Neurol. 2010 Oct 11.
Brüggemann N, Spiegler J, Hellenbroich Y, et al. Beneficial Prenatal **Levodopa** Therapy in Autosomal Recessive **Guanosine Triphosphate Cyclohydrolase 1 Deficiency**. Arch Neurol. 2012 Apr 2.
Callaghan RC, Cunningham JK, Sajeev G, Kish SJ. Incidence of Parkinson's disease among hospital patients with **methamphetamine**-use disorders. Mov Disord. 2010 Aug 24.
Carlesimo GA, Piras F, Assogna F, Pontieri FE, Caltagirone C, Spalletta G. **Hippocampal abnormalities and memory deficits** in Parkinson disease: A multimodal imaging study. Neurology. 2012 Jun 12;78(24):1939-45. Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. **Ten-Year Outcome of Subthalamic Stimulation** in Parkinson Disease: A Blinded Evaluation. Arch Neurol. 2011 Aug 8.
Cereda E, Barichella M, Cassani E, et al. Clinical features of **Parkinson disease when onset of diabetes came first**: A case-control study.Neurology. 2012 May 8;78(19):1507-11.
Chen H, Jacobs E, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ, Ascherio A. **Nonsteroidal antiinflammatory** drug use and the risk for Parkinson's disease. Ann Neurol. 2005 Dec;58(6):963-7.
Chen JJ, Swope DM. **Pharmacotherapy for Parkinson's disease**. Pharmacotherapy. 2007 Dec;27(12 Pt 2):161S-73S.
Cheng EM, Tonn S, Swain-Eng R, et al. American Academy of Neurology Parkinson Disease Measure Development Panel. Quality improvement in neurology: **AAN Parkinson disease quality measures**: report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology. Neurology. 2010 Nov 30;75(22):2021-7.
Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor (donepezil) on reducing falls in Parkinson disease. Neurology. 2010 Sep 1.
Clarke CE. **Parkinson's disease**. BMJ. 2007 Sep 1;335(7617):441-5.
Criswell SR, Perlmutter JS, Videen TO, et al. Reduced uptake of **[18F]FDOPA PET** in asymptomatic **welders** with occupational manganese exposure. Neurology. 2011 Apr 12;76(15):1296-301.
de la Fuente-Fernández R. Role of **DaTSCAN** and clinical diagnosis in Parkinson disease. Neurology 2012;78:696–701.
de Lau LM, Schipper CM, Hofman A, et al. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol. 2005 Aug;62(8):1265-9. (InfoPOEMs: Patients with Parkinson's disease, especially those with at least one apolipoprotein E (APOE) gene epsilon2 allele, are at increased risk of developing dementia. Furthermore, patients with Parkinson's disease have a higher mortality risk, especially those who have had the disease the longest. (LOE = 1b))
Deleu D, et al. Effects of **caffeine** on levodopa pharmacokinetics and pharmacodynamics in Parkinson disease. Neurology. 2006 Sep 12;67(5):897-9. Caffeine administered before levodopa may improve its pharmacokinetics in some parkinsonian patients.
Derkinderen P, Rouaud T, Lebouvier T, et al. Parkinson disease: The **enteric nervous system** spills its guts. Neurology. 2011 Nov 8;77(19):1761-7.
Deuschl G, et al.; German Parkinson Study Group,Neurostimulation Section. A randomized trial of **deep-brain stimulation** for Parkinson's disease. N Engl J Med. 2006 Aug 31;355(9):896-908. (InfoPOEMs: Deep-brain stimulation poses risks, but also offers mild to moderate improvement in motor function for patients with severe Parkinson's disease (PD) who are already using maximal medical therapy. (LOE = 1b-))
Devos D, Dujardin K, Poirot I, Moreau C, Cottencin O, Thomas P, Destée A, Bordet R, Defebvre L. Comparison of **desipramine and citalopram** treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord. 2008 Apr 30;23(6):850-7.
Dickerson LM, Young SE, Simpson WM, Nashelsky J. Treatment of early Parkinson's disease. Am Fam Physician. 2005 Aug 1;72(3):497-500.
Dobkin RD, Menza M, Allen LA, et al. **Cognitive-behavioral therapy for depression in Parkinson's** disease: a random ized, controlled trial. Am J Psychiatry 2011; 168:1066–1074.
Dore DD, Trivedi AN, Mor V, Friedman JH, et al. **Atypical antipsychotic** use and risk of **fracture in persons** with Parkinsonism. Mov Disord. 2009 Jul 30. [Epub ahead of print] Use of an AA was associated with a higher rate of fracture in persons with parkinsonism.
Dorsey ER, Deuel LM, Beck CA, et al. **Group patient visits** for Parkinson disease: A randomized feasibility trial. Neurology. 2011 May 3;76(18):1542-7.
Driver Jane A, Logroscino Giancarlo, Lu Linda, et al. Use of non-steroidal anti-inflammatory drugs **(NSAIDs)** and risk of Parkinson's disease: nested case-control study. BMJ 2011;342:doi:10.1136/bmj.d198 (20 Jan 2011) –no association found
Ekman U, Eriksson J, Forsgren L, et al. **Functional brain activity and presynaptic dopamine uptake** in patients with Parkinson's disease and mild cognitive impairment: a cross-sectional study. Lancet Neurol. 2012 Jun 26.
Elahi B, Phielipp N, Chen R. **N-methyl-d-aspartate antagonists (amantadine)** in levodopa induced dyskinesia: a meta-analysis. Can J Neurol Sci. 2012 Jul;39(4):465-72.
Emre M, Tsolaki M, Bonuccelli Uet al; 11018 Study Investigators. **Memantine** for patients with **Parkinson's disease dementia** or dementia with **Lewy bodies**: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010 Oct;9(10):969-77.
Espay AJ, Dwivedi AK, Payne M, et al. **Methylphenidate for gait** impairment in Parkinson disease: A randomized clinical trial. Neurology. 2011 Apr 5;76(14):1256-62.
Espay AJ, Fasano A, van Nuenen BFL, Payne MM, Snijders AH, Bloem BR. "**On" state freezing** of gait in Parkinson disease: a paradoxical **levodopa-induced** complication. Neurology 2012;78:454 – 457
Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of **vitamin d insufficiency** in patients with Parkinson disease and Alzheimer disease. Arch Neurol. 2008 Oct;65(10):1348-52. This report of 25(OH)D concentrations in a predominantly white PD cohort demonstrates a significantly higher prevalence of **hypovitaminosis in PD** vs both healthy controls and patients with AD. These data support a possible role of vitamin D insufficiency in PD.
Evatt ML, Delong MR, Kumari M, et al; for the Parkinson Study Group DATATOP Investigators. High Prevalence of **Hypovitaminosis D** Status in Patients With Early Parkinson Disease. Arch Neurol. 2011 Mar;68(3):314-319.
Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson's disease with **deep brain stimulation**. Lancet Neurol. 2012 May;11(5):429-42.
FDA Drug Safety Communication: Ongoing Safety Review of **Stalevo** (entacapone/carbidopa/levodopa) and possible development of **Prostate Cancer** in **STRIDE-PD** trial. Mar/10 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm206363.htm In that trial, 3.7% of pts taking Stalevo developed prostate cancer over a mean follow-up of 2.7 years, compared with 0.9% of patients taking carbidopa/levodopa (Sinemet) (odds ratio, 4.2). Previous trials of Stalevo and Comtan (entacapone) did not find an association with prostate cancer.
FDA Drug Safety Communication Aug/10 : Patients taking **Stalevo** (carbidopa/levodopa plus entacapone) for Parkinson disease might be at greater risk for **cardiovascular events** than those taking Sinemet (carbidopa/levodopa), according to the FDA. The agency conducted a meta-analysis after the STRIDE-PD trial found a higher rate of myocardial infarction in patients using Stalevo. The meta-analysis of 15 clinical trials found an association between Stalevo and cardiovascular events (relative risk, 2.46), but the results were no longer significant after excluding the STRIDE-PD data.
Fernandez HH. **Updates in the medical management** of Parkinson disease. Cleve Clin J Med. 2012 Jan;79(1):28-35.
Follett, Kenneth A., Weaver, Frances M., Stern, Matthew, et al. the CSP 468 Study Group, Pallidal versus Subthalamic Deep-Brain **Stimulation** for Parkinson's Disease. N Engl J Med 2010 362: 2077-2091.
Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. A 12-year population-based study of **psychosis in Parkinson disease**. Arch Neurol. 2010 Aug;67(8):996-1001.
Frithsen IL, Simpson WM Jr. Recognition and management of acute medication **poisoning**. Am Fam Physician. 2010 Feb 1;81(3):316-23.
Gagne JJ, Power MC. **Anti-inflammatory drugs** and risk of Parkinson disease: a meta-analysis. Neurology 2010;74:995–1002.
Gan-Or Z, Bar-Shira A, Dahary D, et al. Association of Sequence Alterations in the **Putative Promoter of RAB7L1** With a Reduced Parkinson Disease Risk. Arch Neurol. 2012 Jan;69(1):105-10.
Gao X, Chen H, Schwarzschild MA, et al. Use of **ibuprofen and risk of Parkinson disease**. Neurology. 2011 Mar 8;76(10):863-9.
Gao X, Simon K, Schwarzschild M et al. Prospective Study of **Statin Use** and Risk of Parkinson Disease Arch Neurol. 2012;69(3):380-384.
Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A. Habitual intake of **dietary flavonoids** and risk of Parkinson disease. Neurology 2012;78:1138 –1145.
Giacino JT et al. Placebo-controlled trial of **amantadine for severe traumatic brain injury**. N Engl J Med 2012 Mar 1; 366:819.
Gitchel GT, Wetzel PA, Baron MS. Pervasive **Ocular Tremor** in Patients With Parkinson Disease. Arch Neurol. 2012 Apr 9.
Gjerstad MD, Tysnes OB, Larsen JP. Increased risk of **leg motor restlessness but not RLS** in early Parkinson disease. Neurology 2011;77:1941–1946.
Godau J, Knauel K, Weber K et al. Serum **insulinlike growth factor 1** as possible marker for risk and early diagnosis of Parkinson disease. Arch Neurol. 2011 Jul;68(7):925-31.
Goetz CG, Poewe W, Rascol O, Sampaio C. **Evidence-based medical review** update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Mov Disord. **2005** May;20(5):523-39.
Goldman SM, Quinlan PJ, Ross GW, et al. **Solvent exposures** and parkinson disease risk in twins. Ann Neurol. 2011 Nov 14.
Gottwald MD, Aminoff MJ. Emerging Therapies for **Dopaminergic-induced Dyskineasias** in Parkinson's Disease. Annals of Neurology. Accepted manuscript online: 16 MAR 2011; 1-17.
Gross RE, Watts RL, et al. Spheramine Investigational Group. Intrastriatal transplantation of microcarrier-bound human **retinal pigment epithelial cells versus sham surgery** in patients with advanced Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neurol. 2011 May 10.
Grosset KA, et al. **Problematic gambling** on dopamine agonists: Not such a rarity. Mov Disord. 2006 Sep 29; [Epub ahead of print]
Grosset DG, Macphee GJ, Nairn M; Guideline Development Group. Diagnosis and pharmacological management of Parkinson's disease: summary of **SIGN** guidelines. BMJ. 2010 Jan 12;340:b5614. doi: 10.1136/bmj.b5614.
Hauser RA. Long-term care of Parkinson's disease. Strategies for managing **"wearing off"** symptom re-emergence and dyskinesias. Geriatrics. 2006 Sep;61(9):14-20.
Health Canada Aug/07: Eli Lilly Canada advises Healthcare Professionals that they will **cease sale of Permax** August 30, 2007 due to risk of cardiac valvulopathy.
Hodgins David C, Stea Jonathan N, Grant Jon E. **Gambling disorders**. www.thelancet.com Published online May 19, 2011 DOI:10.1016/S0140-6736(10)62185-X
Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of **pramipexole**, a dopamine agonist, in patients with **fibromyalgia** receiving concomitant medications. Arthritis Rheum. 2005 Aug;52(8):2495-505.
Hutchinson M. At last, a **gene therapy** for Parkinson's disease? Lancet Neurol. 2011 Apr;10(4):290-1.
International Parkinon Disease Genomics Consortium. Imputation of sequence variants for identification of **genetic risks for Parkinson's disease**: a meta-analysis of **genome-wide association studies**. Lancet. Online Feb. 2, 2011.
Jankovic J, Watts RL, Martin W, Boroojerdi B. Transdermal **rotigotine**: double-blind, placebo-controlled trial in Parkinson disease. Arch Neurol. 2007 May;64(5):676-82.
Jung Kang U, Auinger P; On behalf of the Parkinson Study Group ELLDOPA Investigators, Mendis T. **Activity enhances dopaminergic long-duration response** in Parkinson disease. Neurology. 2012 Apr 10;78(15):1146-1149. Junghanns S, Fuhrmann JT, et al. **Valvular heart disease** in Parkinson's disease patients treated with dopamine agonists: A reader-blinded monocenter echocardiography study. Mov Disord. 2006 Nov 8; [Epub ahead of print] Our data suggest that ergot DAs are associated with higher prevalence of VHD compared to non-ergot DAs and controls. Standard echocardiography seems sufficient to detect VHD in PD patients treated with DAs.
Khan S, Gill SS, Mooney L, et al. Combined **pedunculopontine subthalamic stimulation (DBS)** in Parkinson disease. Neurology 2012;78:1090 –1095.
Kipfer S, Stephan MA, Schüpbach WM, et al. **Resting tremor** in Parkinson disease: a negative predictor of levodopa-induced dyskinesia. Arch Neurol. 2011 Aug;68(8):1037-9.
Kirsch-Darrow L, et al. Dissociating **apathy and depression** in Parkinson disease. Neurology. 2006 Jul 11;67(1):33-8.
Klein C, Prokhorov T, et al. Long-term Follow-up (24 Months) of **Quetiapine** Treatment in Drug-induced Parkinson Disease Psychosis. Clin Neuropharmacol. 2006 Jul-Aug;29(4):215-9.
Klibanski, Anne. **Prolactinomas**. N Engl J Med 2010 362: 1219-1226.
Kostic VS, Agosta F, Pievani M et al. Pattern of **brain tissue loss** associated with **freezing of gait** in Parkinson disease. Neurology. 2012 Feb 7;78(6):409-16.
Knekt Paul; Kilkkinen Annamari; Rissanen Harri; et al. Serum **Vitamin D** and the Risk of Parkinson Disease Arch Neurol. 2010;67(7):808-811.
Kumlien E, Lundberg PO. **Seizure risk** associated with **neuroactive drugs**: data from the **WHO** adverse drug reactions database. Seizure. 2010 Mar;19(2):69-73.
Lanier JB, Mote MB, Clay EC. Evaluation and management of **orthostatic hypotension**. Am Fam Physician. 2011 Sep 1;84(5):527-36.
Lees A. Alternatives to levodopa in the initial treatment of early Parkinson's disease. Drugs Aging. 2005;22(9):731-40.

TOP

Lees AJ, Hardy J, Revesz T. **Parkinson's disease**. Lancet. 2009 Jun 13;373(9680):2055-66.

Leentjens AF. The role of **dopamine agonists in the treatment of depression** in patients with Parkinson's disease: a systematic review. Drugs. 2011 Feb 12;71(3):273-86. doi: 10.2165/11585380-000000000-00000.

Lewitt PA, Rezai AR, Leehey MA, et al. **AAV2-GAD gene therapy** for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. Lancet Neurol. 2011 Apr;10(4):309-19.

Lewitt PA, Hauser RA, Lu M, et al. Randomized clinical trial of **fipamezole** (90mg tid) for dyskinesia in Parkinson disease (FJORD study). Neurology. 2012 Jun 27.

Li F et al. **Tai chi** and postural stability in patients with Parkinson's disease. N Engl J Med 2012 Feb 9; 366:511.

Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between **Parkinson disease and melanoma**. Neurology. 2011 Jun 7;76(23):2002-9.

Mamikonyan E, Siderowf AD, Duda JE, Potenza MN, Horn S, Stern MB, Weintraub D. Long-term follow-up of **impulse control disorders** in Parkinson's disease. Mov Disord. 2007 Oct 25; [Epub ahead of print] For PD patients who develop an ICD in the context of DA treatment, discontinuing or significantly decreasing DA exposure, even when offset by an increase in levodopa treatment, is associated with remission of or significant reduction in ICD behaviors without worsening in motor symptoms.

Maraganore DM, et al.; Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium. Collaborative analysis of **alpha-synuclein gene** promoter variability and Parkinson disease. JAMA. 2006 Aug 9;296(6):661-70.

Marks Jr William J, Bartus Raymond T, Siffert Joao, et al. **Gene delivery of AAV2-neurturin** for Parkinson's disease: a double-blind, randomised, controlled trial, The Lancet Neurology, Volume 9, Issue 12, Dec 2010

Marras C, Gruneir A, Rochon P, et al. **Dihydropyridine calcium channel blockers** and the progression of parkinsonism. Ann Neurol. 2012 Mar;71(3):362-9.

Medical Letler. **Rotigotine** (Neupro) for Parkinson's Disease. Aug 27,2007.

Mehrholz J, Friis R, Kugler J, Twork S, Storch A, Pohl M. **Treadmill training** for patients with Parkinson's disease. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007830.

Menza M, Defronzo Dobkin R, Marin H, Mark MH, Gara M, Buyske S, Bienfait K, Dicke A. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 2008 Dec 17. [Epub ahead of print] n=52. Though relatively modest in size, this is the largest placebo-controlled trial done to date in patients with Parkinson disease (PD) and depression. **Nortriptyline** was efficacious in the treatment of depression and paroxetine CR was not.

Mollenhauer Brit, Locascio Joseph J, Schulz-Schaeffer Walter, et al. **[alpha]-Synuclein and tau concentrations** in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study, The Lancet Neurology, Volume 10, Issue 3, March 2011

Monteiro L, Souza-Machado A, Valderramas S et al. The Effect of **Levodopa on Pulmonary Function** in Parkinson's Disease: A Systematic Review and Meta-Analysis. Clin Ther. 2012 Mar 30.

Moreau C, Delval A, Defebvre L, et al; for the Parkgait-II study group. **Methylphenidate for gait hypokinesia and freezing** in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. Lancet Neurol. 2012 May 31.

Morelli M, Arabia G, Novellino F, et al. **MRI measurements predict PSP** in unclassifiable parkinsonisms: A cohort study. Neurology. 2011 Sep 13;77(11):1042-7.

Moro E, Lozano AM, Pollak P, et al. Long-term results of a multicenter study on **subthalamic and pallidal stimulation** in Parkinson's disease. Mov Disord 2010; 25: 578–86.

NICE: National Institute for Health and Clinical Excellence - **Parkinson's disease**: diagnosis and management in primary and secondary care. June 2006. http://www.nice.org.uk/nicemedia/pdf/cg035niceguideline.pdf.

Nielsen HH, Qiu J, Friis S, Wermuth L, Ritz B. Treatment for **Helicobacter pylori** infection and risk of Parkinson's disease in Denmark. Eur J Neurol. 2012 Jun;19(6):864-9.

NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of **creatine and minocycline** in early Parkinson disease. Neurology. 2006 Mar 14;66(5):664-71. Epub 2006 Feb 15.

Nissinen H, Kuoppamäki M, Leinonen M, Schapira AH. **Early** versus delayed initiation of **entacapone** in levodopa-treated patients with Parkinson's disease: a long-term, retrospective analysis. Eur J Neurol. 2009 Jun 30. [Epub ahead of print] These data suggest that early rather than delayed addition of entacapone to levodopa/DDCI in PD patients with wearing-off provides a modest clinical benefit over levodopa/DDCI that is maintained for up to 5 years.

Nutt JG, Wooten GF. Clinical practice. Diagnosis and initial management of Parkinson's disease. N Engl J Med. 2005 Sep 8;353(10):1021-7.

Okun MS, et al. **Testosterone** therapy in men with Parkinson disease: results of the TEST-PD Study. Arch Neurol. 2006 May;63(5):729-35.

Okun MS, Gallo BV, Mandybur G, et al, for the **SJM DBS** Study Group. **Subthalamic deep brain stimulation** with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol 2012

Olanow CW, Rascol O, Hauser R, et al. **ADAGIO Study** Investigators. A double-blind, delayed-start trial of **rasagiline** in Parkinson's disease. N Engl J Med. 2009 Sep 24;361(13):1268-78.

Ondo WG, Kenney C, Sullivan K, et al. Placebo-controlled trial of **lubiprostone** for constipation associated with Parkinson disease. Neurology. 2012 May 22;78(21):1650-4.

Ozelius LJ, et al. **LRRK2** G2019S as a cause of Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2006 Jan 26;354(4):424-5.

Pappatà S, Santangelo G, Aarsland D, et al. Mild cognitive impairment in drug-naive patients with PD is associated with cerebral hypometabolism. Neurology. 2011 Oct 4;77(14):1357-62.

Parkkinen L, O'Sullivan SS, Kuoppamaki M, et al. Does **levodopa accelerate the pathologic process** in Parkinson disease brain? Neurology 2011;77;1420 –1426.

Parkinson Study Group **CALM** Cohort Investigators. Long-term Effect of Initiating Pramipexole vs Levodopa in Early Parkinson Disease. Arch Neurol. 2009 Mar 9. [Epub ahead of print] The policies of initial pramipexole and initial levodopa use followed by open-label levodopa use resulted in similar self-reported disability 6 years after randomization. Persistent differences favoring initial pramipexole were seen in the rates of dopaminergic motor complications, with less severe somnolence favoring initial levodopa.

Pharmacist's Letter Oct 2006. Alternative or **Off-label** Routes of Drug Administration. (Vaginal administration of: bromocriptine; Sublingual Atropine eye drops or Atroven nasal spray to ↓ saliva & drooling))

Pharmacist's Letter Oct 2006. Azilect (**rasagiline** mesylate). (see also Medical Letter Dec 4/18,2006)

Pharmacist's Letter Feb 2007. Drug Induced **heart valve dysfunction**.

Pharmacists Letter. Neupro (**Rotigotine** transdermal system). June 2007.

Pierantozzi M, et al. **Helicobacter pylori eradication** and l-dopa absorption in patients with PD and motor fluctuations. Neurology. 2006 Jun 27;66(12):1824-9.

Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, Rupp M, Boroojerdi B; SP 515 Investigators. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol. 2007 Jun;6(6):513-20. 204 patients were randomly assigned to receive **rotigotine** (up to 16mg per day), 201 to receive **pramipexole** (up to 4.5mg per day), and 101 to receive placebo for 6 months. In terms of change in absolute off time, rotigotine was non-inferior to pramipexole. Continuous delivery of rotigotine as transdermal patches could offer similar efficacy to oral pramipexole in patients with fluctuating Parkinson's disease over 6 months of treatment.

Poewe W. Treatments for Parkinson disease--**past achievements and current clinical needs**. Neurology. 2009 Feb 17;72(7 Suppl):S65-73.

Poewe W, Rascol O, Barone P, et al. For the Pramipexole ER Studies Group. **Extended-release pramipexole** in early Parkinson disease: A 33-week randomized controlled trial. Neurology. 2011 Aug 23;77(8):759-766.

Rabinak Christina A.; Nirenberg Melissa J.. **Dopamine Agonist Withdrawal Syndrome** in Parkinson Disease. Arch Neurol. 2010;67(1):58-63.

Rajabally YA, Martey J. **Neuropathy** in Parkinson disease: prevalence and determinants. Neurology 2011;77:1947–1950. (Vitamin B12 deficiency association)

Rascol O, Brooks DJ, Melamed E, et al. **Rasagiline** as an adjunct to levodopa in patients with Parkinson's disease and motor fl uctuations (**LARGO**, Lasting e□ ect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet 2005; 365: 947–54.

Rascol O, Fitzer-Attas CJ, Hauser R, et al. A double-blind,delayed-start trial of **rasagiline** in Parkinson's disease (the **ADAGIO** study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes. Lancet Neurol. 2011 Apr 7.

Rees K, Stowe R, Patel S, Ives N, Breen K, Clarke CE, Ben-Shlomo Y. **Helicobacter pylori** eradication for Parkinson's disease. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD008453. There is currently a lack of evidence on the effects of screening and treating H pylori in patients with Parkinson'sdisease. There is limited evidence to suggest that H Pylori eradication improves the absorption of levodopa and improves motor symptoms.

Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants (paroxetine, venlafaxine) in Parkinson disease. (**SAD-PD**) Neurology 2012;78:1229–1236.

Rizzo Matthew. **Impaired Driving From Medical Conditions**: A 70-Year-Old Man Trying to Decide if He Should Continue Driving. JAMA. 2011;305(10):1018-1026.Published online March 1, 2011. doi:10.1001/jama.2011.252

Robottom BJ, Weiner WJ, Factor SA. Movement disorders **emergencies part 1: (neuroleptic malignant syndrome, Parkinsonism hyperpyrexia & serotonin syndrome)** hypokinetic disorders. Arch Neurol. 2011 May;68(5):567-72.

Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, et al.. Increased risk of parkinsonism in women who underwent **oophorectomy before menopause**. Neurology. 2007 Aug 29; [Epub ahead of print] Both unilateral and bilateral oophorectomy performed prior to menopause may be associated with an increased risk of parkinsonism and the effect may be age-dependent. However, our findings await independent replication.

Rochon PA, Stukel TA, Sykora K, Gill S, Garfinkel S, et al. **Atypical antipsychotics and parkinsonism**. Arch Intern Med. 2005 Sep 12;165(16):1882-8. CONCLUSIONS: The risk of development of parkinsonism associated with the use of high-dose atypical antipsychotics was similar to that associated with the use of typical antipsychotics. Caution should be used when prescribing atypical antipsychotic therapy at high doses.

Rodriguez-Oroz MC. **Deep brain stimulation** for advanced Parkinson's disease. Lancet Neurol. 2010 Apr 28. [Epub ahead of print]

Rongve A, Aarsland D. Management of Parkinson's disease **dementia** : practical considerations. Drugs Aging. 2006;23(10):807-22.

Ross OA, Soto-Ortolaza AI, Heckman MG, et al. on behalf of the Genetic Epidemiology Of Parkinson's Disease (GEO-PD) Consortium. Association of **LRRK2 exonic variants** with susceptibility to Parkinson's disease:a case-control study. Lancet Neurol. 2011 Oct;10(10):898-908.

Rugbjerg K, Ritz B, Korbo L, Martinussen N, Olsen JH. Risk of Parkinson's disease after hospital **contact for head injury**: population based case-control study. BMJ. 2008 Dec 15;337:a2494. doi: 10.1136/bmj.a2494. The steeply increased frequency of hospital contacts for a head injury during the months preceding the date at which Parkinson's disease was first recorded is a consequence of the evolving movement disorder rather than its cause.

Samii A, Etminan M, Wiens MO, Jafari S. NSAID use and the risk of **Parkinson's disease**: systematic review and meta-analysis of observational studies. Drugs Aging. 2009;26(9):769-79.

Savica R, Matsumoto JY, Josephs KA, et al. **Deep brain stimulation** in benign tremulous parkinsonism. Arch Neurol. 2011 Aug;68(8):1033-6.

Schapira AH, Barone P, Hauser RA, et al. For the Pramipexole ER Studies Group. **Extended-release pramipexole** in advanced Parkinson disease: A randomized controlled trial. Neurology. 2011 Aug 23;77(8):767-774.

Seppi K, Weintraub D, Coelho M, et al. The **Movement Disorder Society** Evidence-Based Medicine Review Update: Treatments for the **non-motor symptoms** of Parkinson's disease. Mov Disord. 2011 Oct;26 Suppl 3:S42-80. The treatments that are efficacious for the management of the different non-motor symptoms are as follows: pramipexole for the treatment of depressive symptoms, clozapine for the treatment of psychosis, rivastigmine for the treatment of dementia, and botulinum toxin A (BTX-A) and BTX-B as well as glycopyrrolate for the treatment of sialorrhea. The practical implications for these treatments, except for glycopyrrolate, are that they are clinically useful.

Sharma JC, Ross IN, et al. Relationship between **weight, levodopa and dyskinesia**: the significance of levodopa dose per kilogram body weight. Eur J Neurol. 2008 May;15(5):493-6. Higher levodopa dose per kilogram body weight is an independently significant factor for developing dyskinesia.

Sharma A, Szeto K, Desilets AR. Efficacy and Safety of **Deep Brain Stimulation** as an Adjunct to Pharmacotherapy for the Treatment of Parkinson Disease (February). Ann Pharmacother. 2012 Jan 10.

Shults CW, Oakes D, Kieburtz K, et al; Parkinson Study Group. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol. 2002 Oct;59(10):1541-50.

Siddiqui MA, Plosker GL. **Rasagiline**. Drugs Aging. 2005;22(1):83-91; discussion 93-4. (Goetz CG, et al.; Parkinson Study Group **TEMPO** and **PRESTO** Investigators. Safety of rasagiline in elderly patients with Parkinson disease. Neurology. 2006 May 9;66(9):1427-9.)(Rascol O, et al;**LARGO** study group. Rasagiline as an adjunct to levodopa in patients with parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet. 2005 Mar 12-18;365(9463):947-4.)(Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol. 2005 Feb;62(2):241-8.) (see also Pharmacist's Letter July 2006: New Treatments: Azilect & Zelapar)

Sixel-Do¨ring F, Trautmann E, Mollenhauer B, Trenkwalder C. Associated factors for **REM sleep behavior disorder** in Parkinson disease. Neurology 2011;77:1048 –1054

South AR, Somers SM, Jog MS. **Gum chewing improves** swallow frequency and latency in Parkinson patients: a preliminary study. Neurology. 2010 Apr 13;74(15):1198-202.

Stepens A, Logina I, Liguts V, et al. A Parkinsonian syndrome in methcathinone users and the role of **manganese**. N Engl J Med. 2008 Mar 6;358(10):1009-17. Our observation of a distinctive extrapyramidal syndrome, changes in the MRI signal in the basal ganglia, and elevated blood manganese

TOP

levels in methcathinone (ephedrone) users suggests that manganese in the methcathinone solution causes a persistent neurologic disorder.
Stocchi F, Vacca L, Ruggieri S, Olanow CW. Intermittent vs **continuous** levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. Arch Neurol. 2005 Jun;62(6):905-10.
Stocchi F, Rascol O, Kieburtz K, et al. Initiating **levodopa/carbidopa therapy with and without entacapone** in early Parkinson disease: the **STRIDE-PD** study. Ann Neurol. 2010 Jul;68(1):18-27.
Stowe R, Ives N, Clarke CE, Deane K; et al. Evaluation of the efficacy and safety of **adjuvant treatment to levodopa therapy** in Parkinson s disease patients with motor complications. Cochrane Database Syst Rev. 2010 Jul 7;7:CD007166. Compared to placebo, adjuvant therapy reduces off-time, levodopa dose, and improves UPDRS scores in PD patients who develop motor complications on levodopa therapy. However, this is at the expense of increased dyskinesia and numerous other side-effects. Indirect comparisons suggest that dopamine agonist therapy may be more effective than COMTI and MAOBI therapy, which have comparable efficacy. However, as indirect comparisons should be interpreted with caution, direct head-to-head randomised trials assessing the impact of these different drug classes on overall patient-rated quality of life are needed.
Storch A, Jost WH, Vieregge P, et al. Randomized, Double-blind, Placebo-Controlled Trial on Symptomatic Effects of **Coenzyme Q10** 100mg tid in Parkinson Disease. Arch Neurol. 2007 May 14; [Epub ahead of print] N=131 3months. Nanoparticular CoQ(10) at a dosage of 300 mg/d is safe and well tolerated and leads to plasma levels similar to 1200 mg/d of standard formulations. Add-on CoQ(10) does not display symptomatic effects in midstage Parkinson disease.
Tanner CM, Kamel F, Ross GW, et al. **Rotenone, Paraquat** and Parkinson's Disease. Environ Health Perspect. 2011 Jan 26.
Tarsy D. Treatment of Parkinson disease: a 64-year-old man with **motor complications** of **advanced Parkinson disease**. JAMA. 2012 Jun 6;307(21):2305-14.
Tolosa E, Wenning G, Poewe W. The **diagnosis** of Parkinson's disease. Lancet Neurol. 2006 Jan;5(1):75-86.
Thomsen TR, Galpern WR, Asante A, Arenovich T, Fox SH. **Ipratropium bromide spray as treatment for sialorrhea** in Parkinson's disease. Mov Disord. 2007 Sep 17; [Epub ahead of print] Ipratropium bromide spray had no significant effect on weight of saliva produced. There was a mild effect of treatment on subjective measures of sialorrhea.
Tsang EW, Hamani C, Moro E, et al. **Subthalamic deep brain stimulation** at individualized frequencies for Parkinson disease. Neurology. 2012 Jun 12;78(24):1930-8.
Uc EY, Rizzo M, et al. **Driving** with distraction in Parkinson disease. Neurology. 2006 Nov 28;67(10):1774-80.
Uc EY, Rizzo M, Johnson AM, et al. **Real-life driving** outcomes in Parkinson disease. Neurology. 2011 May 31;76(22):1894-902.
Vlad SC, Miller DR, Kowall NW, Felson DT. **Protective effects of NSAIDs** on the development of Alzheimer disease. Neurology 2008;70:1672–1677.
Voon V, Sohr M, Lang A, et al. **Impulse Control Disorders** in Parkinson Disease: A Multicenter Case-control study. Annals of Neurology. 2011 Jan 10; 1-33.
Vu TC, Nutt JG, Holford NH. **Progression of Motor and Non-Motor Features** of Parkinson's Disease and Their Response to Treatment. Br J Clin Pharmacol. 2012 Jan 29.
Wahner AD, Bronstein JM, Bordelon YM, Ritz B. **Nonsteroidal anti-inflammatory drugs** may protect against Parkinson disease. Neurology. 2007 Nov 6;69(19):1836-42. Our study contributes to the growing body of literature suggesting a protective role for nonsteroidal anti-inflammatory drugs (NSAIDs) in Parkinson disease (PD).
Weaver FM, Follett K, Stern M, Hur K, et al. 468 Study Group. **Bilateral deep brain stimulation** vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009 Jan 7;301(1):63-73. In this randomized controlled trial of patients with advanced PD, deep brain stimulation was more effective than best medical therapy in improving on time without troubling dyskinesias, motor function, and quality of life at 6 months, but was associated with an increased risk of serious adverse events.
Weaver FM, Follett KA, Stern M, et al; For the CSP 468 Study Group. Randomized trial of **deep brain stimulation** for Parkinson disease: Thirty-six-month outcomes. Neurology. 2012 Jul 3;79(1):55-65.
Weintraub D, et al. Association of dopamine agonist use with **impulse control** disorders in Parkinson disease. Arch Neurol. 2006 Jul;63(7):969-73.
Weintraub D, Hurtig HI. Presentation and management of **psychosis** in **Parkinson's disease and dementia with Lewy bodies**. Am J Psychiatry. 2007 Oct;164(10):1491-8.
Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, Lang AE. **Impulse control disorders** in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010 May;67(5):589-95.
Weintraub D, Chen P, Ignacio RV, et al. Patterns and trends in **antipsychotic prescribing** for Parkinson disease psychosis. Arch Neurol. 2011 Jul;68(7):899-904.
Williams-Gray CH, et al. **Cognitive deficits and psychosis** in Parkinson's disease: a review of pathophysiology and therapeutic options. CNS Drugs. 2006;20(6):477-505.
Williams A, Gill S, Varma T, et al. on behalf of the **PD SURG** Collaborative Group. **Deep brain stimulation plus best medical** therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol. 2010 Apr 28.
Williams JR, Hirsch ES, Anderson K, et al. A comparison of **nine scales to detect depression in Parkinson disease**: Which scale to use? Neurology. 2012 Mar 27;78(13):998-1006. The GDS-30 may be the most efficient depression screening scale to use in PD because of its brevity, favorable psychometric properties, and lack of copyright protection. However, all scales studied, except for the UPDRS Depression, are valid screening tools when PD-specific cutoff scores are used.
Willis AW, Evanoff BA, Lian M, et al. Metal Emissions and Urban Incident Parkinson Disease: A Community Health Study of Medicare Beneficiaries by Using Geographic Information Systems. Am J Epidemiol. 2010 Oct 19. (Copper & manganese associated with risk)
Willis AW, Schootman M, Evanoff BA, Perlmutter JS, Racette BA. **Neurologist care in Parkinson disease**: a utilization, outcomes, and survival study. Neurology 2011;77:851– 857.
Willis AW, Schootman M, Kung N, Evanoff BA, Perlmutter JS, Racette BA. **Predictors of Survival** in Patients With Parkinson Disease. Arch Neurol. 2012 Jan 2. (**Dementia** increases mortality)
Wu SS, Frucht SJ. Treatment of Parkinson's disease : what's on the horizon? CNS Drugs. 2005;19(9):723-43.
Yamamoto M, Uesugi T, Nakayama T. Dopamine agonists and cardiac **valvulopathy** in Parkinson disease: a case-control study. Neurology. 2006 Oct 10;67(7):1225-9. The frequency of valvulopathy was significantly increased in the cabergoline group. Our results indicate that high cumulative dose and long-term treatment with cabergoline are risk factors for valvulopathy in patients with Parkinson disease.
Young GB, Findlay JM, Benstead TJ, et al; Canadian Neurological Sciences Federation team. **Canadian Guidelines on Parkinson's Disease**. Can J Neurol Sci. 2012 July;(39)4.
Zanetti R, Loria D, Rosso S. Melanoma, Parkinson's disease and levodopa: causal or spurious link? A review of the literature. Melanoma Res. 2006 Jun;16(3):201-6.
Zanetti R, Rosso S. Levodopa and the risk of **melanoma**. Lancet. 2007 Jan 27;369(9558):257-8.
Zesiewicz, T. A., Sullivan, K. L., Arnulf, I., et al. **AAN Practice Parameter**: Treatment of **nonmotor symptoms of Parkin**son disease: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010 74: 924-931.

Guidelines AAN:

Cheng EM, Tonn S, Swain-Eng R, et al.; For the American Academy of Neurology Parkinson Disease Measure Development Panel. **Quality improvement** in neurology: AAN Parkinson disease quality measures: Report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology. Neurology. 2010 Nov 30;75(22):2021-2027. http://www.neurology.org/content/75/22/2021.full.pdf+html

Miyasaki JM, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: evaluation and treatment of **depression, psychosis, and dementia** in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):996-1002. http://www.neurology.org/cgi/reprint/66/7/996 Screening tools are available for depression and dementia in patients with PD, but more specific validated tools are needed. There are no widely used, validated tools for psychosis screening in Parkinson disease (PD). Clozapine successfully treats psychosis in PD. Cholinesterase inhibitors are effective treatments for dementia in PD, but improvement is modest and motor side effects may occur.

Pahwa R, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: treatment of Parkinson disease with **motor fluctuations and dyskinesia** (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):983-95. http://www.neurology.org/cgi/reprint/66/7/983 1. Entacapone and rasagiline should be offered to reduce off time (Level A). Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B). Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C). 2. The available evidence does not establish superiority of one medicine over another in reducing off time (Level B). Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C). 3. Amantadine may be considered to reduce dyskinesia (Level C). 4. Deep brain stimulation of the STN may be considered to improve motor function and reduce off time, dyskinesia, and medication usage (Level C). There is insufficient evidence to support or refute the efficacy of DBS of the GPi or VIM nucleus of the thalamus in reducing off time, dyskinesia, or medication usage, or to improve motor function. 5. Preoperative response to levodopa predicts better outcome after DBS of the STN (Level B).

Suchowersky O, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: **neuroprotective strategies and alternative** therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):976-82. http://www.neurology.org/cgi/reprint/66/7/976 1. Levodopa does not appear to accelerate disease progression. 2. No treatment has been shown to be neuroprotective. 3. There is no evidence that vitamin or food additives can improve motor function in PD. 4. Exercise may be helpful in improving motor function. 5. Speech therapy may be helpful in improving speech volume. 6. No manual therapy has been shown to be helpful in the treatment of motor symptoms, although studies in this area are limited. Further studies using a rigorous scientific method are needed to determine efficacy of alternative therapies.

Suchowersky O, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: diagnosis and prognosis of **new onset Parkinson** disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):968-75. http://www.neurology.org/cgi/reprint/66/7/968 1. Early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor, and early autonomic dysfunction are probably useful in distinguishing other parkinsonian syndromes from Parkinson disease (PD). 2. Levodopa or apomorphine challenge and olfactory testing are probably useful in distinguishing PD from other parkinsonian syndromes. 3. Predictive factors for more rapid motor progression, nursing home placement, and shorter survival time include older age at onset of PD, associated comorbidities, presentation with rigidity and bradykinesia, and decreased dopamine responsiveness. Future research into methods for earlier and more accurate diagnosis of the disease and identification and clarification of predictive factors of rapid disease progression is warranted.

Guidelines Canadian 2012:

Young GB, Findlay JM, Benstead TJ, et al; Canadian Neurological Sciences Federation team. **Canadian Guidelines on Parkinson's Disease**. Can J Neurol Sci. 2012 July;(39)4.

Guidelines EFNS 2006:

TOP

Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, Larsen JP, Lees A, Oertel W, Poewe W, Rascol O, Sampaio C, European Federation of Neurological Societies, Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the EFNS and the MDS-ES. Part II: late (complicated) Parkinson's disease. Eur J Neurol 2006 Nov;13(11):1186-202.

Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, Larsen JP, Lees A, Oertel W, Poewe W, Rascol O, Sampaio C, European Federation of Neurological Societies, Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section. Part I: early (uncomplicated) Parkinson's disease. Eur J Neurol 2006 Nov;13(11):1170-85.

Guidelines NICE 2006:
NICE: National Institute for Health and Clinical Excellence - **Parkinson's disease**: diagnosis and management in primary and secondary care. June 2006. http://www.nice.org.uk/nicemedia/pdf/cg035niceguideline.pdf.

Guidelines SIGN 2010:
SIGN-Scottish Intercollegiate Guidelines Network-Diagnosis and management of Parkinson's disease-SIGN-Jan 2010 http://www.sign.ac.uk/pdf/sign113.pdf

TOP

Approach to Migraine: Considerations

- ACUTE: - may consider metoclopramide or domperidone 1st; NSAID and/or triptan also recommended first line;
  - in very severe attacks, SC sumatriptan likely to be most effective & rapid; consider need for rapid onset vs recurrence, GI tolerance of po form, etc.
  - Link to Review Article in AFP Feb 2011: http://www.aafp.org/afp/2011/0201/p271.html
- PROPHYLAXIS: 1st line: beta-blockers (propranolol, metoprolol), TCAs, valproic acid, topiramate.
- MENSTRUAL Related Migraine (MRM): - severity may be increased; duration of headache may be longer and may be harder to treat than regular migraine
  - may consider NSAID or triptan for short-term treatment, several days before and during menstruation [20].

References: RxFiles – MIGRAINE AGENTS

[1] Diener Hc et al. Antimigraine drugs. J Neurol 1999;246:515-19.

[2] Evans RW and Lipton RB. Topics in migraine management. Neurol Clinics 2001:19(1):1-21.

[3] Smith MA and Ross MB. Oral 5HT1 receptor agonists for migraine: comparative considerations. Formulary 1999; 34:324-38.

[4] Gawel MJ, et al. A systematic review of the use of triptans in acute migraine. Can J neurol Sci 2001;28:30-41.

[5] Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice Parameter: Pharmacological treatment of migraine headache in **children and adolescents**: Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. **Neurology. 2004** Dec 28;63(12):2215-24.

[6] Diener HC et al. A practical guide to the management and prevention of migraine. Drugs 1998;56:811-24.

[7] Pryse-Phillips WE et al. Guidelines for the diagnosis and management of migraine in clinical practice. CAN Med Assoc J 1997;156(9): 1273-87.

[8] Dahlof C. Placebo controlled trials with ergotamine in the acute treatment of migraine. Cephalgia 1993;13:166-71.

[9] Ferrari MD et al. Oral triptans in acute migraine treatment: a meta analysis of 53 trials. The Lancet 2001;358: 1668-75.

[10] Limmroth V and Michel M. The prevention of migraine: a critical review with special emphasis on B-adrenoceptor blockers. Br J Cin Pharmacol 2001;52:237-43.

[11] Brandes J, Saper J, Diamond M, et al. Topiramate for Migraine Prevention: A Randomized Controlled Trial. JAMA 2004;291 965-973.

[12] Silberstein SD, Neto W, Schmitt J, Jacobs D; MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol. 2004 Apr;61(4):490-5.

[13] Storey JR et al …Headache 2001;41:968-1000.

[14] Topiramate (Topamax) for prevention of migraine. Med Lett Drugs Ther. 2005 Jan 31;47(1201):9-10.
Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache. 2009 Sep;49(8):1153-62.

[15] Diener HC, Tfelt-Hansen P, Dahlof C, Lainez MJ, Sandrini G, Wang SJ, Neto W, Vijapurkar U, Doyle A, Jacobs D; MIGR-003 Study Group. Topiramate in migraine prophylaxis—results from a placebo-controlled trial with propranolol as an active control. J Neurol. 2004 Aug;251(8):943-50.

[16] Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. Eur Neurol. 2004;51(2):89-97. Epub 2004 Jan 28.

[17] Blumenfeld A. Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. Headache. 2003 Sep;43(8):853-60.
Chilson CN, Brown SJ. Role of botulinum toxin type a in the prophylactic treatment of migraine headaches. Ann Pharmacother. 2005 Dec;39(12):2081-5. Epub 2005 Nov 1.
Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type a and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache. 2008 Feb;48(2):210-20. Epub 2007 Nov 28. Both BoNTA and DVPX significantly reduced disability associated with migraine; BoNTA had a favorable tolerability profile compared with DVPX.
Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 May 6;70(19):1707-14. Botulinum neurotoxin (BoNT) should be offered as a treatment option for the treatment of axillary hyperhidrosis and detrusor overactivity (Level A), should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia after spinal cord injury (Level B), and may be considered for gustatory sweating and low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B). There is presently no consistent or strong evidence to permit drawing conclusions on the efficacy of BoNT in chronic daily headache (mainly transformed migraine) (Level U). While clinicians' practice may suggest stronger recommendations in some of these indications, evidence-based conclusions are limited by the availability of data.
Lipton RB, Varon SF, Grosberg B,et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology. 2011 Oct 11;77(15):1465-72.
Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. 2012 Apr 25;307(16):1736-45.

[18] Linde K, Streng A, Jurgens S, et al. Acupuncture for patients with migraine: a randomized controlled trial. JAMA. 2005 May 4;293(17):2118-25. . (InfoPOEMs: Acupuncture and sham acupuncture are equally more effective than no treatment in patients with migraine headaches. These results defend the adage that doing something is better than doing nothing. (LOE = 1b)). & Coeytaux RR, Kaufman JS, Kaptchuk TJ, et al. A randomized, controlled trial of **acupuncture** for chronic daily headache. Headache. 2005 Oct;45(9):1113-23.
Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. **Acupuncture** for migraine prophylaxis. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD001218. In the previous version of this review, evidence in support of acupuncture for migraine prophylaxis was considered promising but insufficient. Now, with 12 additional trials, there is consistent evidence that acupuncture provides additional benefit to treatment of acute migraine attacks only or to routine care. There is no evidence for an effect of 'true' acupuncture over sham interventions, though this is difficult to interpret, as exact point location could be of limited importance. Available studies suggest that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment, and has fewer adverse effects. Acupuncture should be considered a treatment option for patients willing to undergo this treatment.
Jena S, Witt CM, Brinkhaus B, Wegscheider K, Willich SN. Acupuncture in patients with headache. Cephalalgia. 2008 Sep;28(9):969-79. Epub 2008 Jul 8. Acupuncture plus routine care in patients with headache was associated with marked clinical improvements compared with routine care alone.
Li Y, Zheng H, Witt CM, et al. **Acupuncture** for migraine prophylaxis: a randomized controlled trial. CMAJ. 2012 Jan 9.

TOP

[19] Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis. Cochrane Database Syst Rev. 2004;(3):CD003226.
[20] Mathew NT, Rapoport A, Saper J, et al. Efficacy of **gabapentin** in migraine prophylaxis. Headache. 2001 Feb;41(2):119-28.
Jafarian S, et al. Gabapentin for prevention of **hypobaric hypoxia-induced headache**: randomized double-blind clinical trial. J Neurol Neurosurg Psychiatry. 2008 Mar;79(3):321-3. Epub 2007 Oct 26.
[21] Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. Neurology. 2008 Apr 22;70(17):1555-63

Other sources:

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine – current understanding and treatment. N Engl J Med 2002: 346(4):257-270.
2. Adelman JA and Adelman RD. Current options for the prevention and treatment of migraine. Clinical Therapeutics 2001;23(6):772-788.
3. Silberstein SD, Goadsby PJ, Lipton RB. Management of migraine – an algorithmic approach. Neurololgy 2000; 55(Suppl 2): S46-52.
4. Morey SS. Practice guidelines…on migraine (a 5 part series…) Amer Family Physician 2000;61;1915ff 62: 2145-51, 2359-60, 2535-39.
5. Becker WJ. Evidence based migraine prophylactic drug therapy. Can J Neurol Sci 1999; 26(Suppl 3): S27-32.
6. Drug Information Handbook 8th edition.
7. Drugs in Pregnancy & Lactation 9th edition (Briggs G, Freeman R, Yaffe S). Lippincott Williams & Wilkins 2011, Philidelphia PA.
8. Handbook of Clinical Drug Data 9th edition (Anderson P, Knoben J, Troutman W). Appleton & Lange 1999, Stamford CT.
9. Pharmacotherapy Handbook 2nd edition (Wells B, Dipiro J, Schwinghammer T, Hamilton C). Appleton & Lange 2000, Stamford CT.
10. Therapeutic Choices 4rd edition (Gray J). Canadian Pharmacists Association 2003.
11. Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002 Nov 19;137(10):840-9.
12. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. Arch Intern Med. 2000 Dec 11-25;160(22):3486-92.
13. Lewis DW. Headaches in children and adolescents. Am Fam Physician. 2002 Feb 15;65(4):625-32.
14. Micromedex 2010
15. Treatment Guidelines **Medical Letter: Drugs for Migraine**. March 2008; 6(67):17-22. (**New & Updated Feb 2011**)
16. Schreiber CP, Hutchinson S, Webster CJ, Ames M, Richardson MS, Powers C. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "**sinus**" headache. Arch Intern Med. 2004 Sep 13;164(16):1769-72.
17. Colman I, Brown MD, Innes GD, et al. Parenteral **metoclopramide** for acute migraine: meta-analysis of randomised controlled trials. BMJ. 2004 Dec 11;329(7479):1369-73.
18. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice Parameter: Pharmacological treatment of migraine headache **in children and adolescents**: Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. **Neurology. 2004** Dec 28;63(12):2215-24.
19. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia. 2002 Oct;22(8):633-58. Erratum in: Cephalalgia. 2003 Feb;23(1):71. (**low doses effective**)
20. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology. 2004 Feb 24;62(4):563-8.
21. Mauskop A, Graff-Radford S. Special treatment situations: **alternative** headache **treatments**. In: Standards of care for headache diagnosis and treatment. Chicago (IL): National Headache Foundation; 2004. p. 115-22.
22. Colman I, Brown MD, Innes GD, et al. Parenteral **dihydroergotamine** for acute migraine headache: a systematic review of the literature. Ann Emerg Med 2005;45:393-401.
(InfoPOEMs: Dihydroergotamine is not as effective as sumatriptan (Imitrex) when used by itself for the acute treatment of migraine. When used in combination with an anti-emetic it is at least as effective as analgesics. It should be used as a second-line treatment in patients who don't initially respond to the treatments that are more likely to work. (LOE = 1a-))
23. Schuurmans A, van Weel C. Pharmacologic treatment of migraine. **Comparison of guidelines**. Can Fam Physician. **2005** Jun;51:838-43.
24. Moja P, Cusi C, Sterzi R, Canepari C. Selective serotonin re-uptake inhibitors (**SSRIs**) for preventing migraine and tension-type headaches. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002919. CONCLUSIONS: Over 2 months of treatment, SSRIs are no more efficacious than placebo in patients with migraine. In patients with chronic TTH, SSRIs are less efficacious than tricyclic antidepressants. In comparison with SSRIs, the burden of adverse events in patients receiving tricyclics was greater. These results are based on short-term trials and may not generalise to longer-term treatment.
25. Maizels M. The patient with daily headaches. Am Fam Physician. 2004 Dec 15;70(12):2299-306.
26. Diener HC, Gendolla A, et al. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. Headache. 2005 Jul-Aug;45(7):874-82.
27. Damen L, Bruijn JK, Verhagen AP, et al. Symptomatic treatment of migraine in **children**: a systematic review of medication trials. Pediatrics. 2005 Aug;116(2):e295-302.
28. Combination Use of **Triptans and NSAIDs** for Migraine. Pharmacist's Letter. Dec 05.
29. Smith TR, Sunshine A, Stark SR, et al. **Sumatriptan and naproxen** sodium for the acute treatment of migraine. Headache. 2005 Sep;45(8):983-91.
30. Winner P, Pearlman EM, Linder SL, et al.; **Topiramate Pediatric** Migraine Study Investigators. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache. 2005 Nov-Dec;45(10):1304-12.
31. Bartolini M, Silvestrini M, Taffi R, et al. Efficacy of **topiramate and valproate** in chronic migraine. Clin Neuropharmacol. 2005 Nov-Dec;28(6):277-9.

TOP

32. Silberstein SD, Freitag FG, Rozen TD, et al. CAPSS-223 Investigators. Tramadol/acetaminophen for the treatment of acute migraine pain: findings of a randomized, placebo-controlled trial. Headache. 2005 Nov-Dec;45(10):1317-27.
33. Goadsby PJ. Recent advances in the diagnosis and management of migraine. BMJ. 2006 Jan 7;332(7532):25-9.
34. Tepper SJ, Cady R, Dodick D, et al. Oral sumatriptan for the acute treatment of **probable migraine**: first randomized, controlled study. Headache. 2006 Jan;46(1):115-24.
35. Rothner AD, Wasiewski W, Winner P, Lewis D, et al. Zolmitriptan oral tablet in migraine treatment: high **placebo** responses in **adolescents**. Headache. 2006 Jan;46(1):101-9.
36. Winner P, Rothner AD, et al. Sumatriptan nasal spray in **adolescent** migraineurs: a randomized, double-blind, placebo-controlled, acute study. Headache. 2006 Feb;46(2):212-22.
37. Wheeler SD. **Donepezil** treatment of topiramate-related cognitive dysfunction. Headache. 2006 Feb;46(2):332-5.
38. Modi S, Lowder DM. Medications for migraine **prophylaxis**. Am Fam Physician. 2006 Jan 1;73(1):72-8.
39. Dodick DW. Clinical practice. **Chronic daily headache**. N Engl J Med. 2006 Jan 12;354(2):158-65. Erratum in: N Engl J Med. 2006 Feb 23;354(8):884.
40. Wenzel RG, Schwarz K, Padiyara RS. **Topiramate** for migraine prevention. Pharmacotherapy. 2006 Mar;26(3):375-87.
41. Rigatelli G, Braggion G, Aggio S, Chinaglia M, Cardaioli P. Primary **patent foramen ovale** closure to relieve severe migraine. Ann Intern Med. 2006 Mar 21;144(6):458-60.
42. Diener HC, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalagia. 2006 May;26(5):537-47.
43. Brandes JL. The influence of **estrogen** on migraine: a systematic review. JAMA. 2006 Apr 19;295(15):1824-30. Epidemiological, pathophysiological, and clinical evidence link estrogen to migraine headaches. Triptans appear to provide acute relief and also may be useful for headache prevention.
44. Shaygannejad V, et al. Comparison of the effect of **topiramate & sodium valporate** in migraine prevention: a randomized blinded crossover study. Headache. 2006 Apr;46(4):642-8.
45. Goldstein J, et al. **Acetaminophen, aspirin, and caffeine** (Excedrin) in combination versus ibuprofen for acute migraine: results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. Headache. 2006 Mar;46(3):444-53.
46. Charles JA, et al. Prevention of migraine with **olmesartan** in patients with hypertension/prehypertension. Headache. 2006 Mar;46(3):503-7. Tronvik E, et al. Prophylactic treatment of migraine with an angiotensin II receptor blocker (**candesartan**): a randomized controlled trial. JAMA. 2003 Jan 1;289(1):65-9.
47. Zeeberg P, Olesen J, Jensen R. Probable **medication-overuse headache**: the effect of a 2-month drug-free period. Neurology. 2006 Jun 27;66(12):1894-8. Epub 2006 May 17.
48. Rizatriptan vs risatriptan plus trimebutine for the acute treatment of migraine: a double blind, randomized, cross-over, placebo-controlled study. Cephalgia 2006;26:871-4.
49. Kurth T, et al. Migraine and risk of **cardiovascular** disease in women. JAMA. 2006 Jul 19;296(3):283-91. Erratum in: JAMA. 2006 Jul 19;296(3):1 p following 291. In this large, prospective cohort of women, active migraine with aura was associated with increased risk of major CVD, myocardial infarction, ischemic stroke, and death due to ischemic CVD, as well as with coronary revascularization and angina. (InfoPOEMs: Women suffering from active migraines with aura are at an increased risk of ischemic vascular events, including coronary heart disease and stroke. In general, this correlates to 18 additional cardiovascular events for every 10,000 women per year. Women with active migraine without aura are not at an increased risk of ischemic vascular disease. (LOE = 2b-))
50. van Ettekoven H, Lucas C. Efficacy of **physiotherapy** including a craniocervical training programme for tension-type headache; an RCT. Cephalalgia. 2006 Aug;26(8):983-91.
51. Rapoport A, et al. Long-term migraine prevention with **topiramate**: open-label extension of pivotal trials. Headache. 2006 Jul-Aug;46(7):1151-60.
52. Ahonen K, et al. A randomized trial of rizatriptan in migraine attacks in children. Neurology. 2006 Aug 30; [Epub ahead of print]
53. Ahonen K, et al. **Nasal sumatriptan** is effective in treatment of migraine attacks in **children**: A randomized trial. Neurology. 2004 Mar 23;62(6):883-7.
54. Cittadini E, et al. Effectiveness of **Intranasal Zolmitriptan** in Acute **Cluster** Headache: Randomized, Placebo-Controlled, Double-blind Crossover Study. Arch Neurol. 2006 Sep 11.
55. Detsky ME, et al. Does this patient with headache have a **migraine** or **need neuroimaging**? JAMA. 2006 Sep 13;296(10):1274-83. The best predictors can be summarized by the mnemonic POUNDing (Pulsating, duration of 4-72 hOurs, Unilateral, Nausea, Disabling). The presence of 4 simple historical features can accurately diagnose migraine. Several individual clinical features were found to be associated with a significant intracranial abnormality, and patients with these features should undergo neuroimaging. (InfoPOEMs: Useful clinical criteria from the history and physical for distinguishing migraine from tension-type headache include: nausea, photophobia, phonophobia, and exacerbation by physical activity. Combined findings useful for distinguishing migraine can be summarized by the mnemonic: POUNDing (Pulsatile quality; duration of 4 to 72 hOurs; Unilateral location; Nausea or vomiting; Disabling intensity). Patients with 4 or more of these criteria are most likely to have migraine headaches. Criteria increasing the risk of intracranial pathology include: cluster-type headache; abnormal neurologic examination result; undefined headache; headache with aura; headache aggravated by exertion or valsalva-like maneuver; and headache with vomiting. No clinical features from the history and physical are useful for significantly reducing the likelihood of intracranial pathology. (LOE = 3a))
56. Honkaniemi J, et al. **Haloperidol** in the acute treatment of migraine: a randomized, double-blind, placebo-controlled study. Headache. 2006 May;46(5):781-7.
57. Evers S, et al. Treatment of childhood migraine attacks with **oral zolmitriptan** and **ibuprofen**. Neurology. 2006 Aug 8;67(3):497-9. Epub 2006 Jun 14.
58. Kanai A, Saito M, Hoka S. Subcutaneous **sumatriptan** for refractory **trigeminal neuralgia**. Headache. 2006 Apr;46(4):577-82; discussion 583-4.
59. Tozer BS, Boatwright EA, David PS, et al. Prevention of migraine in **women** throughout the life span. Mayo Clin Proc. 2006 Aug;81(8):1086-91; quiz 1092.
60. Mellick LB, McIlrath ST, Mellick GA. Treatment of headaches in the ED with lower cervical **intramuscular bupivacaine** injections: a 1-year retrospective review of 417 patients. Headache. 2006 Oct;46(9):1441-9.
61. Brighina F, Palermo A, Aloisio A, Francolini M, Giglia G, Fierro B. **Levetiracetam** in the Prophylaxis of Migraine With Aura: A 6-Month Open-label n=16 Study. Clin Neuropharmacol. 2006 November/December;29(6):338-342.
62. Becker WJ, Christie SN, Ledoux S, Binder C. **Topiramate prophylaxis** and response to triptan treatment for acute migraine. Headache. 2006 Oct;46(9):1424-30. Although topiramate prophylaxis did reduce migraine attack frequency, in this pilot study topiramate prophylactic migraine treatment did not increase the proportion of patients pain-free 2 hours after symptomatic triptan therapy.

TOP

63. Monastero R, Camarda C, Pipia C, Camarda R. **Prognosis** of migraine headaches in **adolescents**: A 10-year follow-up study. Neurology. 2006 Oct 24;67(8):1353-6.
64. Wammes-van der Heijden EA, et al. Risk of **ischemic complications** related to the intensity of triptan and **ergotamine** use. Neurology. 2006 Oct 10;67(7):1128-34. In general practice, triptan overuse does not increase the risk of ischemic complications. Overuse of ergotamine may increase the risk of these complications, especially in those simultaneously using cardiovascular drugs.
65. Membe S, McGahan L, Cimon K, et al. Tryptans for Acute Migraine. Technology Report 72. CADTH. March 2007. Accessed at: http://www.cadth.ca/media/pdf/I4001_tr_Triptans_e.pdf .
66. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for the acute treatment of migraine: A randomized trial. JAMA 2007;297:1443-1454. {InfoPOEMs Jun07: A single-tablet combination of sumatriptan (85 mg) plus naproxen sodium (500 mg) was better than either agent alone in the treatment of acute migraine. Outcomes measured included 2-hour headache relief and 24-hour sustained pain-free response. This fixed combination is currently under FDA review and will be marketed under the trade name Trexima. This study used a single pill combination, but separate pills taken concurrently are likely to be equally efficacious (and potentially less expensive as generics). (LOE = 1b-)}
67. EFNS Migraine 2007 Guidelines http://www.efns.org/files/guideline_37.pdf
68. Tfelt-Hansen P, Steiner TJ. **Over-the-Counter** Triptans for Migraine : What are the Implications? CNS Drugs. 2007;21(11):877-83. In 2006, the triptans sumatriptan 50mg and naratriptan 2.5mg were approved as over-the-counter (OTC) drugs in pharmacies in the UK and Germany, respectively. Both drugs have been used in a large number of patients with migraine and are considered to have good safety profiles.
69. Pascual J, Mateos V, Roig C, et al. Marketed oral **triptans** in the acute treatment of migraine: a **systematic review** on efficacy and tolerability. Headache. 2007 Sep;47(8):1152-68.
70. Diener HC, et al. **Cessation versus continuation** of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2007 Dec;6(12):1054-62. Epub 2007 Nov 7. Sustained benefit was reported after discontinuation of topiramate, although number of migraine days did increase. These findings suggest that patients should be treated for 6 months, with the option to continue to 12 months in some patients.
71. Loder E, Rizzoli P. **Tension-type headache**. BMJ. 2008 Jan 12;336(7635):88-92.
72. Dodick D, Freitag F. Evidence-based understanding of **medication-overuse headache**: clinical implications. Headache. 2006 Nov;46 Suppl 4:S202-11.
73. Silberstein S, Saper J, Berenson F, et al. **Oxcarbazepine** in migraine headache: a double-blind, randomized, placebo-controlled study. Neurology. 2008 Feb 12;70(7):548-55. Overall, oxcarbazepine was safe and well tolerated; however, oxcarbazepine did not show efficacy in the prophylactic treatment of migraine headaches.
74. Colman I, Friedman BW, Brown MD, et al. Parenteral **dexamethasone** for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. BMJ. 2008 Jun 9. [Epub ahead of print] When added to standard abortive therapy for migraine headache, single dose parenteral dexamethasone is associated with a 26% relative reduction in headache recurrence (number needed to treat=9) within 72 hours.
Donaldson D, et al. IV dexamethasone vs placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: a multicenter, double-blinded, placebo-controlled randomized clinical trial. Am J Emerg Med. 2008 Feb;26(2):124-30.
Kelly AM, Kerr D, Clooney M. Impact of oral dexamethasone versus placebo after ED treatment of migraine with phenothiazines on the rate of recurrent headache: a randomised controlled trial. Emerg Med J. 2008 Jan;25(1):26-9.
Rowe BH, Colman I, Edmonds ML, Blitz S, Walker A, Wiens S. Randomized controlled trial of intravenous dexamethasone to prevent relapse in acute migraine headache. Headache. 2008 Mar;48(3):333-40. Epub 2007 Nov 28.
Friedman BW, Greenwald P, Bania TC, et al. Randomized trial of IV dexamethasone for acute migraine in the emergency department. Neurology. 2007 Nov 27;69(22):2038-44. Epub 2007 Oct 17.
75. Kurth T, Schürks M, Logroscino G, Gaziano JM, Buring JE. Migraine, **vascular risk**, and cardiovascular events in women: prospective cohort study. BMJ. 2008 Aug 7;337:a636. doi: 10.1136/bmj.a636. The association between migraine with aura and cardiovascular disease varies by vascular risk status. Information on history of migraine and vascular risk status might help to identify women at increased risk for specific future cardiovascular disease events.
76. Friedman BW, Esses D, Solorzano C, et al. A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. Ann Emerg Med. 2008 Oct;52(4):399-406. Epub 2007 Nov 19.
77. Friedman BW, Bender B, Davitt M, et al. A Randomized Trial of Diphenhydramine as Prophylaxis Against Metoclopramide-Induced Akathisia in Nauseated Emergency Department Patients. Ann Emerg Med. 2008 Sep 22. [Epub ahead of print]
78. Bigal M, Sheftell F, Tepper S, Tepper D, Ho TW, Rapoport A. A randomized double-blind study comparing **rizatriptan, dexamethasone**, and the combination of both in the acute treatment of **menstrually related migraine**. Headache. 2008 Oct;48(9):1286-93. Rizatriptan is an effective treatment for MRM. RI+DE is significantly more effective than RI alone, although is associated with higher rate of adverse events.The combination should be considered for subjects with high disability, incomplete relief, or recurrence of pain with triptan monotherapy.The use of DE alone in the treatment of MRM is not justified based on our data.
79. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. **Acupuncture** for migraine prophylaxis. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD001218. In the previous version of this review, evidence in support of acupuncture for migraine prophylaxis was considered promising but insufficient. Now, with 12 additional trials, there is consistent evidence that acupuncture provides additional benefit to treatment of acute migraine attacks only or to routine care. There is no evidence for an effect of 'true' acupuncture over sham interventions, though this is difficult to interpret, as exact point location could be of limited importance. Available studies suggest that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment, and has fewer adverse effects. Acupuncture should be considered a treatment option for patients willing to undergo this treatment.
80. Linder SL, Mathew NT, Cady RK, Finlayson G, Ishkanian G, et al. Efficacy and tolerability of **almotriptan in adolescents**: a randomized, double-blind, placebo-controlled trial. Headache. 2008 Oct;48(9):1326-36. Epub 2008 May 14. Oral almotriptan was efficacious for relieving migraine headache pain in adolescents, with the 12.5-mg dose associated with the most favorable efficacy profile with respect to relieving headache pain and associated symptoms of migraine (photophobia and phonophobia). Almotriptan treatment was well tolerated in this adolescent population.
81. Lewis D, Winner P, Saper J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of **topiramate** for migraine prevention in **pediatric** subjects 12 to 17 years of age. Pediatrics. 2009 Mar;123(3):924-34.
82. Friedman BW, Kapoor A, Friedman MS, et al. The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials. Ann Emerg Med. 2008 Dec;52(6):705-13. Epub 2008 Jul 16. Meperidine (pethidine, Demerol) is much less effective than dihydroergotamine in relieving migraine within 1 hour of treatment. Antiemetics are also more effective than meperidine. Ketorolac (Toradol) is equally effective as meperidine and has a similar gastrointestinal side effect profile. (LOE = 1a-)

TOP

83. Scher Ann I.; Gudmundsson Larus S.; Sigurdsson Sigurdur; et al. Migraine Headache in Middle Age and **Late-Life Brain Infarcts**. JAMA. 2009;301(24):2563-2570.
84. Guerrera M. et al. Therapeutic Uses of **Magnesium**. Am Fam Physician. 2009; 80(1):157-162.
85. Grande RB et al. Severity of Dependence Scale detects people with medication overuse: The **Akershus** study of chronic headache. J Neurol Neurosurg Psychiatry 2009 Jul; 80:784.
86. CADTH HTIS: Botulinum Toxin A for Headaches in Adults: A review of clinicial effectiveness and safety. http://www.cadth.ca/index.php/en/hta/programs/htis
87. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, et al. **EFNS guideline** on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81.
88. Hedlund C, Rapoport AM, Dodick DW, et al. **Zolmitriptan** nasal spray in the acute treatment of **cluster** headache: a meta-analysis of two studies. Headache. 2009Oct;49(9):1315-23.
89. Cunnington M, Ephross S, Churchill P. The Safety of Sumatriptan and Naratriptan in **Pregnancy**: What Have We Learned? Headache. 2009 Oct 5. [Epub ahead of print]
90. Schürks Markus, Rist Pamela M, et al. Migraine and **cardiovascular** disease: systematic review and meta-analysis. BMJ 2009;339:b3914, doi: 10.1136/bmj.b3914 (Published 27Oct09)
91. Etminan M, Takkouche B, et al. Risk of ischaemic **stroke** in people with migraine: systematic review and meta-analysis of observational studies. BMJ. 2005 Jan 8;330(7482):63.
92. Loder EW, Buse DC, Golub JR. Headache and combination estrogen-progestin oral contraceptives: integrating evidence, guidelines, and clinical practice. Headache. 2005 Mar;45(3):224-31.
93. FDA Dec/09 notified health care professionals and patients about the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular **malformations**, in babies exposed to **valproate** sodium and related products (valproic acid and divalproex sodium) during pregnancy.
94. Cohen Anna S.; Burns Brian; Goadsby Peter J. **High-Flow Oxygen** for Treatment of **Cluster** Headache: A Randomized Trial. *JAMA*. 2009;302(22):2451-2457.
95. Silberstein S, Lipton R, Dodick D, et al. **Topiramate** treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache. 2009 Sep;49(8):1153-62.
96. Vikelis M, Rapoport AM. Role of **antiepileptic drugs** as preventive agents for migraine. CNS Drugs. 2010 Jan 1;24(1):21-33. doi: 10.2165/11310970-000000000-00000.
97. Kostic MA, Gutierrez FJ, Rieg TS, et al. A Prospective,Randomized Trial of Intravenous **Prochlorperazine** Versus Subcutaneous Sumatriptan in Acute Migraine Therapy in the Emergency Department. Ann Emerg Med. 2009 Dec31.
98. Kelly AM, Walcynski T, Gunn B. The relative efficacy of **phenothiazines** for the treatment of acute migraine: a meta-analysis. Headache. 2009 Oct;49(9):1324-32. Epub 2009 Jun 2.
99. Gales Barry J, Bailey Emilee K, Reed Ashley N, et al. **Angiotensin**-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers for the Prevention of Migraines. Ann Pharmacother. 2010 Feb;44(2):360-6. Epub 2010 Jan 19.
100. Calhoun AH, Ford S, Millen C, Finkel AG, Truong Y, Nie Y. The Prevalence of **Neck Pain** in Migraine. Headache. 2010 Jan 20.
101. Pringsheim T, Davenport WJ, Becker WJ. **Prophylaxis** of migraine headache. CMAJ. 2010 Feb 16.
102. Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse **transcranial magnetic stimulation** for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol. 2010 Apr;9(4):373-380. Epub 2010 Mar 4.
103. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of **migraine**. Lancet Neurol. 2010 Mar; 9 (3):285-298.
104. Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of **medication-overuse** headache. Lancet Neurol. 2010 Apr;9(4):391-401.
105. Dodick DW, Freitag F, Banks J, et al. CAPSS-277 Investigator Group. **Topiramate versus amitriptyline** in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clin Ther. 2009 Mar;31(3):542-59.
106. Law S, Derry S, Moore RA. **Triptans for acute cluster** headache. Cochrane Database Syst Rev. 2010 Apr 14;4:CD008042. Zolmitriptan and sumatriptan are effective in the acute treatment of cluster headaches & may provide a useful treatment option, potentially offering convenience over oxygen therapy and a better safety and tolerability profile than ergotamine. Non-oral routes of administration are likely to provide better and more rapid responses.
107. Kirthi V, Derry S, Moore RA, McQuay HJ. **Aspirin with or without an antiemetic** for acute migraine headaches in adults. Cochrane Database Syst Rev. 2010 Apr 14;4:CD008041. Aspirin 1000 mg is an effective treatment for acute migraine headaches, similar to sumatriptan 50 mg or 100 mg. Addition of metoclopramide 10 mg improves relief of nausea and vomiting. Adverse events were mainly mild and transient, and were slightly more common with aspirin than placebo, but less common than with sumatriptan 100 mg.
108. Pringsheim T, Davenport WJ, Becker WJ. **Prophylaxis of migraine** headache. CMAJ. 2010 Apr 20;182(7):E269-76. Epub 2010 Feb 16.
109. Verhagen AP, Damen L, Berger MY, et al. **Lack of benefit for prophylactic drugs of tension-type headache in adults: a systematic review.** Fam Pract. 2010 Apr;27(2):151-65.
110. Edvinsson L, Linde M. New drugs in migraine treatment and prophylaxis: **telcagepant and topiramate**. Lancet. 2010 Apr 21. [Epub ahead of print]
111. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. Headache. 2010May;50(5):819-33.
Derry S, Moore RA, McQuay HJ. Paracetamol (**acetaminophen**) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2010 Nov 10;11:CD008040. Paracetamol 1000 mg alone is an effective treatment for acute migraine headaches, and the addition of 10 mg metoclopramide gives short-term efficacy equivalent to oral sumatriptan 100 mg. Adverse events with paracetamol did not differ from placebo; ``major`` adverse events were slightly more common with sumatriptan than with paracetamol plus metoclopramide.
112. Friedman BW, Solorzano C, Esses D,et al. Treating Headache Recurrence After Emergency Department Discharge: A Randomized Controlled Trial of **Naproxen Versus Sumatriptan**. Ann Emerg Med. 2010 Mar 18.
113. Duong S, Bozzo P, Nordeng H, Einarson A. Safety of **triptans** for migraine headaches during **pregnancy and breastfeeding**. Can Fam Physician. 2010 Jun;56(6):537-9.
114. Loder, Elizabeth. **Triptan Therapy** in Migraine. N Engl J Med 2010 363: 63-70.
115. Borhani Haghighi A, Motazedian S, Rezaii R, et al. Cutaneous application of **menthol 10% solution** as an abortive treatment of migraine without aura: a randomised, double-blind, placebo-controlled, crossed-over study. Int J Clin Pract. 2010 Mar;64(4):451-6.

TOP

116. Trucco M, Meineri P, Ruiz L, Gionco M; Gruppo Neurologico Ospedaliero Interregionale per lo Studio delle Cefalee (Neurological Hospital Interregional Group for the Study of Headaches). **Medication overuse headache**: withdrawal and prophylactic therapeutic regimen. Headache. 2010 Jun;50(6):989-97.
117. Johnston MM, Rapoport AM. Triptans for the management of migraine. Drugs. 2010 Aug 20;70(12):1505-18. doi: 10.2165/11537990-000000000-00000.
118. Gudmundsson LS, Scher AI, Aspelund T, et al. **Migraine with aura** and **risk of cardiovascular** and all cause mortality in men and women: prospective cohort study. BMJ. 2010 Aug 24;341:c3966. doi: 10.1136/bmj.c3966.
119. Kurth T, Kase CS, Schürks M, et al. **Migraine and risk of haemorrhagic stroke** in women: prospective cohort study. BMJ. 2010 Aug 24;341:c3659. doi: 10.1136/bmj.c3659.
120. MacGregor EA. Prevention and treatment of **menstrual migraine**. Drugs. 2010 Oct 1;70(14):1799-818. doi: 10.2165/11538090-000000000-00000. Evidence of efficacy, with acceptable safety and tolerability, exists for sumatriptan 50 and 100mg, mefenamic acid 500mg, rizatriptan 10mg and combination sumatriptan/naproxen 85mg/500mg. There is grade B evidence of efficacy for short-term prophylaxis with transcutaneous estradiol 1.5mg, frovatriptan 2.5mg twice daily and naratriptan 1mg twice daily. Contraceptive strategies offer the opportunity for treating menstrual migraine in women who also require effective contraception.
121. Holroyd Kenneth A, Cottrell Constance K, O'Donnell Francis J, et al. Effect of preventive **(β blocker) treatment, behavioural migraine management, or their combination** on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ 341:doi:10.1136/bmj.c4871 (29 Sept 2010).
122. Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of **cluster headache**. Neurology. 2010 Aug 3;75(5):463-73.
123. Rabbie R, Derry S, Moore RA, McQuay HJ. **Ibuprofen with or without an antiemetic for acute migraine headaches** in adults. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD008039. DOI: 10.1002/14651858.CD008039.pub2. Ibuprofen is an effective treatment for acutemigraine headaches, providing pain relief in about half of sufferers, but complete relief from pain and associated symptoms for only aminority.NNTs for all efficacy outcomes were better with 400mg than 200 mg in comparisons with placebo, and soluble formulations provided more rapid relief. Adverse events were mostly mild and transient, occurring at the same rate as with placebo.
124. Jackson JL, Shimeall W, Sessums L, et al. **Tricyclic antidepressants and headaches**: systematic review and meta-analysis. BMJ 341:doi:10.1136/bmj.c5222 (Published 20 Oct 10).
125. Robberstad L, Dyb G, Hagen K, et al.An **unfavorable lifestyle** and recurrent headaches among adolescents: the HUNT study. Neurology. 2010 Aug 24;75(8):712-7.
126. Spector JT, Kahn SR, Jones MR, et al. Migraine headache and **ischemic stroke risk**: an updated meta-analysis. Am J Med 2010;123:612–24.
127. Pringsheim T, Davenport WJ, Becker WJ. **Prophylaxis of migraine headache**. CMAJ. 2010 Apr 20;182(7):E269-76.
128. Raieli V, Compagno A, Brighina F, et al. Prevalence of **red ear syndrome in juvenile** primary headaches. Cephalalgia. 2010 Dec 1.
129. Medical Letter: Treatment Guidelines. **Drugs for Migraine. Feb 2011**.
130. Gilmore B, Michael M. **Treatment of acute migraine headache**. Am Fam Physician. 2011 Feb 1;83(3):271-80.
131. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a **longitudinal population based Study** (**AMPP**). Headache 2008;48:1157–1168.
132. Manack A, Buse DC, Serrano D, et al. **Rates, predictors, and consequences of remission** from chronic migraine to episodic migraine. Neurology 2011; 76:711–718.
133. Fenstermacher N, Levin M, Ward T. Pharmacological **prevention of migraine**. BMJ. 2011 Feb 18;342:d583. doi: 10.1136/bmj.d583.
134. Sun-Edelstein C, Mauskop A. Alternative headache treatments: **nutraceuticals, behavioral and physical treatments**. Headache. 2011 Mar;51(3):469-83.
135. Bond DS, Vithiananthan S, Nash JM, et al. Improvement of migraine headaches in severely obese patients after **bariatric surgery**. Neurology. 2011 Mar 29;76(13):1135-8.
136. Russell MB, Ducros A. Sporadic & familial **hemiplegic** migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management. Lancet Neurol. 2011 Mar 30.
137. Krymchantowski AV, Jevoux CC. **Topiramate vs Divalproex** Sodium in the Preventive Treatment of Migraine:A Prospective "Real-World" Study. Headache.2011Apr;51(4):554-8.
138. Hakim SM. **Warfarin** for refractory chronic cluster headache: a randomized pilot study. Headache 2011;51:713-25.
139. **ICSI**: Institute for Clinical Systems Improvement. Diagnosis and treatment of **headache**. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Jan.
140. Mancia G, Agabiti-Rosei E, Ambrosioni E, et al. **Hypertension and migraine** comorbidity: Prevalence and risk of **cerebrovascular** events. Evidence from a large, multicenter, cross-sectional survey in Italy (MIRACLES study). J Hypertens 2011; 29:309-318.
141. Schafer AM, Rains JC, Penzien DB, et al. Direct costs of preventive headache treatments: comparison of **behavioral and pharmacologic** approaches. Headache. 2011 Jun;51(6):985-91. doi: 10.1111/j.1526-4610.2011.01905.x.
142. Health Canada July/11 is informing health professionals and consumers that the labelling information for the drug **metoclopramide** is being updated to include stronger warnings on the risk of a movement disorder known as "**tardive dyskinesia**."
143. McCandless RT, Arrington CB, Nielsen DC, Bale et al. **Patent foramen ovale in children** with migraine headaches. J Pediatr. 2011 Aug;159(2):243-247.e1.
144. Cady RK, Goldstein J, Nett R, et al. A Double-Blind Placebo-Controlled Pilot Study of Sublingual **Feverfew and Ginger** (LipiGesic(TM) M) in the Treatment of Migraine. Headache. 2011 Jul;51(7):1078-86.
145. Posadzki P, Ernst E. **Spinal manipulations for cervicogenic headaches**: a systematic review of randomized clinical trials.Headache. 2011 Jul;51(7):1132-9.
146. Basurto Ona X, Martínez García L, Solà I, Bonfill Cosp X. Drug therapy for treating **post-dural puncture headache**. Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD007887.
147. Pluta Ryszard M., Lynm Cassio, Golub Robert M.. JAMA Patient Page: **Tension-Type Headache**. JAMA. 2011;306(4):450.doi:10.1001/jama.2011.886
148. Khatami R, Tartarotti S, Siccoli MM, et al. Long-term efficacy of **sodium oxybate** in 4 patients with chronic cluster headache. Neurology. 2011 Jul 5;77(1):67-70.
149. Leroux E, Valade D, Taifas I, et al. **Suboccipital steroid injections** for transitional treatment of patients with more than two cluster headache attacks per day: a randomised,

TOP

double-blind,placebo-controlled trial. Lancet Neurol. 2011 Sep 6.
150. Marine L, Castro P, Enriquez A, et al. **Four-limb acute ischemia** induced by **ergotamine** in an AIDS patient treated with **protease inhibitors**. Circulation. 2011 Sep 20;124(12):1395-7.
151. Merikangas KR, Cui L, Richardson AK, et al. Magnitude, impact, and stability of **primary headache subtypes**: 30 year prospective Swiss cohort study. BMJ. 2011 Aug 25;343:d5076.
152. Varkey E, Cider A, Carlsson J, Linde M. **Exercise** as migraine prophylaxis: A randomized study using relaxation and topiramate as controls. Cephalalgia. 2011 Sep 2.
153. Dakka Y, Warra N, Albadareen RJ, et al. Headache rate and cost of care **following lumbar puncture** at a single tertiary care hospital. Neurology. 2011 Jul 5;77(1):71-4.
154. Lipton RB, Varon SF, Grosberg B,et al. **OnabotulinumtoxinA** improves quality of life and reduces impact of chronic migraine. Neurology. 2011 Oct 11;77(15):1465-72.
155. Nagy AJ, Gandhi S, Bhola R, Goadsby PJ. Intravenous **dihydroergotamine** for inpatient management of refractory primary headaches. Neurology. 2011 Nov 15;77(20):1827-32.
156. Lipton RB, Bigal ME, Diamond M, et al.; AMPP Advisory Group. **Migraine prevalence**, disease burden, and the need for preventive therapy. Neurology. 2007 Jan 30;68(5):343-9.
157. Li Y, Zheng H, Witt CM, et al. **Acupuncture** for migraine prophylaxis: a randomized controlled trial. CMAJ. 2012 Jan 9.
158. Kelley NE, Tepper DE. **Rescue therapy for acute migraine**, part 1: triptans, dihydroergotamine, and magnesium. Headache. 2012 Jan;52(1):114-28.
159. Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of **Raynaud's phenomenon**. BMJ. 2012 Feb 7;344:e289.
160. Pringsheim T, Davenport WJ, Mackie G, et al, for the **Canadian Headache Society Prophylactic Guidelines** Development Group. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci 2012; 39(2 Suppl 2):S1-61.
161. Smelt AF, Blom JW, Dekker F, et al. A proactive approach to **migraine in primary care**: a pragmatic randomized controlled trial. CMAJ. 2012 Mar 6;184(4):E224-31.
162. Silberstein SD, Dodick DW, Lindblad AS, et al. Randomized, placebo-controlled trial of **propranolol added to topiramate** in chronic migraine. Neurology. 2012 Feb 29.
163. Kelley NE, Tepper DE. Rescue therapy for acute migraine, **part 1: triptans, dihydroergotamine**, **and magnesium**. Headache. 2012 Jan;52(1):114-28.
164. Kelley NE, Tepper DE. Rescue therapy for acute migraine, **part 2: neuroleptics,antihistamines**, **and others**. Headache. 2012 Feb;52(2):292-306.
165. Kelley NE, Tepper DE. Rescue therapy for acute migraine, **part 3: opioids, NSAIDs, steroids, and post-discharge medications**. Headache. 2012 Mar;52(3):467-82.
166. Nesbitt AD, Goadsby PJ. **Cluster headache**. BMJ. 2012 Apr 11;344:e2407.
167. Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: **NSAIDs and other complementary treatments** for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) and American Headache Society (AHS). Neurology. 2012 Apr 24;78(17):1346-53.
168. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: **Pharmacologic treatment for episodic migraine prevention in adults**: Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) and American Headache Society (AHS). Neurology. 2012 Apr 24;78(17):1337-45.
169. Jackson JL, Kuriyama A, Hayashino Y. **Botulinum toxin A for prophylactic** treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. 2012 Apr 25;307(16):1736-45.
170. Derosier FJ, Lewis D, Hershey AD, et al. Randomized Trial of **Sumatriptan and Naproxen** Sodium Combination in Adolescent Migraine. Pediatrics. 2012 May 14.
171. Tfelt-Hansen P, Olesen J. Taking the **negative view of current migraine treatments**: the unmet needs. CNS Drugs. 2012 May 1;26(5):375-82.
172. Bryans R, Descarreaux M, Duranleau M, et al. Evidence-based guidelines for **chiropractic treatment** of **adults** with headache. J Manipulative Physiol Ther 2011 Jun;34(5):274-89. http://files.chiropracticcanada.ca/Headache%20CPG%20final%20Jan2012_English.pdf
173. Canadian Agency for Drugs and Technologies in Health, 2012. **Triptans** for migraine headaches: a review of clinical evidence on **safety** [online]. Available: http://www.cadth.ca/media/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf
174. Ozkurt B, Cinar O, Cevik E, et al. Efficacy of **high-flow oxygen** therapy in all types of headache: prospective, randomized, placebo-controlled trial. Am J Emerg Med. 2012 May 2.
175.

TOP

Antiepileptics- References:

Useful websites: www.epilepsy.org.uk , www.epilepsyfoundation.org , www.epilepsy.com , www.ibe-epilepsy.org , www.sign.ac.uk , www.nice.org.uk , & www.aana.com .

1. Browne TR, Holmes GL. Epilepsy. N Engl. J Med 2001;344:1145-51.
2. Holmes LB, Harvey EA. The Teratogenicity of Anticonvulsant Drugs. N Engl. J Med 2001;344:1132-38.
3. Medical Letter-Zonisamide for Epilepsy. Vol.42 (Issue 1089) Oct2,2000.
4. Medical Letter-Two new drugs Oxcarbazepine &Levetiracetam for Epilepsy. Vol.42 (Issue 1076) Apr 17,2000.
5. Sabers A, Gram L. Newer Anticonvulsants-Comparative Review of Drug Interactions & Adverse Effects. Drugs 2000 Jul; 60 (1):23-33.
6. Expert Consensus Guideline Series- Treatment of Epilepsy; Epilepsy & Behavior 2, A1-A50 2001.
7. Drugs for **Epilepsy**: **Treatment Guidelines** from the Medical Letter, May **2003** (**Updated June 2008**)
8. Drug Information Handbook 10th edition, 2002-2003
9. Drugs in Pregnancy & Lactation 9th edition, 2011 (see also http://www.aedpregnancyregistry.org/.)
10. Geriatric Dosage Handbook 7th Edition, 2002
11. Handbook of Clinical Drug Data 10th edition, 2002
12. Therapeutic Choices 4rd edition, 2003
13. Clinical Handbook of Psychotropic Drugs 13th edition (Bezchlibnyk-Butler,Jeffries) 2003
14. Pharmacotherapy Handbook 2nd edition (Wells,Dipiro et al.)
15. Therapeutic Choices 4th edition 2003
16. Micromedex 2011
17. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol. 2003 Jun;2(6):347-56.
18. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. Lancet Neurol. 2003 Aug;2(8):473-81.
19. Sirven JI, Waterhouse E. Management of status epilepticus. Am Fam Physician. 2003 Aug 1;68(3):469-76.
20. Chang BS, Lowenstein DH. Epilepsy. N Engl J Med. 2003 Sep 25;349(13):1257-66.
21. Blume WT. Diagnosis and management of epilepsy. CMAJ. 2003 Feb 18;168(4):441-8.
22. Suzette M. LaRoche, MD; Sandra L. Helmers, MD **The New Antiepileptic Drugs** -Scientific Review *JAMA*. 2004;291:605-614. (& Clinical Applications p. 615-620).
23. Tatum WO 4th, Liporace J, Benbadis SR, Kaplan PW. Updates on the treatment of epilepsy in women. Arch Intern Med. 2004 Jan 26;164(2):137-45.
24. French JA, Kanner AM, Bautista J, et al.; Therapeutics & Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the AAN; American Epilepsy Society. **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy**: report of the Therapeutics & Technology Assessment Subcommittee & Quality Standards Subcommittee of the American Academy of Neurology & the American Epilepsy Society. **Neurology. 2004** Apr 27;62(8):1252-60. http://www.neurology.org/cgi/reprint/62/8/1252.pdf
25. French JA, Kanner AM, Bautista J et al.; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the AAN; American Epilepsy Society. **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. **Neurology. 2004** Apr 27;62(8):1261-73. http://www.neurology.org/cgi/reprint/62/8/1261.pdf
26. National Institute for Clinical Excellence. Newer drugs for epilepsy. London: **NICE London, March 2004** http://www.nice.org.uk/pdf/TA076fullguidance.pdf
    NICE: National Institute for Health and Clinical Excellence. The **epilepsies**: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). (Clinical guideline 137.) Jan **2012**. http://guidance.nice.org.uk/CG137.
27. de Haan GJ, Edelbroek P, Segers J, et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology. 2004 Aug 10;63(3):571-3.
28. Beghi E. Efficacy and tolerability of the new antiepileptic drugs: **comparison of two recent guidelines**. Lancet Neurol. 2004 Oct;3(10):618-21.
29. McCorry D, Chadwick D, Marson A. Current drug treatment of epilepsy in adults. Lancet Neurol. 2004 Dec;3(12):729-35.
30. Bialer M, et al. Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. 2004;43(12):763-80.
31. Doose DR, et al. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. Epilepsia. 2003 Apr;44(4):540-9.
32. Leppik IE, Bergey GK, Ramsay RE, et al. Advances in antiepileptic drug treatments. A rational basis for selecting drugs for older patients with epilepsy. Geriatrics. 2004 Dec;59(12):14-8, 22-4.
33. P-Codrea Tigaran S, Sidenius P, Dam M. Lamotrigine-induced rash--worth a rechallenge. Acta Neurol Scand. 2005 Mar;111(3):191-4.
34. Camfield P, Camfield C. The frequency of intractable seizures after stopping AEDs in seizure-free children with epilepsy. Neurology. 2005 Mar 22;64(6):973-5.
35. Cunnington M, et al; International **Lamotrigine Pregnancy Registry** Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. Neurology. 2005 Mar 22;64(6):955-60. CONCLUSIONS: The risk of all major birth defects after first-trimester exposure to lamotrigine monotherapy (2.9%) was similar to that in the general population and in other registries enrolling women exposed to antiepileptic monotherapy (3.3% to 4.5%). However, the sample size was too small to detect any but very large increases in specific birth defects.
36. Wyszynski DF, et al.; Antiepileptic Drug Pregnancy Registry. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology. 2005 Mar 22;64(6):961-5.
37. Mockenhaupt M, Messenheimer J, et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology. 2005 Apr 12;64(7):1134-8. (see also http://www.fda.gov/medwatch/SAFETY/2005/trileptal_hcp.pdf ; April/05 Health Canada warning http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/trileptal_hpc_e.html)
38. Marson A, Jacoby A, Johnson A, et al.; Medical Research Council **MESS** Study Group. **Immediate versus deferred** antiepileptic drug treatment for **early epilepsy and single** seizures: a randomised controlled trial. Lancet. 2005 Jun 28;365(9476):2007-13 & ACP Journal Club . (INTERPRETATION: Immediate antiepileptic drug treatment reduces the occurrence of seizures in the next 1-2 years, but does not affect long-term remission in individuals with single or infrequent seizures.) (Hirtz D, et al.; Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Practice parameter: treatment of the child with a **first unprovoked** seizure: Report of the Quality Standards Subcommittee of the American Academy of Neurology & the Practice Committee of the Child

TOP

Neurology Society. Neurology. 2003 Jan 28;60(2):166-75)(Pohlmann-Eden B, et al. The **first seizure** and its management in adults and children. BMJ. 2006 Feb 11;332(7537):339-42) Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. **Febrile seizures**: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008 Jun;121(6):1281-6.

Perucca Emilio, Tomson Torbjorn, The pharmacological **treatment of epilepsy** in adults, The Lancet Neurology, Volume 10, Issue 5, May 2011, Pages 446-456, ISSN 1474-4422.

39. Rowan AJ, Ramsay RE, Collins JF, et al.; VA Cooperative Study 428 Group. New onset **geriatric epilepsy**: a randomized study of **gabapentin, lamotrigine, and carbamazepine**. Neurology. 2005 Jun 14;64(11):1868-73. CONCLUSIONS: The main limiting factor in patient retention was adverse drug reactions. Patients taking lamotrigine (LTG) or gabapentin (GBP) did better than those taking carbamazepine. Seizure control was similar among groups. LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.
40. Johnson BA, et al. Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers in an RCT. Arch Intern Med. 2005 Jul 25;165(14):1600-5.
41. Artama M, Auvinen A, Raudaskoski T, et al. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology. 2005 Jun 14;64(11):1874-8. CONCLUSION: Excess risk was confined to patients using **valproate** during pregnancy. The risk for malformations was not elevated in offspring of mothers using carbamazepine, oxcarbazepine, or phenytoin (as monotherapy or polytherapy without valproate).
42. Eberhard-Gran M, Eskild A, Opjordsmoen S. Treating mood disorders during pregnancy: safety considerations. Drug Saf. 2005;28(8):695-706.
43. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. Epileptic Disord. 2004 Jun;6(2):57-75.
44. Nadkarni S, LaJoie J, Devinsky O. Current treatments of epilepsy. Neurology. 2005 Jun 28;64(12 Suppl 3):S2-11.
45. Geerts AT, Niermeijer JM, Peters AC, et al. Four-year outcome after early withdrawal of antiepileptic drugs in childhood epilepsy. Neurology. 2005 Jun 28;64(12):2136-8.
46. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. N Engl J Med. 1992 Sep 10;327(11):765-71.
47. Smith DB, Mattson RH, Cramer JA, et al. Results of a nationwide Veterans Administration Cooperative Study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. Epilepsia. 1987;28 Suppl 3:S50-8.
48. Wyszynski DF, Nambisan M, Surve T, et al.; Antiepileptic Drug Pregnancy Registry. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology. 2005 Mar 22;64(6):961-5.
49. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) **pregnancy registry**: a **6-year** experience. Arch Neurol. 2004 May;61(5):673-8.
50. Polycarpou A, Papanikolaou P, Ioannidis J, Contopoulos-Ioannidis D. Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005064.
51. Ratilal B, Costa J, Sampaio C. Anticonvulsants for preventing seizures in patients with chronic subdural haematoma. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004893.
52. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001133. CONCLUSIONS: Although anticonvulsants are used widely in chronic pain surprisingly few trials show analgesic effectiveness. Only one studied considered cancer pain. There is no evidence that anticonvulsants are effective for acute pain. In chronic pain syndromes other than trigeminal neuralgia, anticonvulsants should be withheld until other interventions have been tried. While gabapentin is increasingly being used for neuropathic pain the evidence would suggest that it is not superior to carbamazepine.
53. Pandya KJ, Morrow GR, Roscoe JA, et al. **Gabapentin** for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. Lancet. 2005 Sep 3-9;366(9488):818-24. Gabapentin is effective in the control of hot flashes at a dose of 900 mg/day, but not at a dose of 300 mg/day. This drug should be considered for treatment of hot flashes in women with breast cancer. (InfoPOEMs: Women with a history of breast cancer may obtain some relief from hot flashes with 900 mg gabapentin daily. The 300 mg daily dose was not effective. (LOE = 1b-))
54. Williams LJ, Rasmussen SA, Flores A, et al. Decline in the prevalence of **spina bifida** and anencephaly by race/ethnicity: 1995-2002. Pediatrics. 2005 Sep;116(3):580-6.
55. **Pregabalin** for Neuropathic Pain & Epilepsy. The Medical Letter Sept 12,2005 p. 75-76.
56. Walker M. **Status epilepticus**: an evidence based guide. BMJ. 2005 Sep 24;331(7518):673-7.
57. Rickels K, Pollack MH, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry. 2005 Sep;62(9):1022-30.
58. Kalviainen R, Eriksson K, Parviainen I. Refractory generalised convulsive status epilepticus : a guide to treatment. CNS Drugs. 2005;19(9):759-68.
59. Health Canada Sept/04 Lamictal warning with birth control pills http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_pa-ap_e.pdf
60. Prasad K, Al-Roomi K, Krishnan P, Sequeira R, Prasad K. Anticonvulsant therapy for **status epilepticus**. **Cochrane** Database Syst Rev. 2005 Oct 19;(4):CD003723. AUTHORS' CONCLUSIONS: **Lorazepam is better than diazepam or phenytoin** alone for cessation of seizures and carries a lower risk of continuation of status epilepticus requiring a different drug or general anaesthesia. Both lorazepam and diazepam are better than placebo for the same outcomes. In the treatment of premonitory seizures, diazepam 30 mg in an intrarectal gel is better than 20 mg for cessation of seizures without a statistically significant increase in adverse effects. Universally accepted definitions of premonitory, early, established and refractory status epilepticus are required.

Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, Holtkamp M, European Federation of Neurological Societies. **EFNS** guideline on the management of status epilepticus in adults. Eur J Neurol 2010 Mar;17(3):348-55.
61. Perucca E. **Birth defects** after prenatal exposure to antiepileptic drugs. Lancet Neurol. 2005 Nov;4(11):781-6.

Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of **malformations** with antiepileptic drugs: an analysis of data from the **EURAP** epilepsy and pregnancy registry. *Lancet Neurol* 2011; published online June 6. DOI:10.1016/S1474-4422(11)70107-7.
62. Chen DK, So YT, Fisher RS; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Use of **serum prolactin** in diagnosing epileptic seizures: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2005 Sep 13;65(5):668-75.
63. Berry JD, Petersen KL. A single dose of **gabapentin** reduces acute pain and allodynia in patients with **herpes zoster**. Neurology. 2005 Aug 9;65(3):444-7.
64. Steinhoff BJ, et al. The LAM-SAFE Study Group. The **LAM-SAFE** Study: Lamotrigine versus carbamazepine or valproic acid in newly diagnosed focal and generalised epilepsies in adolescents and adults. Seizure. 2005 Nov 5 CONCLUSIONS: This study indicates that the effectiveness of LTG in focal and generalised epilepsy syndromes as initial monotherapy in patients >/=12 years is in the range of standard first-line antiepileptic drugs.
65. Leppik IE; Epilepsy Foundation of America. Choosing an antiepileptic. Selecting drugs for **older patients** with epilepsy. Geriatrics. 2005 Nov;60(11):42-7. (Sirven JI, Ozuna J;

TOP

Epilepsy Foundation of America. **Diagnosing epilepsy in older adults**: what does it mean for the primary care physician? Geriatrics. 2005 Oct;60(10):30-5.
66. Treatment Guidelines from The **Medical Letter**: **Drugs for Epilepsy. Nov 2005**.
67. Ficker DM, Privitera M, Krauss G, et al. Improved tolerability and efficacy in epilepsy patients with **extended-release carbamazepine**. Neurology. 2005 Aug 23;65(4):593-5.
68. Meador KJ, Loring DW, Vahle VJ, et al. **Cognitive** and behavioral effects of **lamotrigine** and topiramate in healthy volunteers. Neurology. 2005 Jun 28;64(12):2108-14.
69. Biton V, Bourgeois BF; YTC/YTCE Study Investigators. **Topiramate** in patients with **juvenile myoclonic** epilepsy. Arch Neurol. 2005 Nov;62(11):1705-8.
70. Crawford P. Best practice guidelines for the management of **women with epilepsy**. Epilepsia. 2005 Nov;46 Suppl 9:117-24.
71. Abou-Khalil B. Benefit-risk assessment of **levetiracetam** in the treatment of partial seizures. Drug Saf. 2005;28(10):871-90.
72. Tatum WO 4th, Liporace J, Benbadis SR, Kaplan PW. Updates on the treatment of **epilepsy in women**. Arch Intern Med. 2004 Jan 26;164(2):137-45.
73. Kaaja E, Kaaja R, Matila R, Hiilesmaa V. Enzyme-inducing antiepileptic drugs in **pregnancy and the risk of bleeding** in the neonate. Neurology. 2002 Feb 26;58(4):549-53.
74. Brodie MJ, Kwan P. Epilepsy in **elderly people**. BMJ. 2005 Dec 3;331(7528):1317-22.
75. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between **lamotrigine and carbamazepine** in **elderly** patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res. 1999 Oct;37(1):81-7.
76. Walker M, Cross H, Smith S, Yet al. **Nonconvulsive status epilepticus**: Epilepsy Research Foundation Workshop Reports. Epileptic Disord. 2005 Sep;7(3):253-96.
77. Biton V, Sackellares JC, et al. Double-blind, placebo-controlled study of **lamotrigine in primary generalized tonic-clonic seizures**. Neurology. 2005 Dec 13;65(11):1737-43.
78. Seizure control & treatment in pregnancy. Observations from the EURAP Epilepsy Pregnancy Registry. Neurology. 2005 Dec 28; CONCLUSIONS: The majority of patients with epilepsy maintain seizure control during pregnancy. The apparently higher risk of seizures among women treated with oxcarbazepine & the more frequent increases in drug load in the oxcarbazepine & lamotrigine cohorts prompts further studies on relationships with pharmacokinetic changes. Risks associated with status epilepticus appear to be lower than previously reported.
79. EURAP Study Group. Seizure control and treatment in **pregnancy**: observations from the EURAP epilepsy pregnancy registry. Neurology. 2006 Feb 14;66(3):354-60.
80. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006 Feb 16;354(7):731-9. (Bohan TP, et al. Effect of L-carnitine treatment for valproate-induced hepatotoxicity. Neurology. 2001 May 22;56(10):1405-9.)
81. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2006 Mar;61(3):246-55.
82. Merideth CH. A single-center, double-blind, placebo-controlled evaluation of lamotrigine in the treatment of obesity in adults. J Clin Psychiatry. 2006 Feb;67(2):258-62.
83. Zupanc ML. Antiepileptic drugs and hormonal contraceptives in adolescent women with epilepsy. Neurology. 2006 Mar 28;66(6 Suppl 3):S37-45.
84. Pohlmann-Eden B, et al. The **first seizure** and its management in adults and children. BMJ. 2006 Feb 11;332(7537):339-42.
85. Gamble C, et al. A meta-analysis of individual patient responses to lamotrigine or carbamazepine monotherapy.Neurology. 2006 May 9;66(9):1310-7.
86. Meierkord H, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol. 2006 May;13(5):445-50. The preferred treatment pathway for generalised convulsive status epilepticus (GCSE) is intravenous (i.v.) administration of 4 mg of lorazepam or 10 mg of diazepam directly followed by 15-18 mg/kg of phenytoin or equivalent fosphenytoin. If seizures continue for more than 10 min after first injection another 4 mg of lorazepam or 10 mg of diazepam is recommended. Refractory GCSE is treated by anaesthetic doses of midazolam, propofol or barbiturates; the anaesthetics are titrated against an electroencephalogram burst suppression pattern for at least 24 h. The initial therapy of non-convulsive SE depends on the type and the cause. In most cases of absence SE, a small i.v. dose of lorazepam or diazepam will terminate the attack. Complex partial SE is initially treated such as GCSE, however, when refractory further non-anaesthetising substances should be given instead of anaesthetics. In subtle SE i.v. anaesthesia is required.
87. Pressler RM, et al. Effect of lamotrigine on cognition in children with epilepsy. Neurology. 2006 May 23;66(10):1495-9.
88. Bekkelund SI, Lilleng H, Tonseth S. **Gabapentin** may cause reversible **visual field constriction**. BMJ. 2006 May 20;332(7551):1193.
89. Health Canada Aug/06 **Lamictal** warning with non-syndromic **oral clefts**. Emerging data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry suggest an association between LAMICTAL and an increased risk of non-syndromic oral clefts over the reference population for the registry (ie. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston, USA)1. Recently published data from the Registry report three cases of isolated, non syndromic cleft palate and two cases of isolated, non syndromic cleft lip without cleft palate in infants from 564 first trimester lamotrigine monotherapy exposures giving a rate of 8.9 per 1,000, as compared to 0.37 per 1000 in the reference population for that registry. The prevalence of oral clefts noted in the NAAED registry is also higher than the background prevalence of non-syndromic oral clefts reported in the literature, including studies from the United States, Australia and Europe. While different studies have differing results due to geographic and case ascertainment variations, the reported range is 0.50 to 2.16/1000 3-17. To assist with the assessment of risk, analysis of data from additional pregnancy registries, with approximately 2200 additional lamotrigine monotherapy first trimester exposures has been conducted, and 4 additional non-syndromic cases of oral cleft have been identified.
http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/lamictal_2_hpc-cps_e.html (see also Pharmacist's Letter Sept 2006.)
Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT; EUROCAT Antiepileptic Drug Working Group. Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology. 2008 Sep 2;71(10):714-22. Epub 2008 Jul 23. We find no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine (LTG) monotherapy. Our study is not designed to assess whether there is a generalized increased risk of malformations with LTG exposure.
Madadi P, Ito S. **Perinatal exposure to maternal lamotrigine**: Clinical considerations for the mother and child. Can Fam Physician. 2010 Nov;56(11):1132-4.
Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL, Wyszynski DF. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology. 2008 May 27;70(22 Pt 2):2152-8.
90. Trevathan E, et al. **Lamotrigine** adjunctive therapy among **children** & **adolescents** with primary generalized tonic-clonic seizures.Peds.2006 Aug;118(2):e371-8.Epub2006Jul 17.
91. Siddall PJ, et al. **Pregabalin** (150-600mg/d) in central neuropathic pain assoc. with **spinal cord** injury: a placebo-controlled trial.Neurology.2006Nov28;67(10):1792-800.12wk n=137
92. Hunt S, Craig J, Russell A, et al. **Levetiracetam** in **pregnancy**: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology. 2006 Nov 28;67(10):1876-9. Three of 117 exposed pregnancies had an MCM (2.7%; 95% CI 0.9% to 7.7%); all 3 were exposed to other AEDs.
93. Banu SH, et al. Side effects of **phenobarbital** and **carbamazepine** in childhood epilepsy: randomised controlled trial. BMJ. 2007 Jun 9;334(7605):1207. Epub 2006 Dec 4. n=108 12 months. There was no excess in behavioural side effects with phenobarbital in children with epilepsy in a country with limited resources.
94. Pugh MJ, Foreman PJ, et al. Prescribing Antiepileptics for the **Elderly** : Differences between Guideline Recommendations and Clinical Practice. Drugs Aging. 2006;23(11):861-75.
95. Nikolajsen L, et al. A Randomized Study of the Effects of **Gabapentin** on **Postamputation** Pain. Anesthesiology. 2006 Nov;105(5):1008-1015. Gabapentin administered in the first 30 postoperative days after amputation does not reduce the incidence or intensity of postamputation pain.
96. Christensen J, Sabers A, Sidenius P. **Oxcarbazepine** concentrations during **pregnancy**: a retrospective study in patients with epilepsy. Neurology. 2006 Oct 24;67(8):1497-9. The

TOP

mean dose-corrected concentration of MHD was decreased during 9 pregnancies (analysis of variance, p = 0.0016), being 72% (SD = 13%) in the first trimester, 74% (SD = 17%) in the second trimester, 64% (SD = 6%) in the third trimester, and 108% (SD = 18%) after pregnancy vs the dose-corrected concentration before pregnancy.
97. Welch BJ, et al. Biochemical and **stone-risk** profiles with **topiramate** treatment. Am J Kidney Dis. 2006 Oct;48(4):555-63.
98. Tomson T, et al. **Valproate** effects on kinetics of **lamotrigine** in **pregnancy** and treatment with oral contraceptives. Neurology. 2006 Oct 10;67(7):1297-9. Valproate seems to reduce the induction of lamotrigine metabolism associated with pregnancy or use of contraceptives.
99. Pharmacist's Letter Oct 2006. Alternative or **Off-label** Routes of Drug Administration. (Rectal carbamazepine, clonazepam, diazepam, phenobarbital & valproic acid)
100. Vajda FJ, et al. **Foetal malformations** and seizure control: 52 months data of the **Australian** Pregnancy Registry. Eur J Neurol. 2006 Jun;13(6):645-54.
101. Vajda FJ, et al. Critical relationship between sodium **valproate** dose and human **teratogenicity**: results of the Australian register of anti-epileptic drugs in pregnancy. J Clin Neurosci. 2004 Nov;11(8):854-8.
102. Adab N, et al. Common antiepileptic drugs in **pregnancy** in women with epilepsy. Cochrane Database Syst Rev. 2004;(3):CD004848.
103. Breen DP, Davenport RJ. **Teratogenicity** of antiepileptic drugs. BMJ. 2006 Sep 23;333(7569):615-6.
104. Malaga I, Sanmarti FX. Two cases of painful **gynecomastia** and lower extremity pain in association with **pregabalin** therapy. Epilepsia. 2006 Sep;47(9):1576-9.
105. Harden CL, et al. **Hormone replacement therapy** in women with epilepsy: a randomized, double-blind, placebo-controlled study. Epilepsia. 2006 Sep;47(9):1447-51. CEE/MPA is associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy.
106. Adab N. Therapeutic Monitoring of Antiepileptic Drugs during **Pregnancy** and in the Postpartum Period : Is It Useful? CNS Drugs. 2006;20(10):791-800.
107. Varghese SP, et al. **Lamotrigine**-induced toxic **epidermal necrolysis** in three patients treated for bipolar disorder. Pharmacotherapy. 2006 May;26(5):699-704.
108. Donati F, et al. Oxcarbazepine Cognitive Study Group. Effects of **oxcarbazepine** on **cognitive** function in children and adolescents with partial seizures. Neurology. 2006 Aug 22;67(4):679-82.
109. Meador KJ, et al.; **NEAD** Study Group. In utero antiepileptic drug exposure: **fetal** death and **malformations**. Neurology. 2006 Aug 8;67(3):407-12. More adverse outcomes were observed in pregnancies with in utero valproate exposure vs the other antiepileptic drugs (AEDs). These results combined with several recent studies provide strong evidence that valproate poses the highest risk to the fetus. For women who fail other AEDs and require valproate, the dose should be limited if possible.
110. Nicolaidou P, et al. Effects of anticonvulsant therapy on **vitamin D** status in children: prospective monitoring study. J Child Neurol. 2006 Mar;21(3):205-9.
111. van der Lee MJ, et al. **Lopinavir/ritonavir** reduces lamotrigine plasma concentrations in healthy subjects. Clin Pharmacol Ther. 2006 Aug;80(2):159-68.
112. Bates DE, Herman RJ. Carbamazepine toxicity induced by **lopinavir/ritonavir** and **nelfinavir**. Ann Pharmacother. 2006 Jun;40(6):1190-5. Epub 2006 May 23.
113. Ho KY, Gan TJ, Habib AS. **Gabapentin** and **postoperative pain** - a systematic review of randomized controlled trials. Pain. 2006 Jul 15; [Epub ahead of print]
114. Misra UK, Kalita J, Patel R. Sodium **valproate vs phenytoin** in **status epilepticus**: a pilot study. Neurology. 2006 Jul 25;67(2):340-2.
115. EURAP Study Group. Seizure control and treatment in **pregnancy**: observations from the **EURAP** epilepsy pregnancy registry. Neurology. 2006 Feb 14;66(3):354-60. Epub 2005 Dec 28.
116. Morrow J, et al. Malformation risks of antiepileptic drugs in **pregnancy**: a prospective study from the **UK Epilepsy** and Pregnancy Register. J Neurol Neurosurg Psychiatry. 2006 Feb;77(2):193-8. Epub 2005 Sep 12. Only 4.2% of live births to women with epilepsy had an MCM. The MCM rate for polytherapy exposure was greater than for monotherapy exposure. Polytherapy regimens containing valproate had significantly more MCMs than those not containing valproate. For monotherapy exposures, carbamazepine was associated with the lowest risk of MCM.
117. Zupanc ML. Antiepileptic drugs and **hormonal contraceptives** in adolescent women with epilepsy. Neurology. 2006 Mar 28;66(6 Suppl 3):S37-45.
118. Blum D, et al. **Cognitive** effects of **lamotrigine** compared with **topiramate** in patients with epilepsy. Neurology. 2006 Aug 8;67(3):400-6.
119. Koren G, et al. Major **malformations** with valproic acid. Can Fam Physician. 2006 Apr;52:441-2, 444, 447. The risks appear to begin increasing at doses of 600 mg/d and to become more prominent at doses above 1000 mg/d.
120. Sadleir LG, Scheffer IE. **Febrile seizures**. BMJ. 2007 Feb 10;334(7588):307-11.
121. McIntyre J, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet. 2005 Jul 16-22;366(9481):205-10. Buccal midazolam was more effective than rectal diazepam for children presenting to hospital with acute seizures and was not associated with an increased incidence of respiratory depression.
122. Widdess-Walsh P, Kotagal P, Jeha L, Wu G, Burgess R. Multiple auras: clinical significance and pathophysiology. Neurology. 2007 Aug 21;69(8):755-61. Most patients who report **multiple aura** types have localized epilepsy in the nondominant hemisphere, and are **good surgical candidates.**
123. Lyseng-Williamson KA, Yang LP. Topiramate: a review of its use in the treatment of epilepsy. Drugs. 2007;67(15):2231-56.
124. Tomson T, Hiilesmaa V. **Epilepsy in pregnancy**. BMJ. 2007 Oct 13;335(7623):769-73.
125. Berkovic SF, Knowlton RC, Leroy RF, Schiemann J, Falter U; Levetiracetam N01057 Study Group. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. Neurology. 2007 Oct 30;69(18):1751-60. Epub 2007 Jul 11. Adjunctive levetiracetam is an effective and well-tolerated antiepileptic drug for treating generalized tonic-clonic seizures in patients with idiopathic generalized epilepsies.
126. Johnson BA, Rosenthal N, Capece JA, et al, for the Topiramate for Alcoholism Advisory Board and the Topiramate for Alcoholism Study Group. Topiramate for alcohol dependence. A randomized controlled trial. JAMA 2007;298(14):1641-1651. { InfoPOEMs: Topiramate (Topamax) is somewhat more effective than placebo in helping adults with alcohol dependence reduce heavy drinking (number needed to treat [NNT] = 7) and achieve abstinence (NNT = 9). Unfortunately, less than one-third of the patients in the active treatment group significantly reduced their drinking compared with baseline amounts and less than one-fifth achieved continuous abstinence for 28 days or more. As a safety precaution, topiramate was discontinued after 14 weeks and no further follow up is reported. Thus, long-term efficacy remains unknown. (LOE = 1b)}

TOP

127. Marson AG, Al-Kharusi AM, Alwaidh M, et al; **SANAD** Study group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007 Mar 24;369(9566):1016-26. Valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies. However, because of known potential adverse effects of valproate during pregnancy, the benefits for seizure control in women of childbearing years should be considered.
128. Marson AG, Al-Kharusi AM, Alwaidh M, et al. **SANAD** Study group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblended randomised controlled trial. Lancet. 2007 Mar 24;369(9566):1000-15. Lamotrigine is clinically better than carbamazepine, the standard drug treatment, for time to treatment failure outcomes and is therefore a cost-effective alternative for patients diagnosed with partial onset seizures.
129. Pennell PB, Peng L, Newport DJ, et al. **Lamotrigine in pregnancy**. Clearance, therapeutic drug monitoring, and seizure frequency. Neurology. 2007 Nov 28; [Epub ahead of print]
130. Krumholz A, Wiebe S, Gronseth G, et al. Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society. Practice Parameter: **evaluating** an apparent **unprovoked first seizure in adults** (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2007 Nov 20;69(21):1996-2007. EEG should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B). Brain imaging with CT or MRI should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B). Laboratory tests, such as blood counts, blood glucose, and electrolyte panels (particularly sodium), lumbar puncture, and toxicology screening may be helpful as determined by the specific clinical circumstances based on the history, physical, and neurologic examination, but there are insufficient data to support or refute recommending any of these tests for the routine evaluation of adults presenting with an apparent first unprovoked seizure (Level U).
131. Battino D, Tomson T. Management of **Epilepsy during Pregnancy**. Drugs. 2007;67(18):2727-46.
132. Brodtkorb E, Reimers A. Seizure control and pharmacokinetics of antiepileptic drugs in pregnant women with epilepsy. Seizure. 2007 Dec 22; [Epub ahead of print]
133. Westin AA, Reimers A, Helde G, Nakken KO, Brodtkorb E. Serum concentration/dose ratio of **levetiracetam** before, during and after **pregnancy**. Seizure. 2008 Jan 2; [Epub ahead of print] Serum concentrations of LEV declined significantly in the third trimester of pregnancy and increased rapidly after delivery.
134. Noachtar S, Andermann E, Meyvisch P, Andermann F, Gough WB, Schiemann-Delgado J; N166 Levetiracetam Study Group. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. Neurology. 2008 Feb 19;70(8):607-16.
135. Obermann M, Yoon MS, Sensen K, Maschke M, Diener HC, Katsarava Z. Efficacy of **pregabalin** in the treatment of **trigeminal neuralgia**. Cephalalgia. 2008 Feb;28(2):174-81. Epub 2007 Nov 26.
136. Butt DA, Lock M, Lewis JE, Ross S, et al. Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause. 2007 Oct 2; [Epub ahead of print]
137. Purcell TB, McPheeters RA, Feil M, Chavez R. Rapid oral loading of carbamazepine in the emergency department. Ann Emerg Med. 2007 Aug;50(2):121-6.
138. Pack AM, Morrell MJ, Randall A, et al. Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. Neurology. 2008 Apr 29;70(18):1586-93. In contrast, those treated with carbamazepine, lamotrigine, and valproate did not have detectable adverse effects on bone turnover or bone mineral density. These results raise **concerns about the long-term effects of phenytoin monotherapy on bone** in young women with epilepsy.
139. Neal EG, Chaffe H, Schwartz RH, et al. The **ketogenic diet** for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008 Jun;7(6):500-6. Epub 2008 May 2. The results from this trial of the ketogenic diet support its use in children with treatment-intractable epilepsy.
140. Alvestad S, Lydersen S, Brodtkorb E. Cross-reactivity pattern of rash from current aromatic antiepileptic drugs. Epilepsy Res. 2008 May 17. [Epub ahead of print] LTG appears to be involved in cross-reactions less often than CBZ, OXC and PHT.
141. Woods SW, Saksa JR, Baker CB, Cohen SJ, Tek C. Effects of levetiracetam (0.5-3g/d) on **tardive dyskinesia**: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2008 Apr;69(4):546-54. (n=50 12+12 weeks) Levetiracetam appeared effective for TD in this study. The mechanisms of its therapeutic effect are unclear but may involve reducing neuronal hypersynchrony in basal ganglia.
142. LeLorier J, Duh MS, Paradis PE, Lefebvre P, Weiner J, Manjunath R, Sheehy O. Clinical consequences of generic substitution of lamotrigine for patients with epilepsy. Neurology. 2008 May 27;70(22 Pt 2):2179-86. A higher propensity to switch back to branded medications was observed among antiepileptic drug users compared to users of antihypertensives and antihyperlipidemics, similar to findings from Andermann et al. Switch to **generic lamotrigine** was significantly associated with increased physician visits and hospitalizations.
143. Johnson BA, Rosenthal N, et al.**Topiramate for Alcoholism** Advisory Board; Topiramate for Alcoholism Study Group. Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. Arch Intern Med. 2008 Jun 9;168(11):1188-99.
144. Hunt S, Russell A, Smithson WH, Parsons L, Robertson I, Waddell R, Irwin B, Morrison PJ, Morrow J, Craig J; UK Epilepsy and Pregnancy Register. **Topiramate** in pregnancy: preliminary experience from the UK Epilepsy and **Pregnancy Register**. Neurology. 2008 Jul 22;71(4):272-6. The number of outcomes of human pregnancies exposed to topiramate is low, but the major congenital malformation rate for topiramate polytherapy raises some concerns. Overall, the rate of oral clefts observed was 11 times the background rate. Although the present data provide new information, they should be interpreted with caution due to the sample size and wide confidence intervals.
FDA Mar/11 notified healthcare professionals and patients of an increased risk of development of cleft lip and/or cleft palate (oral clefts) in infants born to women treated with Topamax (topiramate) during pregnancy. Because of new human data that show an increased risk for oral clefts, topiramate is being placed in Pregnancy Category D.
145. Vestergaard M, Pedersen MG, Ostergaard JR, et al. Death in children with **febrile seizures**: a population-based cohort study. Lancet. 2008 Aug 9;372(9637):457-63. Long-term mortality is not increased in children with febrile seizures, but there seems to be a small excess mortality during the 2 years after complex febrile seizures. Parents should be reassured that death after febrile seizures is very rare, even in high-risk children.
146. French JA, Pedley TA. Clinical practice. **Initial management of epilepsy**. N Engl J Med. 2008 Jul 10;359(2):166-76.
147. Faught E, Duh MS, Weiner JR, Guérin A, Cunnington MC. **Nonadherence** to antiepileptic drugs and increased mortality. Findings from the RANSOM Study. Neurology. 2008 Jun 18. [Epub ahead of print] These findings suggest that nonadherence to antiepileptic drugs can have serious or fatal consequences for patients with epilepsy.

TOP

148. Bell GS, et al. Drowning in people with epilepsy: how great is the risk? Neurology. 2008 Aug 19;71(8):578-82. The risk of drowning in people with epilepsy is raised 15- to 19-fold compared with people in the general population. It is important that people with epilepsy and their carers be informed of these risks so that deaths can be prevented.
149. Michael B, Marson AG. **Clobazam** as an add-on in the management of refractory epilepsy. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD004154.Clobazam as an add-on treatment may reduce seizure frequency and may be most effective in partial onset seizures. However, it is not clear who will best benefit and over what time-frame.
150. Boardman LA, Cooper AS, Blais LR, Raker CA. Topical gabapentin in the treatment of localized and generalized **vulvodynia**. Obstet Gynecol. 2008 Sep;112(3):579-85.
151. Hirsch LJ, Arif H, Nahm EA, Buchsbaum R, Resor SR Jr, Bazil CW. **Cross-sensitivity of skin rashes** with antiepileptic drug use. Neurology. 2008 Nov 4;71(19):1527-34. There was evidence of specific cross-sensitivity between CBZ and PHT, and between CBZ and PB. Cross-sensitivity rates between certain antiepileptic drugs (AEDs) are high, especially when involving carbamazepine and phenytoin. Specific cross-sensitivity rates provided here may be useful for AED selection and counseling in individual patients.
152. Cheuk DK, Wong V. Acupuncture for epilepsy. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD005062. The current evidence does not support acupuncture as a treatment for epilepsy.
153. Bromley RL, Mawer G, Clayton-Smith J, Baker GA; Liverpool and Manchester Neurodevelopment Group. **Autism** spectrum disorders following in utero exposure to antiepileptic drugs. Neurology. 2008 Dec 2;71(23):1923-4.
154. Choi H, Sell RL, Lenert L, Muennig P, et al. Epilepsy **surgery** for pharmacoresistant temporal lobe epilepsy: a decision analysis. JAMA. 2008 Dec 3;300(21):2497-505.
155. Kimia AA, Capraro AJ, Hummel D,et al. Utility of **lumbar puncture** for first simple febrile seizure among children 6 to 18 months of age. Pediatrics. 2009 Jan;123(1):6-12. The risk of bacterial meningitis presenting as first simple febrile seizure at ages 6 to 18 months is very low. American Academy of Pediatrics recommendations should be reconsidered.
156. Levi N, Bastuji-Garin S, Mockenhaupt M, Roujeau JC, et al. Medications as risk factors of **stevens-johnson syndrome** and toxic epidermal necrolysis in children: a pooled analysis. Pediatrics. 2009 Feb;123(2):e297-304. Epub 2009 Jan 19. We confirmed 4 previously highly suspected drug risk factors for Stevens-Johnson syndrome/toxic epidermal necrolysis in children: antiinfective sulfonamides, phenobarbital, carbamazepine, and lamotrigine. Among more unexpected risk factors, we suspect that acetaminophen (paracetamol) use increases the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.
157. Medical Letter Mar 9/09. **Rufinamide**-Banzel for Epilepsy.
158. Schomer DL, Black PM. A 24-year-old woman with **intractable seizures**: review of surgery for epilepsy. JAMA. 2008 Dec 3;300(21):2527-38. Epub 2008 Nov 4. (Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314-9.)
159. Harden CL, et al. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Reassessment: **neuroimaging** in the emergency patient presenting with seizure (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the AAN. Neurology 2007 Oct 30;69(18):1772-80.
160. Christensen J, et al. Long-term risk of epilepsy **after traumatic brain injury** in children and young adults: a population-based cohort study. Lancet. 2009 Feb 20. [Epub ahead print]
161. Meador KJ, Baker GA, Browning N, et al. **Cognitive function** at 3 years of age after **fetal exposure** to antiepileptic drugs. N Engl J Med. 2009 Apr 16;360(16):1597-605.
162. Harden CL, Meador KJ, Pennell PB, et al. American Academy of Neurology (**AAN**); American Epilepsy Society. Management issues for women with epilepsy-**Focus on pregnancy** (an evidence-based review): II. **Teratogenesis and perinatal outcomes**: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009 May;50(5):1237-46. (Valproate should be avoided during the first trimester of pregnancy. Among the other findings: Women with epilepsy who take antiepileptic drugs have twice the risk for delivering babies with Apgar scores under 7. Valproate is associated with increased risk for congenital malformations. Avoiding valproate, phenobarbital, and phenytoin during pregnancy may reduce the risk for poor cognitive outcomes (all are class D drugs), while carbamazepine (class C) "probably does not produce cognitive impairments." Monotherapy for epilepsy is preferable to polytherapy, if possible, to reduce poor cognitive outcomes. http://www.aan.com/globals/axon/assets/5476.pdf
163. Jacob K, Trainer PJ. **Topiramate** can induce **hypoadrenalism** in patients taking oral corticosteroid replacement. BMJ. 2009 Jan 8;338:a1788. doi: 10.1136/bmj.39588.561840.BD.
164. Christensen J, Pedersen MG, Pedersen CB, et al. Long-term risk of epilepsy **after traumatic brain injury** in children and young adults: a population-based cohort study. Lancet. 2009 Mar 28;373(9669):1105-10. Epub 2009 Feb 21.
165. Hamed SA, Abdella MM. The risk of asymptomatic **hyperammonemia** in children with idiopathic epilepsy treated with valproate: Relationship to blood **carnitine** status. Epilepsy Res. 2009 May 13. [Epub ahead of print]
166. Harden CL, Pennell PB, Koppel BS, et al. American Academy of Neurology (**AAN**); American Epilepsy Society. Management issues for women with epilepsy--focus on pregnancy (an evidence-based review): III. **Vitamin K, folic acid, blood levels, and breast-feeding**: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009 May;50(5):1247-55. PubMed PMID: 19507305.
Primidone and levetiracetam probably transfer into breast milk in clinically important amounts. Valproate, phenobarbital, phenytoin, and carbamazepine probably are not transferred into breast milk in clinically important amounts. Pregnancy probably causes an increase in the clearance and a decrease in the concentrations of lamotrigine, phenytoin, and, to a lesser extent carbamazepine, and possibly decreases the level of levetiracetam and the active oxcarbazepine metabolite, the monohydroxy derivative (MHD). Supplementing WWE with at least 0.4 mg of folic acid before pregnancy may be considered. Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered, and monitoring of levetiracetam and oxcarbazepine (as MHD) levels may be considered.
167. Yoo L, Matalon D, Hoffman RS, et al. Treatment of **Pregabalin** Toxicity by Hemodialysis in a Patient With Kidney Failure. Am J Kidney Dis. 2009 Jun 2. [Epub ahead of print]
168. Mindikoglu AL, Magder LS, Regev A. Outcome of **liver transplantation** for drug-induced acute liver failure in the United States: analysis of the united network for organ sharing database. Liver Transpl. 2009 Jul;15(7):719-29. Being on life support, DIALF due to antiepileptics (at age less than 18), and elevated serum creatinine were independent pretransplant predictors of poor survival after LT for DIALF.
169. **Lacosamide** for epilepsy. Med Lett Drugs Ther. 2009 Jun 29;51(1315):50-2.
170. **Driving**: Determining Medical Fitness to Operate Motor Vehicles CMA Driver's Guide 7th Ed http://www.cma.ca/index.cfm/ci_id/18223/la_id/1.htm
Seizures: http://www.cma.ca/multimedia/CMA/Content_Images/Inside_cma/WhatWePublish/Drivers_Guide/Section10_e.pdf

TOP

171. McNally MA, Pyzik PL, et al. Empiric use of potassium citrate reduces **kidney-stone** incidence with the ketogenic diet. Pediatrics. 2009 Aug;124(2):e300-4. Epub 2009 Jul 13.
172. Scarmeas N, Honig LS, Choi H, et al. Seizures in **Alzheimer** disease: who, when, and how common? Arch Neurol. 2009 Aug;66(8):992-7.
173. Lossius MI, Taubøll E, Mowinckel P, Gjerstad L. Reversible effects of antiepileptic drugs on **thyroid hormones** in men & women with epilepsy: A prospective randomized double-blind withdrawal study. Epilepsy Behav. 2009 Jul 29. [Epub ahead of print]
174. Stöllberger C, Höftberger R, et al. **Lamotrigine**-trigged obstructive hypertrophic **cardiomyopathy**, epilepsy & metabolic myopathy. Int J Cardiol. 2009 Jul 4. [Epub ahead of print]
175. Motamedi M, Karvigh SA, Sahraian MA, Azimi AR, et al. **Lamotrigine** and **twin pregnancy**, incidental event or possible correlation? Seizure. 2009 Jul 6. [Epub ahead of print]
176. Moore RA, Straube S, Wiffen PJ, et al. **Pregabalin** for **acute and chronic pain** in adults. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007076. Pregabalin has proven efficacy in neuropathic pain conditions and fibromyalgia. A minority of patients will have substantial benefit with pregabalin, and more will have moderate benefit. Many will have no or trivial benefit, or will discontinue because of adverse events. Individualisation of treatment is needed to maximise pain relief and minimise adverse events. There is no evidence to support the use of pregabalin in acute pain scenarios.
177. Longo B, Forinash AB, Murphy JA. **Levetiracetam** Use in Pregnancy (October). Ann Pharmacother. 2009 Aug 18. [Epub ahead of print]
178. Daniels ZS, et al. **Obesity** is a common comorbidity for pediatric patients with untreated, newly diagnosed epilepsy.Neurology.2009 Sep1;73(9):658-64.Epub 2009May 27.
179. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia. 2009 Sep;50(9):2130-9. Epub 2009 Jun 1. Adverse pregnancy and birth outcome in women with epilepsy is mainly confined to AED-exposed pregnancies, although some risks are associated also with untreated epilepsy. The risk for congenital malformations was lower than previously reported. This could be due to a shift in AED selection, folic acid supplement, or possibly reflect the true risks in an unselected epilepsy population.
180. Fortinguerra, Filomena, Clavenna, Antonio, Bonati, Maurizio. Psychotropic Drug Use During **Breastfeedi**ng: A Review of the Evidence. Pediatrics 2009 124: e547-e556.
181. Striano P, Zara F, Minetti C, et al. **Chitosan** may decrease serum valproate and increase the risk of seizure reappearance. BMJ. 2009 Sep 24;339:b3751. doi: 10.1136/bmj.b3751.
182. Vajda FJ, et al. The **teratogenic** risk of antiepileptic drug polytherapy. Epilepsia. 2009 Oct 8. Coadministration with lamotrigine may lower the fetal risk of valproate therapy.
183. Brandt C, et al. Retention rate of **pregabalin** in drug-resistant epilepsy: 1-year follow-up, single-centre observation in 105 consecutive, adult patients. Seizure.2009 Nov;18(9):634-8.
184. Kelly VM, Nelson LM, Chakravarty EF. **Obstetric outcomes** (pregnancy) in women with multiple sclerosis and epilepsy. Neurology. 2009 Nov 18. [Epub ahead of print]
185. FDA Dec/09 notified health care professionals and patients about the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular **malformations**, in babies exposed to **valproate** sodium and related products (valproic acid and divalproex sodium) during pregnancy.
186. Gibbons RD.; Hur Kwan; et al. Relationship Between Antiepileptic Drugs and **Suicide** Attempts in Patients With Bipolar Disorder. Arch Gen Psychiatry. 2009;66(12):1354-1360.
187. Robson WL. Clinical practice. Evaluation and management of **enuresis**. N Engl J Med. 2009 Apr 2;360(14):1429-36.
188. Kumlien E, Lundberg PO. **Seizure risk** associated with neuroactive drugs: Data from the WHO adverse drug reactions database. Seizure. 2009 Dec 23.
The 10 drugs most frequently associated with convulsive ADRs were maprotilene (14.42%), escitaloprame (9.78%), buproprione (9.49%), clozapine (9.0%), chlorprothiexene (8.89%), amoxapine (8.74%), donepezil (8.40%), rivastigmine (6.41%), quetiapine (5.90%) and trimipramine (5.69%).
189. Vikelis M, Rapoport AM. Role of **antiepileptic drugs** as preventive agents for migraine. CNS Drugs. 2010 Jan 1;24(1):21-33. doi: 10.2165/11310970-000000000-00000.
190. Kwan J, Wood E. Antiepileptic drugs for the primary and secondary prevention of seizures **after stroke**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD005398.
191. Powell G, Saunders M, Marson AG. Immediate-release vs controlled-release **carbamazepine** in the treatment of epilepsy. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007124.
192. Wiffen PJ, Collins S, McQuay HJ, Carroll D, Jadad A, Moore RA. Anticonvulsant drugs for **acute and chronic pain**. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD001133.
193. Koch MW, Polman SK. **Oxcarbazepine versus carbamazepine** monotherapy for partial onset seizures. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006453.
194. RA, Gallagher JC. **Drug Fever**. Pharmacotherapy. 2010 Jan;30(1):57-69.
195. van Rooij LG, Toet MC, van Huffelen AC, et al. Effect of treatment of subclinical **neonatal seizures** detected with aEEG: randomized, controlled trial. Pediatrics. 2010 Feb;125(2):e358-66. Epub 2010 Jan 25.
196. Patel A, Pyzik PL, Turner Z, Rubenstein JE, Kossoff EH. Long-term outcomes of children treated with the **ketogenic diet** in the past. Epilepsia. 2010 Feb 1.
197. Glauser, Tracy A., Cnaan, Avital, Shinnar, Shlomo, et al. the Childhood **Absence Epilepsy** Study Group, **Ethosuximide**, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy. N Engl J Med 2010 362: 790-799. Ethosuximide and valproic acid are more effective than lamotrigine in the treatment of childhood absence epilepsy. Ethosuximide is associated with fewer adverse attentional effects.
198. Mazurkiewicz-Bełdzińska M, Szmuda M, Matheisel A. Long-term efficacy of **valproate** versus lamotrigine in treatment of idiopathic generalized epilepsies in children and adolescents. Seizure. 2010 Feb 16.
199. Michoulas A, Farrell K. Medical Management of **Lennox-Gastaut Syndrome**. CNS Drugs. 2010 Feb 16.
200. Cumbo E, Ligori LD. **Levetiracetam**, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease. Epilepsy Behav. 2010 Feb 24.
201. Salinsky M, Storzbach D, Munoz S. Cognitive effects of **pregabalin** in healthy volunteers: A double-blind, placebo-controlled trial. Neurology. 2010 Mar 2;74(9):755-61.
202. Simpson DM, Schifitto G, Clifford DB, et al. 1066 HIV Neuropathy Study Group.**Pregabalin** for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology. 2010 Feb 2;74(5):413-20. In this study, patients with HIV-associated peripheral neuropathy taking pregabalin (Lyrica) had no more pain relief than patients taking placebo. (LOE = 2b)
203. Patorno E; Bohn RL.; Wahl PM.; Avorn Jerry; et al. Anticonvulsant Medications and the Risk of **Suicide**, **Attempted Suicide**, or Violent Death. JAMA. 2010;303(14):1401-1409.
204. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in **industry-sponsored trials of gabapentin** for off-label use. N Engl J Med. 2009 Nov 12;361(20):1963-71.
205. Harden CL, Hopp J, Ting TY, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): obstetrical **complications and change in seizure frequency**. Report of the Quality Standards Subcommittee [trunc]. Neurology 2009 Jul 14;73(2):126-32.
206. Ziegler D, Hidvégi T, Gurieva I, et al.; **Lacosamide** SP743 Study Group. Efficacy and safety of lacosamide in painful diabetic neuropathy. Diabetes Care. 2010 Apr;33(4):839-41.
207. Labiner DM et al. **Generic antiepileptic drugs** and associated medical resource utilization in the United States. *Neurology* 2010 Apr 14.
208. Jentink, Janneke, Loane, Maria A., Dolk, Helen, et al. the EUROCAT Antiepileptic Study Working Group, **Valproic** Acid Monotherapy in Pregnancy and Major **Congenital**

TOP

Malformations. N Engl J Med 2010 362: 2185-2193. Six of the 14 were significantly associated with valproic acid use, compared with no exposure to antiepileptic drugs: spina bifida (odds ratio, 12.7), atrial septal defect (2.5), cleft palate (5.2), hypospadias (4.8), polydactyly (2.2), and craniosynostosis (6.8).
209. Straube S, Derry S, Moore RA, et al. Single dose oral **gabapentin** for established **acute postoperative pain** in adults. Cochrane Database Syst Rev. 2010 May 12;5:CD008183.
210. Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for **alcohol withdrawal**. Cochrane Database Syst Rev. 2010 Mar 17;3:CD005064.
211. Arana A et al. **Suicide-related events** in patients treated with antiepileptic drugs. N Engl J Med 2010 Aug 5; 363:542.
212. Dressler A, Stöcklin B, Reithofer E, et al. Long-term outcome & tolerability of the **ketogenic diet** in drug-resistant childhood epilepsy-The Austrian experience. Seizure.2010Jun 30.
213. McMullan J, Sasson C, Pancioli A, et al. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. Acad Emerg Med. 2010 Jun;17(6):575-82. Non-IV midazolam, compared to non-IV or IV diazepam, is safe and effective in treating SE. Comparison to lorazepam, evaluation in adults, and prospective confirmation of safety and efficacy is needed.
214. Ramsay E, Faught E, Krumholz A, et al.; for the CAPSS-272 Study Group. Efficacy, tolerability, and safety of rapid initiation of **topiramate versus phenytoin** in patients with new-onset epilepsy: A randomized double-blind clinical trial. Epilepsia. 2010 Jul 14.
215. Kimia A et al. **Yield of lumbar puncture** among children who present with their first complex febrile seizure. Pediatrics 2010 Jul; 126:62.
216. Goldstein LH, Chalder T, Chigwedere C, et al. **Cognitive-behavioral therapy** for psychogenic nonepileptic seizures: a pilot RCT. Neurology. 2010 Jun 15;74(24):1986-94.
217. Andersohn F, Schade R, Willich SN, Garbe E. Use of antiepileptic drugs in epilepsy and the **risk of self-harm or suicidal behavior**. Neurology. 2010 Jul 27;75(4):335-40.
218. Labiner DM et al. **Generic antiepileptic drugs** and associated medical resource utilization in the United States. Neurology 2010 Apr 14. In this retrospective study of adults with seizure disorders in managed care settings, the use of generic anticonvulsants was associated with slightly more hospitalizations and usage of outpatient services. But keep in mind that retrospective studies have many limitations and randomized trials often negate their findings. (LOE = 2b)
219. Tengstrand M, Star K, van Puijenbroek EP, Hill R. **Alopecia** in association with **lamotrigine** use: an analysis of individual case safety reports in a global database. Drug Saf. 2010 Aug 1;33(8):653-8. doi: 10.2165/11536190-000000000-00000.
220. Holsti M et al. **Intranasal midazolam** vs **rectal diazepam** for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med* 2010 Aug; 164:747.
221. Pontari Michel A.; Krieger John N.; Litwin Mark S.; et al.; for the Chronic Prostatitis Collaborative Research Network-2. **Pregabalin** for the Treatment of Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Randomized Controlled Trial. Arch Intern Med. 2010;170(17):1586-1593. Pregabalin therapy for 6 weeks was not superior to placebo use in the rate of a 6-point decrease (improvement) in the NIH-CPSI total score in men with CP/CPPS.
222. Visser, Annemarie M., Jaddoe, Vincent W. V., Hofman, Albert, et al. **Fetal Growth** Retardation and Risk of **Febrile Seizures**. Pediatrics 2010 0: peds.2010-0518.
223. Sukumaran SC et al. **Polytherapy increases the risk of infertility** in women with epilepsy. *Neurology* 2010 Oct 12; 75:1351.
224. Madadi P, Ito S. **Perinatal exposure to maternal lamotrigine**: Clinical considerations for the mother and child. Can Fam Physician. 2010 Nov;56(11):1132-4.
225. Meador KJ, Baker GA, Browning N, et al.; For the NEAD Study Group. Effects of **breastfeeding in children** of women taking antiepileptic drugs. Neurology. 2010 Nov 24.
226. Lee SA, Lee HW, Heo K, et al. **Cognitive and behavioral effects of lamotrigine and carbamazepine** monotherapy in patients with newly diagnosed or untreated partial epilepsy. Seizure. 2010 Nov 9.
227. Jentink Janneke, Dolk Helen, Loane Maria A, et al., for the EUROCAT Antiepileptic Study Working Group. Intrauterine exposure to **carbamazepine** and specific congenital **malformations**: systematic review and case-control study. BMJ 341:doi:10.1136/bmj.c6581 (Published 2 Dec 2010). (eg. **spina bifida**, though the risk is less than with valproic acid) Nulman I. **Carbamazepine in pregnancy**. BMJ. 2010 Dec 2;341:c6582. doi: 10.1136/bmj.c6582.
228. Kazmin, Aleksey, Wong, RC., Sermer, M, et al. **Antiepileptic drugs in pregnancy** and hemorrhagic disease of the newborn: An update. Can Fam Physician 2010 56: 1291-1292
229. Bonnett L J, Tudur-Smith C, Williamson P R, et al.. **Risk of recurrence after a first seizure and implications for driving**: further analysis of the Multicentre study of early Epilepsy and Single Seizures. BMJ 341:doi:10.1136/bmj.c6477 (Published 7 Dec 2010).
230. Sillanpää Matti, Shinnar Shlomo, **Long-Term Mortality** in Childhood-Onset Epilepsy. N Engl J Med 2010; 363:2522-2529.
231. Jette Nathalie; Lix Lisa M; Metge CJ; et al. Association of Antiepileptic Drugs With **Nontraumatic Fractures**: Population-Based Analysis. Arch Neurol. 2011;68(1):107-112.
232. Warlow C. **Driving** after a first seizure. BMJ. 2010 Dec 7;341:c6890. doi: 10.1136/bmj.c6890.
233. Subcommittee on Febrile Seizures, **Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure.** Pediatrics 2011 127: 389-394.
234. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. **Normal intelligence** in children with prenatal exposure to **carbamazepine**. Neurology. 2004 Jan 13;62(1):28-32.
235. Linnebank M, Moskau S, Semmler A, et al Antiepileptic drugs interact with **folate and vitamin B12** serum levels. Ann Neurol. 2011 Jan 19. doi: 10.1002/ana.22229.
236. FDA Mar/11 notified healthcare professionals and patients of an increased risk of development of **cleft lip and/or cleft palate (oral clefts)** in infants born to women treated with Topamax (**topiramate**) during pregnancy. Because of new human data that show an increased risk for oral clefts, topiramate is being placed in Pregnancy Category D.
237. Rizzo Matthew. **Impaired Driving From Medical Conditions**: A 70-Year-Old Man Trying to Decide if He Should Continue Driving. JAMA. 2011;305(10):1018-1026.
238. Pesaturo KA, Spooner LM, Belliveau P. **Vigabatrin for infantile spasms**. Pharmacotherapy. 2011 Mar;31(3):298-311.
239. Kwon C, Liu M, Quan H, et al. **Motor vehicle accidents, suicides, and assaults** in epilepsy: A population-based study. Neurology. 2011 Mar 1;76(9):801-6.
240. Sethi NK, Labiner DM, Helmers SL. **Generic antiepileptic** drugs and associated medical resource utilization in the United States. Neurology. 2011 Feb 8;76(6):583-4.
241. McClelland S 3rd, Guo H, Okuyemi KS. Population-Based Analysis of Morbidity and **Mortality Following Surgery** for Intractable Temporal Lobe Epilepsy in the United States. Arch Neurol. 2011 Feb 14.
242. Drazkowski JF, Sirven JI. **Motor vehicle crashes, suicides, and assaults**: The dangers of epilepsy? Neurology. 2011 Mar 1;76(9):770-1.
243. Patel A, Wordell C, Szarlej D. **Alternatives to sodium amobarbital in the wada test**. Ann Pharmacother. 2011 Mar;45(3):395-401.

TOP

244. McCormack Mark, Alfirevic Ana, Bourgeois S, et al. **HLA-A*3101** and Carbamazepine-Induced Hypersensitivity Reactions in Europeans. N Engl J Med 2011; 364:1134-1143.
245. Chen Pei, Lin Juei-Jueng, et al. Taiwan SJS Consortium. Carbamazepine-Induced Toxic Effects and **HLA-B*1502** Screening in Taiwan. N Engl J Med 2011; 364:1126-1133.
246. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Charlie Foundation, Practice Committee of the Child Neurology Society; Practice Committee of the Child Neurology Society; International **Ketogenic Diet** Study Group. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia. 2009 Feb;50(2):304-17.
247. Abend NS, Gutierrez-Colina AM, Topjian AA, et al. **Nonconvulsive seizures** are common in **critically ill children**. Neurology. 2011 Mar 22;76(12):1071-7.
248. Mindikoglu AL, King D, Magder LS, et al. **Valproic Acid-associated acute liver failure in children**: case report and analysis of liver transplantation outcomes in the United States. J Pediatr. 2011 May;158(5):802-7.
249. Modi AC., Rausch JR., Glauser TA. Patterns of **Nonadherence** to Antiepileptic Drug Therapy in Children With Newly Diagnosed Epilepsy. JAMA. 2011;305(16):1669-1676.
250. Parmet Sharon, Lynm Cassio, Golub Robert M. JAMA **Patient Page Epilepsy**. JAMA. 2011;305(16):1722.doi:10.1001/jama.305.16.1722.
251. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ, Levetiracetam Monotherapy Study Group. Comparison of **levetiracetam and controlled-release carbamazepine** in newly diagnosed epilepsy. Neurology. 2007 Feb 6;68(6):402-8.
252. Arya R, Gulati S, Kabra M, Sahu JK, Kalra V. **Folic acid** supplementation prevents phenytoin-induced gingival overgrowth in children. Neurology. 2011 Apr 12;76(15):1338-43.
253. Linnebank M, Moskau S, Semmler A, et al. **Antiepileptic drugs interact with folate** and vitamin B12 serum levels. Ann Neurol. 2011 Feb;69(2):352-9. doi: 10.1002/ana.22229.
254. Perucca Emilio, Tomson Torbjorn, The pharmacological **treatment of epilepsy** in adults, The Lancet Neurology, Volume 10, Issue 5, May 2011, Pages 446-456, ISSN 1474-4422.
255. Wightman Rachel S, Zell-Kanter Michele, Van Roo Jon, et al. **Zonisamide Toxicity** in a Patient with an Intentional Overdose. Articles Ahead of Print published on 1 April 2011.
256. Sun Y, Vestergaard M, Christensen J, Olsen J. **Breastfeeding** and risk of epilepsy in childhood: a birth cohort study. J Pediatr. 2011 Jun;158(6):924-9.
257. Josephson CB, Leach JP, Duncan R, et al. On behalf of the Scottish Audit of Intracranial Vascular Malformations (SAIVMs) steering committee and collaborators. Seizure risk from **cavernous or arteriovenous malformations**: Prospective population-based study. Neurology. 2011 May 3;76(18):1548-1554.
258. Mølgaard-Nielsen D, Hviid A. **Newer-generation antiepileptic drugs and the risk of major birth defects**. JAMA. 2011 May 18;305(19):1996-2002.
259. Cunnington MC, Weil JG, Messenheimer JA, et al. Final results from 18 years of the International **Lamotrigine Pregnancy Registry**. Neurology. 2011 May 24;76(21):1817-23.
260. French JA, Abou-Khalil BW, Leroy RF, et al.; On behalf of the RESTORE 1/Study 301 Investigators. Randomized, double-blind, placebo-controlled trial of **ezogabine (retigabine)** in partial epilepsy. Neurology. 2011 May 3;76(18):1555-1563.
261. Sendra JM, Junyent TT, Pellicer MJR. **Pregabalin-Induced Hepatotoxicity**. Ahead of Print 1 June 2011, DOI 10.1345/aph.1Q032. Ann Pharmacother ;45:e32.
262. See S, Hendriks E, Hsiung L. **Akathisia Induced by Gabapentin Withdrawal**. Ahead of Print on 1 June 2011, DOI 10.1345/aph.1Q057. Ann Pharmacother ;45:e31.
263. McClelland S 3rd, Guo H, Okuyemi KS. Population-based analysis of morbidity and mortality following **surgery for intractable temporal lobe epilepsy** in the United States. Arch Neurol. 2011 Jun;68(6):725-9.
264. Holmes LB, Mittendorf R, Shen A, Smith CR, Hernandez-Diaz S. Fetal Effects of Anticonvulsant **Polytherapies: Different Risks From Different Drug Combinations**. Arch Neurol. 2011 Jun 13. (Monotherapy risk: with lamotrigine 1.9% & carbamazepine 2.9%, but increased if combined with valproate).
265. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of **malformations** with antiepileptic drugs: an analysis of data from the **EURAP** epilepsy and pregnancy registry. *Lancet Neurol* 2011; published online June 6. DOI:10.1016/S1474-4422(11)70107-7. (Data: on lamotrigine, carbamazepine, valproate & phenobarbital).
266. Engel J Jr, Wiebe S, French J, et al; Quality Standards Subcommittee of the American Academy of Neurology (AAN); American Epilepsy Society; American Association of Neurological Surgeons. Practice parameter: **temporal lobe and localized neocortical resections** for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology. 2003;60(4):538-547.
Mohammed HS, Kaufman CB, Limbrick DD, et al. Impact of epilepsy surgery on seizure control and quality of life: A **26-year follow-up study**. Epilepsia. 2012 Feb 7.
Engel J Jr, McDermott MP, Wiebe S, et al. Early **surgical therapy** for drugresistant **temporal lobe epilepsy**: a randomized trial. (ERSET) JAMA. 2012;307(9):922-930.
Hildreth CJ, Lynm C, Golub RM. JAMA **patient page. Epilepsy surgery**. JAMA. 2012 Mar 7;307(9):985.
267. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of **drug resistant epilepsy**: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-1077.
268. Robottom BJ, Factor SA, Weiner WJ. Movement disorders emergencies part 2: hyperkinetic disorders (chorea, tics, ballism, myoclonus, dystonia). Arch Neurol. 2011 Jun;68(6):719-24.
269. Krumholz SD, Egilman DS, Ross JS. Study of Neurontin: Titrate to Effect, Profile of Safety (STEPS) trial: a narrative account of a **gabapentin seeding trial**.Arch Intern Med. 2011;171(12):1100-1107.
270. FDA & CDN June-July/11 notified healthcare professionals: children born to mothers who take the anti-seizure medication **valproate** sodium or related products (valproic acid and divalproex sodium) during pregnancy have an increased risk of **lower cognitive test scores** than children exposed to other anti-seizure medications during pregnancy.
271. Shorvon Simon, Tomson Torbjorn. **Sudden unexpected death** (SUDEP) in epilepsy. www.thelancet.com Online July 6, 2011. (↑: GTC, Males, long-duration hx & on polytherapy)
272. Mu J, Liu L, Zhang Q, et al. Causes of **death among people with convulsive epilepsy** in rural West China: A prospective study. Neurology. 2011 Jul 12;77(2):132-7.
273. Cummings C, et al. **Neurodevelopment** of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child. 2011 Jul;96(7):643-7.
274. Hesdorffer DC, Logroscino G, Benn EKT, et al. **Estimating risk for developing epilepsy**: a population-based study in Rochester, Minnesota. Neurology 2011;76:23–2.

TOP

275. Kwan P, Schachter SC, Brodie MJ. **Drug-resistant epilepsy**. N Engl J Med. 2011 Sep 8;365(10):919-26.
276. Kwan P, Brodie MJ, Kälviäinen R, Yurkewicz L, Weaver J, Knapp LE. Efficacy and safety of **pregabalin versus lamotrigine** in patients with newly diagnosed partial seizures: a phase 3, double-blind, randomised, parallelgroup trial. Lancet Neurol 2011; published online Sept 1. (n=660 with a 52 week efficacy assessment phase.)
277. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of **surgery for temporal-lobe epilepsy**. N Engl J Med 2001;345:311-8.
278. Téllez-Zenteno JF, Dhar R, Wiebe S. **Long-term seizure outcomes following epilepsy surgery**: a systematic review and meta-analysis. Brain 2005;128:1188-98.
279. Samuels N, Finkelstein Y, Singer SR, Oberbaum M. **Herbal medicine and epilepsy**: proconvulsive effects and interactions with antiepileptic drugs. Epilepsia 2008;49:373-80.
280. Weller M, Gorlia T, Cairncross JG, et al. Prolonged survival with **valproic acid** use in the EORTC/NCIC temozolomide trial for **glioblastoma**. Neurology 2011;77:1156 –1164.
281. Morrell MJ, **RNS System** in Epilepsy Study Group. **Responsive cortical stimulation** for the treatment of medically intractable partial epilepsy. Neurology 2011;77:1295–1304.
282. Fisher R, Salanova V, Witt T, et al. **Electrical stimulation** of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899 –908.
283. George R, Salinsky M, Kuzniecky R, et al. **Vagus nerve stimulation** for treatment of partial seizures: 3: long-term follow-up on first 67 patients exiting a controlled study:First International Vagus Nerve Stimulation Study Group. Epilepsia 1994;35:637– 643.
284. Fleisher AS, Truran D, Mai JT, et al. For the Alzheimer's Disease Cooperative Study. Chronic **divalproex** sodium use and brain atrophy in **Alzheimer** disease. Neurology. 2011 Sep 27;77(13):1263-1271.
285. Spriet I, Willems L. No interaction between valproate and **meropenem** in a cirrhotic patient. Ann Pharmacother. 2011 Sep;45(9):1167-8.
286. Ngugi AK, Kariuki SM, Bottomley C, et al..**Incidence of epilepsy**: A systematic review and meta-analysis. Neurology. 2011 Sep 6;77(10):1005-12.
287. Singh RK, Zecavati N, Singh J, et al. Seizures in Acute **Childhood** Stroke. J Pediatr. 2011 Sep 10.
288. de Tisi J, Bell GS, et al. The **long-term** (up to 19yrs) outcome of adult **epilepsy surgery**, patterns of seizure remission, and relapse: a cohort study. Lancet 2011; 378: 1388–95.
289. Bonnett LJ, Tudur-Smith C, Williamson PR, et al. **Risk of recurrence** after a first seizure and implications for driving: further analysis of the Multicentre study of early Epilepsy and Single Seizures . BMJ 2010; 341: c6477.
290. Fitzgerald CL, Jacobson MP. **Generic substitution of levetiracetam** resulting in increased incidence of breakthrough seizures (May). Ann Pharmacother. 2011 Apr 26.
291. Ho JM, Juurlink DN. Considerations when prescribing **trimethoprim-sulfamethoxazole**. CMAJ. 2011 Oct 11. (phenytoin DIs)
292. Holmes LB, Mittendorf R, Shen A, et al. **Fetal effects of anticonvulsant polytherapies** (especially with valproate): different risks from different drug combinations. Arch Neurol. 2011 Oct;68(10):1275-81.
293. Naeije G, Lorent S, Vincent JL, Legros B. Continuous **epileptiform discharges** in patients treated with **cefepime** or meropenem. Arch Neurol. 2011 Oct;68(10):1303-7.
294. Bausell R, Svoronos A, Lennihan L, Hirsch LJ. **Recovery after severe refractory status epilepticus and 4 months** of coma. Neurology. 2011 Oct 11;77(15):1494-5.
295. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA; On behalf of the OV-1012 Study Investigators. Randomized, phase III study results of **clobazam in Lennox-Gastaut syndrome**. Neurology. 2011 Oct 11;77(15):1473-1481.
296. See S, Hendriks E, Hsiung L. **Akathisia induced by gabapentin** withdrawal. Ann Pharmacother. 2011 Jun;45(6):e31.
297. Cummings C, Stewart M, Stevenson M, et al. **Neurodevelopment** of children exposed in utero to **lamotrigine, sodium valproate and carbamazepine**. Arch Dis Child. 2011 Jul;96(7):643-7.
298. Tzatha E, Karceski SC. **Responsive neurostimulation** for the treatment of seizures that do not respond to medication. Neurology. 2011 Sep 27;77(13):e79-81.
299. Chaluvadi S, Chiang S, Tran L, Goldsmith CE, Friedman DE. Clinical experience with **generic levetiracetam** in people with epilepsy. Epilepsia. 2011 Apr;52(4):810-5.
300. Crump C, Sundquist K, Winkleby MA, Sundquist J. **Preterm birth** and risk of epilepsy in Swedish adults. Neurology. 2011 Oct 4;77(14):1376-82.
301. Nadebaum C, Anderson VA, Vajda F, et al. **Language skills** of school-aged children prenatally exposed to antiepileptic drugs (**valproate**). Neurology 2011;76:719–26.
302. Beghi E, D'Alessandro R, Beretta S, et al. Incidence and predictors of **acute symptomatic seizures after stroke**. Neurology 2011;77:1785–1793.
303. De Herdt V, Dumont F, Hénon H, et al. **Early seizures in intracerebral hemorrhage**: incidence, associated factors, and outcome. Neurology 2011;77:1794 –1800.
304. Devinsky O. **Sudden, unexpected death in epilepsy**. (SUDEP) N Engl J Med. 2011 Nov 10;365(19):1801-11.
305. Neligan A, Bell GS, Sander JW. **Sudden death in epilepsy**. (SUDEP) BMJ. 2011 Nov 15;343:d7303.
306. Hesdorffer DC, et al. ILAE Commission on Epidemiology; Subcommission on Mortality. Combined analysis of risk factors for **SUDEP**. Epilepsia. 2011 Jun;52(6):1150-9.
307. British National Formulary. What's new in BNF 62? Available: http://bnf.org/bnf/extra/current/450035.htm. [Accessed October 30 2011].
308. Yamada M, Welty TE. **Generic substitution** of antiepileptic drugs: a systematic review of prospective and retrospective studies. Ann Pharmacother. 2011 Nov;45(11):1406-15.
309. Fernandez EM, Franck AJ. **Lacosamide** for the treatment of **refractory status epilepticus**. Ann Pharmacother. 2011 Nov;45(11):1445-9.
310. Finkelstein Y, Soon GS, Acuna P, et al. Recurrence and outcomes of **stevens-johnson syndrome** and toxic epidermal necrolysis in children. Pediatrics. 2011 Oct;128(4):723-8.
311. Ryvlin P, Cucherat M, Rheims S. Risk of **sudden unexpected death** in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol 2011; 10: 961–68.
312. Claassen C. Epilepsy therapeutics update: highlights from a pediatric pharmacist perspective. Pharmacy Practice CE Lesson, November 2011.
313. Irving G et al. Efficacy and tolerability of gastric-retentive gabapentin for the treatment of postherpetic neuralgia: results of a double-blind, randomized, placebo-controlled clinical trial. Clin J Pain 2009; 25:185. (gabapentin daily not better than placebo)

TOP

314. Wallace MS et al. Gabapentin extended-release tablets for the treatment of patients with postherpetic neuralgia: a randomized, double-blind, placebo-controlled, multicentre study. Clin Drug Investig 2010; 30:765. (gabapentin not better than placebo)
315. Syed TU et al. Can **semiology predict psychogenic nonepileptic seizures**? A prospective study. Ann Neurol 2011 Mar 17
316. Birbeck GL, French JA, Perucca E, et al. Evidence-based guideline: **Antiepileptic drug selection for people with HIV/AIDS**: Report of the Quality Standards Subcommittee of the American Academy of Neurology (**AAN**) and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy.Neurology. 2012 Jan 10;78(2):139-45.
317. Hamid H et al. Long-term association between **seizure outcome and depression** after resective epilepsy surgery. Neurology. 2011 Nov 9; 77(22):1972-6.
318. Salinsky M, Spencer D, Boudreau E, et al. **Psychogenic nonepileptic seizures in US veterans**. Neurology 2011;77:945–950.
319. Poolos NP, Warner LN, Humphreys SZ et al. Comparative efficacy of **combination drug therapy in refractory epilepsy**. Neurology. 2012 Jan 3;78(1):62-8. (combination valproate & lamotrigine showed superior efficacy)
320. Asadi-Pooya AA, Nikseresht A, Yaghoubi E et al. **Physical injuries** in patients with epilepsy and their associated risk factors. Seizure. 2011 Nov 28.
321. García-Morales I, Delgado RT, Falip M et al. Early clinical experience with **lacosamide** as adjunctive therapy in patients with **refractory focal epilepsy and nocturnal seizures**. Seizure. 2011 Dec;20(10):801-4.
322. Caraballo R, Vaccarezza M, Cersósimo R et al. Long-term follow-up of the **ketogenic diet** for refractory epilepsy: multicenter Argentinean experience in 216 pediatric patients. Seizure. 2011 Oct;20(8):640-5.
323. Legros B, Boon P, Ceulemans B et al. Development of an **electronic decision tool** to support appropriate treatment choice in adult patients with epilepsy - Epi-Scope(®). Seizure. 2012 Jan;21(1):32-9.
324. Sharma S, Sankhyan N, Gulati S et al. Use of the **modified Atkins diet** in infantile spasms refractory to first-line treatment. Seizure. 2012 Jan;21(1):45-8.
325. Yang CY et al. **Severe cutaneous adverse reactions** to antiepileptic drugs in Asians. Neurology. 2011 Dec 6;77(23):2025-33. (CBZ, PHT, and LTG were the major causative AEDs for SCARs.)
326. **NICE**: National Institute for Health and Clinical Excellence. The **epilepsies**: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). (Clinical guideline 137.) Jan **2012**. http://guidance.nice.org.uk/CG137.
Delgado V, Sawyer L, Neilson J et al. Diagnosis and management of the epilepsies in adults and children: summary of updated NICE guidance. BMJ 2012;344:e281 Jan26,2012.
327. Russ SA, Larson K, Halfon N. A **National Profile of Childhood** Epilepsy and Seizure Disorder. Pediatrics. 2012 Jan 23.
328. Graves, R, Oehler K, et al. **Febrile Seizures**: Risks, Evaluation, and prognosis. Am Fam Physician. 2012 Jan 15;85(2):149-153.
329. Mohammed HS, Kaufman CB, Limbrick DD, et al. Impact of **epilepsy surgery** on seizure control and quality of life: A 26-year follow-up study. Epilepsia. 2012 Feb 7.
330. Adelöw C, Andersson T, Ahlbom A et al. **Hospitalization for psychiatric disorders** before and after onset of unprovoked seizures/epilepsy. Neurology. 2012 Feb 7;78(6):396-401.
331. Faught E, Richman J, Martin R, et al. **Incidence and prevalence** of epilepsy among **older** US Medicare beneficiaries. Neurology 2012;78:448 – 453
332. Silbergleit R, et al. **Intramuscular (midazolam) versus intravenous (lorazepam)** therapy for prehospital **status epilepticus**. (Rampart) N Engl J Med 2012;366:591-600. Intramuscular (IM) midazolam is the preferred initial treatment for patients with status epilepticus in the prehospital setting. Primary care physicians may want to keep a vial of midazolam around the office in case that rare patient has a seizure that continues for more than 5 minutes. (LOE = 1b)
333. Treiman DM, Meyers PD, Walton NY, et al. A comparison of **four treatments** for generalized convulsive **status epilepticus**. N Engl J Med 1998;339:792-8.
334. Alldredge BK, Gelb AM, et al. A comparison of **lorazepam, diazepam, and placebo** for the treatment of out-ofhospital **status epilepticus**. N Engl J Med 2001;345:631-7.
335. Hearn L, Derry S, Moore RA. **Lacosamide** for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2012 Feb 15;2:CD009318. Lacosamide has limited efficacy in the treatment of peripheral diabetic neuropathy. Higher doses did not give consistently better efficacy, but were associated with significantly more adverse event withdrawals.
336. Striano P, Weber YG, Toliat MR, et al. **GLUT1 mutations** are a rare cause of familial idiopathic generalized epilepsy. Neurology 2012;78:557–562.
337. Bonnett L, Tudur-Smith C, Smith D, et al. **Prognostic factors** for time to treatment failure and time to 12 months of remission for patients with focal epilepsy: post-hoc, subgroup analyses of data from the **SANAD** trial. Lancet Neurol 2012.
338. Engel J Jr, McDermott MP, Wiebe S, et al. Early **surgical therapy** for drugresistant **temporal lobe epilepsy**: a randomized trial. (ERSET) JAMA. 2012;307(9):922-930. n=38
339. Irizarry M, Jin S; He F et al. Incidence of New-Onset Seizures in Mild to Moderate **Alzheimer Disease** Arch Neurol. 2012;69(3):368-372.
340. Baca CB et al. **Psychiatric and medical comorbidity** and quality of life outcomes in **childhood-onset epilepsy**. Pediatrics. 2011 Dec;128(6):e1532-43.
341. Schober E, Otto KP, Dost A, et al; German/Austrian DPV Initiative and the BMBF Competence Network Diabetes. Association of Epilepsy and **Type 1 Diabetes Mellitus** in Children and Adolescents: Is There an Increased Risk for Diabetic Ketoacidosis? J Pediatr. 2011 Nov 3.
342. Simms KM, Kortepeter C, Avigan M. **Lamotrigine and aseptic meningitis**. Neurology 2012;78:921–927.
343. Kimia AA et al. Yield of emergent **neuroimaging among children presenting with a first complex febrile seizure**. Pediatr Emerg Care 2012 Apr; 28:316.
344. Talati R, Scholle JM, et al. Efficacy and Safety of **Innovator versus Generic Drugs** in Patients with Epilepsy: Systematic Review. Pharmacotherapy. 2012 Apr;32(4):314-22.
345. Hesdorffer D, Ishihara L, Mynepalli L, et al. **Epilepsy, suicidality, and psychiatric disorders**: A bidirectional association Ann Neurol. 2012 Mar 29.

TOP

346. Forcelli P, Janssen M, Vicini S et al. **Neonatal exposure** to antiepileptic drugs disrupts striatal synaptic development Ann Neurol. 2012 Mar 29.
347. Quek AML, Britton JW, McKeon A, et al. **Autoimmune epilepsy**: clinical characteristics and response to immunotherapy [published online March 26, 2012]. Arch Neurol. 2012.
348. Lackner P, Koppelstaetter F, Ploner P, et al. **Cerebral vasospasm** following temporal lobe epilepsy surgery. Neurology 2012;78:1215–1220.
349. Englot DJ, Ouyang D, Garcia PA, Barbaro NM, Chang EF. **Epilepsy surgery trends** in the United States, 1990– 2008. Neurology 2012;78:1200 –1206.
350. Yang S-Y, Kim DG, Chung H-T, Paek SH. **Radiosurgery for unruptured cerebral arteriovenous malformations**: long-term seizure outcome. Neurology 2012;78:1292–1298.
351. Westwood AJ, Vendrame M, Montouris G, Auerbach SH. Pearls & Oy-sters: Treatment of central sleep apnea with topiramate. Neurology. 2012 Apr 17;78(16):e97-9.
352. Neligan A, Bell GS, Giavasi C, et al. Long-term risk of developing **epilepsy after febrile seizures**: A prospective cohort study. Neurology. 2012 Apr 10;78(15):1166-70.
353. Meador KJ, Baker GA, et al; NEAD Study Group. Effects of **fetal antiepileptic drug exposure**: Outcomes at age 4.5 year. Neurology. 2012 Apr 17;78(16):1207-1214.
354. Kinikar SA, Delate T, Menaker-Wiener CM, et al. Clinical Outcomes Associated with **Brand-to-Generic Phenytoin** Interchange. Ann Pharmacother. 2012 May;46(5):650-8.
355. Ludvigsson JF, Zingone F, Tomson T, et al. Increased risk of epilepsy in biopsy-verified **celiac disease**: A population-based cohort study. Neurology. 2012 May 1;78(18):1401-7.
356. Krauss GL, Serratosa JM, et al. Randomized phase III study 306: Adjunctive **perampanel** for refractory partial-onset seizures. Neurology. 2012 May 1;78(18):1408-15.
357. Pavlova MK, Woo Lee J, Yilmaz F, et al. **Diurnal pattern** of seizures outside the hospital: Is there a time of circadian vulnerability? Neurology. 2012 May 8;78(19):1488-92.
358. Brodie MJ, Barry SJE, Bamagous GA, Norrie JD, Kwan P. **Patterns of treatment response in newly** diagnosed epilepsy. Neurology 2012;78:1548 –1554.
359. Larson AM, Ryther RC, Jennesson M, et al. Impact of pediatric epilepsy on **sleep patterns** and behaviors in children and parents. Epilepsia. 2012 May 17.
360. Hernández-Díaz S, Smith CR, Shen A, et al; For the North American AED Pregnancy Registry; North American AED(Antiepileptic Drug) Pregnancy Registry; Scientific Advisory Committee; North American AED Pregnancy Registry. Comparative safety of **antiepileptic drugs during pregnancy**. Neurology. 2012 May 22;78(21):1692-1699.
361. Sanchez Ferna´ndez I, Takeoka M, Tas E, et al. **Early thalamic lesions** in patients with sleep-potentiated epileptiform activity. Neurology 2012;78:1721–1727.
362. Baulac M, Brodie MJ, Patten A, Segieth J, Giorgi L. Efficacy and tolerability of **zonisamide versus controlled-release carbamazepine** for newly diagnosed partial epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Neurol 2012; online June 8.
363. Herzog AG, Fowler KM, Smithson SD, et al; For the Progesterone Trial Study Group. **Progesterone** vs placebo therapy for women with epilepsy: A randomized clinical trial. Neurology. 2012 Jun 12;78(24):1959-1966. (Class III: cyclic progesterone is ineffective)
364. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: Medical treatment of **infantile spasms**: Report of the Guideline Development Subcommittee of the **American** Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2012 Jun 12;78(24):1974-80.
365. **Ketogenic diets** in the treatment of epilepsy. Drug Ther Bull. 2012 Jun;50(6):66-8.
366. Mbuba CK, Ngugi AK, Fegan G, et al. Risk factors associated with the **epilepsy treatment gap** in Kilfi , Kenya: a cross-sectional study. *Lancet Neurol* 2012; online July 6.
367. Shiek Ahmad B, Hill KD, O'Brien TJ, et al. **Falls and fractures** in patients chronically treated with antiepileptic drugs. Neurology. 2012 Jun 13.
368. de Laat SA, Hillegers MH, Jansen FE, et al. **Hallucinations After Withdrawal of Valproic Acid**. Pediatrics. 2012 Jun 11.
369. Stern RS. Clinical practice. **Exanthematous drug eruptions**. N Engl J Med. 2012 Jun 28;366(26):2492-501. (penicillin, cephalosporins, sulfonamides, antiseizure meds etc)

TOP

Extras:

Preventing Gaps when Switching Contraceptives. Lesnewski '11

Switching from →	Switching to	Comments
Combined OC, progestin only pill	Combined OC, progestin only pill	♦switch **directly** from one pill to another; do not miss a day
Combined OC	Patch or Ring	♦start patch **day before** last pill; start ring **day after** last pill ♦Do not need to complete pill cycle before switch
Patch or Ring	Combined OC	♦start pill day **before** scheduled to remove patch/ring; i.e. no more than 8 days after last patch (effective up to 9 days) or 34 days after ring (effective up to 35days) ♦Do not need to complete full cycle for patch/ring before pill starts
Patch	Ring	♦insert ring & remove patch on **same day**
Ring	Patch	♦Apply patch **2 days before** ring removal
Combined OC, patch or ring	Progestin IUD or injection	♦Continue pill, patch or ring x **7days** (or use barrier)
Copper IUD	Progestin IUD (i.e Mirena)	♦Use barrier **x 7 days**; return to fertility may be immediate
Copper IUD	Progestin injection (i.e. Depo-Provera)	♦Give injection **7 days before** IUD removal; if done on same day, use **barrier x 7days**
Copper IUD	Combined OC, patch, or ring	♦Start new method **7 days before** removal of IUD or use **barrier x 7days**
Progestin IUD (i.e. Mirena) or injection (i.e. Depo-Provera)	Combined OC, patch, or ring	♦Start new method **7 days before** removal of IUD or next injection (i.e. may start new method **up to 15 weeks after** last injection)
Combined OC, patch or ring	Copper IUD	♦Can insert copper IUD up to **five days** after stopping pill, patch or ring
Progestin IUD (i.e. Mirena)	Copper IUD	♦Can insert copper IUD **right after removing** progestin IUD
Progestin injection (i.e. Depo-Provera)	Copper IUD	♦Can insert copper IUD **up to 16weeks after** the last shot

Consider: Abstain from sexual intercourse or use a barrier method (condoms +/- spermicide) if no overlap in methods for a minimum of 7days for most switches (see above table for exact number of days in bold print)

"Patient Friendly" Statistics for Contraceptive Failure Rates: http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118465.htm#hormonal

Out of 100 women who use the following method for 1 year:

- Injection, progestin IUD – 1 may get pregnant
- COC, POP, patch & ring – 5 may get pregnant
- Male condoms – 11 to 16 may get pregnant
- Diaphragm – 15 may get pregnant
- Sponge – 16 to 32 may get pregnant
- Female condoms – 20 may get pregnant
- Spermicide along – 30 may get pregnant

References: 1. Biological activity and therapeutic management. OC Chart. Organon Canada Ltd. 1997. 2. Dickey R. Managing Oral Contraceptive Patients, 9th edition. Essential Medical Information Systems, Durant, OK. 1998. 3. Product monographs. 4. www.RxFiles.ca-Jan00.

Contraceptive, Combination Hormonal Products Additional references:

Abou-Setta AM, et al. **Levonorgestrel**-releasing intrauterine device (LNG-IUD) for symptomatic **endometriosis** following surgery. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005072.

Agostino H, Di Meglio G. **Low-dose** oral contraceptives in adolescents: how low can you go? J Pediatr Adolesc Gynecol. 2010 Aug;23(4):195-201.

Almstedt Shoepe H, Snow CM. Oral contraceptive use in young women is associated with lower bone mineral density than that of controls. Osteoporos Int. 2005 May 19; [Epub ahead of print]

American College of Obstetricians and Gynecologists (ACOG). Emergency contraception. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2005 Dec. 10 p. (ACOG practice bulletin; no. 69).

American College of Obstetricians and Gynecologists (ACOG). **Emergency contraception**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2010 May. (ACOG practice bulletin; no. 112).

American College of Obstetricians and Gynecologists (ACOG). **Noncontraceptive uses of hormonal contraceptives**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2010 Jan. 13 p. (ACOG practice bulletin; no. 110).

American College of Obstetricians and Gynecologists (ACOG): Practice Bulletin #121 "Long-Acting Reversible Contraception: **Implants and Intrauterine Devices**" in the July 2011 issue of Obstetrics & Gynecology.

Amy JJ, Tripathi V. Contraception for women: an evidence based overview. BMJ. 2009 Aug 7;339:b2895. doi: 10.1136/bmj.b2895.

Anderson FD, Hait H. A multicenter, randomized study of an extended cycle oral contraceptive. Contraception. 2003 Aug;68(2):89-96. Erratum in: Contraception. 2004 Feb;69(2):175.

Austin Harland, Lally Cathy, et al. Hormonal contraception, **sickle cell** trait, and risk for venous thromboembolism among **African American** women. American Journal of Obstetrics & Gynecology - June 2009 (Vol. 200, Issue 6, Pages 620.e1-620.e3, DOI: 10.1016/j.ajog.2009.01.038)

Baillargeon JP, McClish DK, et al. Association between the current use of low-dose oral contraceptives and **cardiovascular arterial disease**: a meta-analysis. J Clin Endocrinol Metab. 2005 Jul;90(7):3863-70.Epub 2005Apr 6.

Beksinska ME, Smit JA, et al. Prospective study of weight change in new adolescent users of **DMPA**, NET-EN, COCs, nonusers and discontinuers of hormonal contraception. Contraception. 2010 Jan;81(1):30-4.

Bermas BL. Oral contraceptives in systemic **lupus** erythematosus -- a tough pill to swallow? N Engl J Med. 2005 Dec 15;353(24):2602-4.

Bernier MO, Mikaeloff Y, Hudson M, Suissa S. Combined oral contraceptive use and the risk of systemic **lupus** erythematosus. Arthritis Rheum. 2009 Apr 15;61(4):476-81.

Bialer M, et al. Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. 2004;43(12):763-80.

Black A, Francoeur D, Rowe T, Collins J, Miller D, Brown T, David M, Dunn S, Fisher WA, Fleming N, Fortin CA, Guilbert E, Hanvey L, Lalonde A, Miller R, Morris M, O'Grady T, Pymar H, Smith T, Hennet

TOP

Society of Obstetricians and Gynaecologists of Canada. **SOGC** clinical practice guidelines: Canadian contraception consensus. J Obstet Gynaecol Can. 2004 Mar;26(3):219-96.
Blumenthal PD, Edelman A. Hormonal contraception. Obstet Gynecol. 2008 Sep;112(3):670-84.
Bonnema RA., McNamara MC., Spencer AL.,**Contraception Choices in Women with Underlying Medical Conditions**. Am Fam Physician. 2010 Sep 15;82(6):621-628.
British National Formulary 2005
Calhoun A. Combined hormonal contraceptives: Is it time to reassess their role in **migraine**? Headache 2011. Published online ahead of print January 6, 2012.
Camacho EM, Lunt M, Farragher TM, et al. The relationship between oral contraceptive use and functional outcome in women with recent **onset inflammatory polyarthritis**: Results from the Norfolk Arthritis Register (NOAR). Arthritis Rheum. 2011 Apr 22. doi: 10.1002/art.30416.
Castellsagué X, Díaz M, et al. **Intrauterine device use**, cervical infection with human papillomavirus, and risk of **cervical cancer**: a pooled analysis of 26 epidemiological studies. Lancet Oncol 2011; online Sept 13.
CDA Diane 35 response http://www.dermatology.ca/english/public-patients/Diane35-Fact-Sheet_e.pdf
CDC: Centers for Disease Control and Prevention (CDC). U.S. medical eligibility criteria for contraceptive use, 2010: adapted from the World Health Organization medical eligibility criteria for contraceptive use, 4th edition. MMWR Recomm Rep 2010 Jun 18;59(RR-4):1-86. **CDC** has released **medical eligibility criteria for contraceptive use to help U.S. healthcare providers** counsel patients about their contraceptive choices. The criteria, published in MMWR, are modified from the World Health Organization's 2009 guidance. The CDC offers modified recommendations about contraception for U.S. women who have venous thromboembolism, valvular heart disease, ovarian cancer, and uterine fibroids, as well as women who are postpartum and breast-feeding. It also gives additional guidance on contraception for women with rheumatoid arthritis, previous bariatric surgery, peripartum cardiomyopathy, endometrial hyperplasia, inflammatory bowel disease, and organ transplantation. http://www.cdc.gov/mmwr/pdf/rr/rr59e0528.pdf
CDC: Update to **CDC's U.S. Medical Eligibility Criteria** for Contraceptive Use, 2010: Revised Recommendations for the Use of Contraceptive Methods During the Postpartum Period. http://www.cdc.gov/mmwr/pdf/wk/mm6026.pdf
CDC: Centers for Disease Control and Prevention. **Sexual experience and contraceptive use among female teens** — United States, 1995, 2002, and 2006–2010. MMWR Morb Mortal Wkly Rep 2012 May 4; 61:297.
Cheng L, et al. Interventions for **emergency contraception**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD001324. Mifepristone middle dose (25-50 mg) was superior to other hormonal regimens. Mifepristone low dose (<25 mg) could be more effective than levonorgestrel 0.75 mg (two doses) but this was not conclusive. Levonorgestrel proved more effective than the Yuzpe regimen. The copper IUD was another effective emergency contraceptive that can provide ongoing contraception.
Clark MK, et al. **Bone mineral density** loss and recovery during 48 months in first-time users of depot **medroxyprogesterone** acetate. Fertil Steril. 2006 Nov;86(5):1466-74. Epub 2006 Sep 25.
Cleland K, Raymond E, Trussell J, Cheng L, Zhu H. **Ectopic pregnancy and emergency contraceptive pills**: a systematic review. Obstet Gynecol. 2010 Jun;115(6):1263-6.
Cleland K, Zhu H, Goldstuck N, Cheng L, Trussell J. The efficacy of **intrauterine devices for emergency contraception**: a systematic review of 35 years of experience. Human Reproduction doi:10.1093/humrep/des140.
Clinical Effectiveness Unit. **Drug interactions** with hormonal contraception. London (UK): Faculty of Sexual and Reproductive Healthcare; 2012 Jan.
Collaborative Group on Epidemiological Studies of **Ovarian Cancer**, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008 Jan 26;371(9609):303-14. Use of oral contraceptives confers long-term protection against ovarian cancer. These findings suggest that oral contraceptives have already prevented some 200,000 ovarian cancers and 100,000 deaths from the disease, and that over the next few decades the number of cancers prevented will rise to at least 30,000 per year.
Compassionate Contraceptive Assistance Program SGOC: http://www.sogc.org/projects/ccap_e.asp
Creinin MD, et al. **Progesterone receptor modulator** for emergency contraception: a randomized controlled trial. Obstet Gynecol. 2006 Nov;108(5):1089-97.
Creinin MD, Meyn LA, Borgatta L, et al. Multicenter comparison of the contraceptive ring and patch: a randomized controlled trial. Obstet Gynecol. 2008 Feb;111(2 Pt 1):267-77. The majority of women who are using oral contraceptives (OCs) and try the vaginal ring continue with the ring rather than go back to OCs. Most women who try patches go back to OCs. It is uncertain whether the nonmasked nature of the trial, which was funded by the manufacturer of the vaginal ring, introduced bias into the study. (LOE = 1b-)
D'Cruz DP. Systemic **lupus** erythematosus. BMJ. 2006 Apr 15;332(7546):890-4.
Davis AR, Westhoff C, O'Connell K, Gallagher N. Oral contraceptives for dysmenorrhea in adolescent girls. Obstet Gynecol 2005; 106:97-104. (InfoPOEMs: This trial substantiates previous observational data that low-dose oral contraceptives (OCs) are effective treatment for dysmenorrhea in adolescents. Although just one formulation was used in this study, the results are likely generalizable to all combination oral contraceptives. (LOE = 1b))
de Ziegler D, Gayet V, Aubriot FX, et al. Use of oral contraceptives in women with **endometriosis** before assisted reproduction treatment improves outcomes. Fertil Steril. 2010 Jul 21.
Dinger JC, Cronin M, Möhner S, Schellschmidt I, et al. Oral contraceptive effectiveness according to **body mass** index, weight, age, and other factors. Am J Obstet Gynecol. 2009 Sep;201(3):263.e1-9. Epub 2009 May 30.
Dinger JC, Heinemann LA, Kühl-Habich D. The safety of a **drospirenone**-containing oral contraceptive: final results from the **European Active Surveillance Study** on oral contraceptives based on 142,475 women-years of observation. Contraception. 2007 May;75(5):344-54.
Dinger J, Assmann A, Möhner S, Minh TD. Risk of **venous thromboembolism** and the use of **dienogest- and drospirenone-containing** oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care. 2010 Jul;36(3):123-9.
Dinger J, Minh TD, Buttmann N, Bardenheuer K. **Effectiveness of oral contraceptive** pills in a large U.S. cohort comparing progestogen and regimen. Obstet Gynecol. 2011 Jan;117(1):33-40. There are fewer unintended pregnancies with the use of an oral contraceptive (OC) regimen with a progestogen of long half-life, such as drospirenone or norethisterone, when taken for a cycle of 24 days plus 4 days as compared with the standard 21 days plus 7 days (LOE = 2b)
Doose DR, et al. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. Epilepsia. 2003 Apr;44(4):540-9.
Dunn Nick. Oral contraceptives and **venous thromboembolism**. BMJ 2009;339:b3164, doi: 10.1136/bmj.b3164 (Published 13 August 2009)
Edelman AB, et al. Continuous oral contraceptives: are bleeding patterns dependent on the hormones given? Obstet Gynecol. 2006 Mar;107(3):657-65. CONCLUSION: The addition of 10 mug of ethinyl E2 to a 20 mug ethinyl E2 pill containing levonorgestrel or norethindrone acetate did not improve bleeding patterns. During continuous dosing, the use of oral contraceptives containing 1,000 mug norethindrone acetate resulted in more days of amenorrhea and fewer days of spotting than preparations containing 100 mug levonorgestrel.
Edelman AB, et al. Continuous or extended cycle vs. cyclic use of combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004695.
Edelman AB, Carlson NE, Cherala G, et al. Impact of **obesity** on oral contraceptive pharmacokinetics and hypothalamic-pituitary-ovarian activity. Contraception. 2009 Aug;80(2):119-27. Epub 2009 Jun 4.
Etminan, Mahyar, Delaney, Joseph A.C., Bressler, Brian, et al. Oral contraceptives and the risk of **gallbladder disease**: a comparative safety study. CMAJ 2011 0: cmaj.110161. (small significant increase)
FDA Oct/11 released the final report of an FDA-funded study looking into the risk for venous thromboembolism (VTE) in women taking oral contraceptives containing drospirenone. As previously reported by Medscape Medical News, on September 26 the FDA said preliminary findings from the study indicate that women who use **drospirenone-containing birth control pills have an approximately 1.5-fold increase** in the risk of developing blood clots relative to women using other types of hormonal contraceptives.
FDA Drug Safety Communication Sept/11: Safety review update on the possible increased risk of blood clots with birth control pills containing drospirenone. http://www.fda.gov/Drugs/DrugSafety/ucm273021.htm (Accessed November 29th, 2011).
FDA Apr/12 has completed its review of recent observational (epidemiologic) studies regarding the risk of blood clots in women taking drospirenone-containing birth control pills.Based on this review, FDA has concluded that **drospirenone**-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills. . Report that some epidemiologic studies reported as high as a three-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or some other progestins, whereas other epidemiological studies found no additional risk of blood clots with drospirenone-containing products.
Fine P et al. **Ulipristal acetate** taken 48-120 hours after intercourse for emergency contraception. Obstet Gynecol 2010; 115:257.
Fisher WA, Black A. Contraception in Canada: a **review** of method choices, characteristics, adherence and approaches to counselling. CMAJ 2007;176:953-61.
Foster DG, Hulett D, Bradsberry M, Darney P, Policar M. Number of oral contraceptive pill **packages dispensed** and subsequent unintended pregnancies. Obstet Gynecol. 2011 Mar;117(3):566-72.
Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking **anticonvulsant therapy**. Contraception. 2011 Jan;83(1):16-29. Epub 2010 Sep 15.
Gallo MF, et al. Combination contraceptives: effects on weight. *The Cochrane Database of Systematic Reviews* 2006, Issue 1.

TOP

CONCLUSIONS: Available evidence was insufficient to determine the effect of combination contraceptives on weight, but no large effect was evident.
Gallo MF, Grimes DA, Schulz KF. **Cervical cap versus diaphragm** for contraception. Cochrane Database Syst Rev. 2002;(4):CD003551.
Gallo MF, Lopez LM, Grimes DA, et al. **Combination contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Sep 7;9:CD003987. Available evidence was insufficient to determine the effect of combination contraceptives on weight, but no large effect was evident.
Gemzell-Danielsson K. Mechanism of action of **emergency contraception**. Contraception. 2010 Nov;82(5):404-9.
Gentile GP, et al. Hormone levels before and after **tubal sterilization**. Contraception. 2006 May;73(5):507-11. Epub 2006 Feb 23. There were no significant hormonal changes in sterilized women over a period of 2 yrs when compared with their baseline levels or when compared with unsterilized age-matched controls.
Glasier AF, Cameron ST, Fine PM, et al. **Ulipristal** acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet. 2010 Jan 28. 375:555.
Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. Arch Intern Med. 2004 Oct 11;164(18):1965-76.
Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of Raynaud's phenomenon. BMJ. 2012 Feb 7;344:e289.
Greene Foster D, Hulett D, Bradsberry M, et al. Number of oral contraceptive pill **packages dispensed** and subsequent unintended pregnancies. Obstet Gynecol 2011;117:566-72.
Grimes DA, Jones LB, Lopez LM, Schulz KF. Oral contraceptives for functional **ovarian cysts**. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006134. Although widely used for treating functional ovarian cysts, combined oral contraceptives appear to be of no benefit. Watchful waiting over several cycles is appropriate. Should cysts persist, surgical management is often indicated.
Grimes DA, Jones LB, Lopez LM, et al. Oral contraceptives for functional **ovarian cysts**. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006134. Although widely used for treating functional ovarian cysts, combined oral contraceptives appear to be of no benefit. Watchful waiting for two or three cycles is appropriate. Should cysts persist, surgical management is often indicated.
Gronich N, Lavi I, Rennert G. Higher risk of venous **thrombosis** associated with **drospirenone**-containing oral contraceptives: population-based cohort study. CMAJ 2011Nov 7.
Guilbert E, Black A, Dunn S, Senikas V, Berube J, et al. **Missed hormonal contraceptives**: new recommendations. (SOGC) J Obstet Gynaecol Can 2008 Nov;30(11):1050-62, 1063-77. http://www.sogc.org/jogc/abstracts/200811_SOGCClinicalPracticeGuidelines_1.pdf
Guilbert E, Boroditsky R, Black A, Kives S, Leboeuf M, Mirosh M, Senikas V, Wagner MS, Weir E, York-Lowry J, Reid R, Trussell J; Society of Obstetricians and Gynaecologists of Canada. Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception, 2007. J Obstet Gynaecol Can. 2007 Jul;29(7 Suppl 2):S1-32.
Gurtcheff SE, Turok DK, et al. **Lactogenesis after early postpartum use of the contraceptive implant (Implanon)**: a randomized controlled trial. Obstet Gynecol. 2011 May;117(5):1114-21. (1-3 day postpartum vs 4 wks)
Hannaford PC, Selvaraj S, Elliott AM, et al. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner?s oral contraception study. BMJ 2007;335(7621):651-659. {InfoPOEMs Jan07: Oral contraceptive (OC) use does not increase a woman's overall risk of cancer and may slightly decrease it. However, the risk for particular cancers may be increased or decreased, depending on the duration of use & the length of time since last use. (LOE = 1b)}
Hannaford Philip C, Iversen Lisa, Macfarlane Tatiana V, et al. **Mortality** among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. BMJ 2010
Harel Z et al. Recovery of **bone mineral density** in adolescents following the use of depot **medroxyprogesterone** acetate contraceptive injections. Contraception 2010 Apr; 81:281.
Health Canda June/10 **MIRENA** (Levonorgestrel-Releasing Intrauterine System) - Potential Risk of Uterine Perforation - Bayer Inc. Bayer Inc., in collaboration with Health Canada, would like to remind you of important safety information regarding reports of uterine perforation in women treated with MIRENA.
Health Canada Dec/11 has completed a safety review of drospirenone-containing oral contraceptives (marketed under the brand names Yasmin and Yaz) with respect to the risk of blood clots (venous thromboembolism, or VTE). The review determined that **drospirenone-containing birth** control pills may be associated with a risk of blood clots that is **1.5 to 3 times higher than other birth control pills**.
Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous **thromboembolism during pregnancy** or postpartum: a 30-year population-based study. Ann Intern Med. 2005 Nov 15;143(10):697-706.
Herndon EJ, Zieman M. New contraceptive options. Am Fam Physician. 2004 Feb 15;69(4):853-60. Review. Erratum in: Am Fam Physician. 2004 Apr 15;69(8):1863.
HHS Aug 2011.: Affordable Care Act Ensures Women Receive **Preventive Services at No Additional Cost** (including **contraception**). http://www.hhs.gov/news/press/2011pres/08/20110801b.html
Hicks CW, Rome ES. **Menstrual manipulation**: options for suppressing the cycle. Cleve Clin J Med. 2010 Jul;77(7):445-53.
Hou MY, Hurwitz S, Kavanagh E, et al. Using daily **text-message reminders** to improve adherence with oral contraceptives: a randomized controlled trial. Obstet Gynecol. 2010 Sep;116(3):633-40.
Huber J, Walch K. Treating **acne** with oral contraceptives: use of lower doses. Contraception. 2006 Jan;73(1):23-9. Epub 2005 Sep 26.
Huq FY et al. Menstrual problems and contraception in women of reproductive age **receiving oral anticoagulation**. Contraception2011 Aug; 84:128.
Iliadou A, Milsom I, Pedersen NL, et al. Risk of **urinary incontinence** symptoms in oral contraceptive users: a national cohort study from the Swedish Twin Register. Fertil Steril. 2009 Aug;92(2):428-33. Epub 2008 Aug 15.
International Collaboration of Epidemiological Studies of **Cervical Cancer**, Appleby P, Beral V, Berrington de González A, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007 Nov 10;370(9599):1609-21. The relative risk of cervical cancer is increased in current users of oral contraceptives and declines after use ceases. 10 years' use of oral contraceptives from around age 20 to 30 years is estimated to increase the cumulative incidence of invasive cervical cancer by age 50 from 7.3 to 8.3 per 1000 in less developed countries and from 3.8 to 4.5 per 1000 in more developed countries.
James AH, et al. Incidence & risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol. 2005 Sep;106(3):509-16. (InfoPOEMs: Hospitalization with a diagnosis of stroke in pregnancy or puerperium occurs in 34 per 100,000 deliveries in the United States. It occurs in more that 50 per 100,000 in African American women and women older than 35 years. The most common comorbid conditions associated with increased risk are migraine headache and hypertension (including gestational hypertension). (LOE = 2c))
Jensen, Jeffrey T. Effective **Treatment of Heavy Menstrual Bleeding** With Estradiol Valerate and Dienogest (**Natazia**): A Randomized Controlled Trial. *Obstet Gynecol.* 2011;117:773-774, 777-787.
Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel. Contraception. 2006 Jun;73(6):566-70. Epub 2006 Mar 29. The incidence rates of VTE were 30.6 (95% CI, 25.5-36.5), **53.5** (95% CI, 42.9-66.0) and 27.1 (95% CI, 21.1-34.3) per 100,000 woman-years for users of norgestimate-, **desogestrel**- and levonorgestrel-containing OCs, respectively.
Jick SS, Hernandez RK. Risk of non-fatal **venous thromboembolism** in women using oral contraceptives containing **drospirenone** compared with women using oral contraceptives containing **levonorgestrel**: case-control study using United States claims data. BMJ 2011;342:d2151.
Jones, Claire, Chan, Crystal, Farine, Dan. **Sex in pregnancy**. CMAJ 2011 0: cmaj.091580.
Kahlenborn C, Modugno F, Potter DM, Severs WB. Oral contraceptive use as a risk factor for premenopausal **breast cancer**: a meta-analysis. Mayo Clin Proc. 2006 Oct;81(10):1290-302. Use of OCs is associated with an increased risk of premenopausal breast cancer, especially with use before first full term pregnancy in parous women.
Katzman DK, Taddeo D; **Canadian Paediatric Society**, Adolescent Health Committee. **Emergency contraception**. Paediatr Child Health 2010;15(6):363-372. http://www.cps.ca/english/statements/am/ah10-02.htm
Kaunitz AM. Clinical practice. **Hormonal contraception in women of older reproductive age**. N Engl J Med. 2008 Mar 20;358(12):1262-70.
Keenan Jeffrey A. **Ulipristal Acetate**: Contraceptive or Contragestive? Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1Q248. Ann Pharmacother ;45:813-815.
Koulouri O, Conway GS. Management of **hirsutism**. BMJ. 2009 Mar 27;338:b847. doi: 10.1136/bmj.b847.
Kroll R, et al. The efficacy and safety of a low-dose, **91-day, extended-regimen** oral contraceptive with continuous ethinyl estradiol. Contraception. 2010 Jan;81(1):41-8.
Legro RS, Pauli JG, Kunselman AR, et al. Effects of **Continuous versus Cyclic** Oral Contraception: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2007 Dec 4; [Epub ahead of print] Continuous oral contraception does not result in a reduction of bleeding days over a 168d period of observation, but provides greater suppression of the ovary and endometrium. These effects are associated with improved patient symptomatology.
Lesnewski R, Prine L, Ginzburg R. **Preventing Gaps when Switching** Contraceptives. Am Fam Physician. 2011 Mar 1;83(5):567-570.
Leyland N, Casper R, Laberge P, Singh SS, Allen L, Arendas K. **Endometriosis**: diagnosis and management. J Obstet Gynaecol Can 2010 Jul;32(7 Suppl 2):S1-32.
Lidegaard Øjvind, Løkkegaard Ellen, Svendsen Anne Louise, et al. Hormonal contraception and risk of **venous thromboembolism**: Denmark national follow-up study. BMJ 2009;339:b2890, doi: 10.1136/bmj.b2890
Lidegaard Ø, Nielsen LH, Skovlund CW, et al. Risk of **venous thromboembolism** from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423.
Lidegaard O, Nielsen LH, Skovlund CW, et al. **Venous thrombosis** in users of **non-oral hormonal contraception**: follow-up study, Denmark 2001-10. BMJ. 2012 May 10;344:e2990. doi: 10.1136/bmj.e2990.
Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. **Thrombotic stroke and myocardial infarction** with hormonal contraception. N Engl J Med 2012;366:2257-66. Linden JA. Clinical practice. Care of the adult patient **after sexual assault**. N Engl J Med. 2011 Sep 1;365(9):834-41.

TOP

Lopez LM, Newmann SJ, Grimes DA, Nanda K, Schulz KF. **Immediate start** of hormonal contraceptives for contraception. *Cochrane Database Syst Rev.* 2008;(2):CD006260.

Lopez LM, et al. **Skin patch and vaginal ring versus combined oral contraceptives** for contraception. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003552. Effectiveness rates were similar for the methods compared. The patch group had better compliance than the COC group. Compared to COC users, patch users had more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge. The patch could lead to more discontinuation while the vaginal ring showed little difference. High losses to follow up can affect the validity of the results.

Lopez LM, Grimes DA, Chen-Mok M, et al. Hormonal contraceptives for **contraception in overweight or obese women**. Cochrane Database Syst Rev. 2010 Jul 7;7:CD008452. Body weight addresses overall body size, while BMI generally reflects the amount of fat. Only one of three studies using BMI found a higher pregnancy risk for overweight women. The efficacy of implants and injectable contraceptives may be unaffected by body mass. The field could use trials of contraceptive methods with groups stratified by BMI. The current evidence on effectiveness by BMI is limited. However, the contraceptive methods examined here are still among the most effective when the recommended regimen is followed.

Lopez LM, Edelman A, Chen-Mok M, Trussell J, Helmerhorst FM. **Progestin-only contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Apr 13;4:CD008815. We found little evidence of weight gain when using POCs. Mean gain was less than 2 kg for most studies up to 12 months, and usually similar for the comparison group using another contraceptive.

Loder EW, et al. **Headache** as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 1):636-49. (InfoPOEMs: There is not a clearly documented causal relationship between headaches and oral contraceptives (OCs). Headaches that patients attribute to initiation of OCs tend to improve over time. There is no evidence to support change of formulation to manage headache. Manipulation of estrogen withdrawal has not been sufficiently studied. (LOE = 1a-))

Loder EW, Buse DC, Golub JR. **Headache** and combination estrogen-progestin oral contraceptives: integrating evidence, guidelines, and clinical practice. Headache. 2005 Mar;45(3):224-31.

Lopez L, et al. Oral contraceptives containing **drospirenone for premenstrual syndrome**. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006586. Drospirenone plus EE 20 mug may help treat premenstrual symptoms in women with PMDD.

Lopez LM, Grimes DA, Gallo MF, Schulz KF. Skin patch and **vaginal ring versus combined oral contraceptives** for contraception. Cochrane Database Syst Rev. 2010 Mar 17;3:CD003552. Effectiveness was similar for the methods compared. The patch could lead to more discontinuation while the vaginal ring showed little difference. The patch group had better compliance than the COC group but more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge.

Lopez LM, Edelman A, Chen-Mok M, et al. **Progestin-only contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Apr 13;4:CD008815. We found little evidence of weight gain when using POCs. Mean gain was less than 2 kg for most studies up to 12 months, and usually similar for the comparison group using another contraceptive. Appropriate counseling about typical weight gain may help reduce discontinuation of contraceptives due to perceptions of weight gain.

Maloney JM, Dietze P Jr, Watson D, et al. Treatment of **Acne** Using a 3-Milligram Drospirenone/20-Microgram Ethinyl Estradiol Oral Contraceptive Administered in a 24/4 Regimen: A Randomized Controlled Trial. Obstet Gynecol. 2008 Oct;112(4):773-781.

Margel David, Fleshner Neil E. Oral contraceptive use is associated with **prostate cancer**: an ecological study. BMJ Open 2011;1:e000311 doi:10.1136/bmjopen-2011-000311.

Marions L et al. Effect of **emergency contraception** with levonorgestrel or mifepristone on ovarian function. Contraception2004 May; 69:373-7.

Medical Letter. Three new oral contraceptives. (Yaz, Seasonique, Loestrin 24 Fe) Sept 25, 2006.

Medical Letter. A New Progestin Implant (Implanon) Oct 9,2006.

Medical Letter. **Plan B** OTC. Sept 11, 2006.

Medical Letter. Combination Oral Contraceptives and the Risk of **Venous Thromboembolism**. Mar 22, 2010.

Medical Letter- Treatment Guidelines: **Choice of Contraceptives**. Dec 2007; p. 101-108. (**Updated Dec 2010**)

Morch Lina Steinrud; Lokkegaard Ellen; Andreasen Anne Helms; et al. Hormone Therapy and **Ovarian Cancer**. JAMA. 2009;302(3):298-305.

Munro MG, et al. Oral **medroxyprogesterone** acetate and combination oral contraceptives for **acute uterine bleeding**: a randomized controlled trial. Obstet Gynecol. 2006 Oct;108(4):924-9. This randomized trial is limited by sample size but suggests that both regimens may be effective and reasonably well tolerated.

Noé G, Croxatto HB, Salvatierra AM, et al. Contraceptive efficacy of emergency contraception with **levonorgestrel** given before or after ovulation. Contraception. 2011 Nov;84(5):486-92. The efficacy of LNG-EC has been overestimated in studies using presumptive menstrual cycle data. Our results confirm previous similar studies and demonstrate that LNG-EC does not prevent embryo implantation and therefore cannot be labeled as abortifacient.

Odmark IS, Bixo M, Englund D, Risberg B, Jonsson B, Olsson SE. Endometrial safety and bleeding pattern during a five-year treatment with long-cycle hormone therapy. Menopause. 2005 Nov-Dec;12(6):699-707. Epub 2005 Nov 8. (InfoPOEMs: In this small study, continuous estrogen therapy combined with 14 days of progestin every 3 months (long-cycle therapy) did not result in endometrial hyperplasia or cancer. (LOE = 1b))

Panzer C, et al. Impact of oral contraceptives on sex hormone-binding globulin & androgen levels: a retrospective study in women with sexual dysfunction. J Sex Med. 2006 Jan;3(1):104-13.

Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of **venous thromboembolism** in users of oral contraceptives containing **drospirenone or levonorgestrel**: nested case-control study based on UK General Practice Research Database. BMJ 2011;342:d2139.

Petri M, Kim MY, Kalunian KC, Grossman J, et al. Combined Oral Contraceptives in Women with Systemic **Lupus** Erythematosus. N Engl J Med. 2005 Dec 15;353(24):2550-2558. (InfoPOEMs: This study found that oral contraceptives are safe and do not increase the risk of flares in women with systemic lupus erythematosus (SLE). Another study in the same issue of the journal found no difference in clinical outcomes for women randomized to an oral contraceptive, progestin-only pill, or intrauterine device (N Engl J Med 2005;353:2539-49). (LOE = 1b))

Pharmacist's Letter: **Hormonal Contraception** July 2006

Pharmacists Letter. Single dose regimen (1.5mg) for **Plan B**. June 2007.

Polis CB, Grimes DA, Schaffer K, Blanchard K, Glasier A, Harper C. **Advance provision of emergency contraception** for pregnancy prevention. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005497.

Raymond EG, Halpern V, Lopez LM. **Pericoital oral contraception with levonorgestrel**: a systematic review. Obstet Gynecol. 2011 Mar;117(3):673-81.

Rose SB, Lawton BA. Impact of **long-acting reversible contraception on return for repeat abortion**. Am J Obstet Gynecol. 2012 Jan;206(1):37.e1-6. (esp. IUD)

Rosenfield RL. **Hirsutism**. N Engl J Med. 2005 Dec 15;353(24):2578-88.

Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, et al. A Trial of Contraceptive Methods in Women with Systemic **Lupus** Erythematosus. N Engl J Med. 2005 Dec 15;353(24):2539-2549.

Schürks Markus, Rist Pamela M, et al. **Migraine** and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914, doi: 10.1136/bmj.b3914 (Published 27Oct09)

Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstet Gynecol. 2007 Sep;110(3):587-93. **Ethinylestradiol/drospirenone** initiators and initiators of other oral contraceptives are **similarly** likely to experience **thromboembolism**.

sexualityandU.ca website (supported by SOGC) http://sexualityandu.ca/professionals/index.aspx

Shaarawy M, et al. Effects of the long-term use of depot medroxyprogesterone acetate as hormonal contraceptive on bone mineral density and biochemical markers of bone remodeling. Contraception. 2006 Oct;74(4):297-302. Epub 2006 Jun 16.

Shrader SP, Hall LN, Ragucci KR, Rafie S. Updates in hormonal **emergency contraception**. Pharmacotherapy. 2011 Sep;31(9):887-95.

Shufelt CL, Bairey Merz CN. Contraceptive hormone use and **cardiovascular disease**. *J Am Coll Cardiol* 2009; 53:221-231

Snow Sara E, Melillo Stephanie N, Jarvis Courtney I. **Ulipristal Acetate** for Emergency Contraception. Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1P704. Ann Pharmacother ;45:780-786.

Smulders B, van Oirschot SM, Farquhar C, et al. Oral contraceptive pill, progestogen or estrogen pre-treatment for **ovarian stimulation protocols** for women undergoing assisted reproductive techniques. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006109.

Speroff, Leon, and Daniel R. Mishell Jr. "The postpartum visit: it's time for a change in order to optimally initiate contraception." Contraception 78 (2008): 90-98

Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and management of **abnormal uterine bleeding** in premenopausal women. Am Fam Physician. 2012 Jan 1;85(1):35-43.

Stewart FH, Kaunitz AM, Laguardia KD, et al. Extended use of transdermal norelgestromin/ethinyl estradiol: a randomized trial. Obstet Gynecol. 2005 Jun;105(6):1389-96.

Templeton A, Grimes DA. A **Request for Abortion**. N Engl J Med 2011; 365:2198-2204.

Thonneau P, et al. Risk factors for **IUD failure**: results of a large multicentre case-control study. Hum Reprod. 2006 Oct;21(10):2612-6. Epub 2006 Jun 14. Only a history of previous IUD expulsion was found to

TOP

factor for failure, indicating that these women should have regular medical and echographical follow-up. Comparing the efficacy rate of various types of IUDs, we found a clear advantage for levonorgestrel-releasing devices.

Tozer BS, Boatwright EA, David PS, et al. Prevention of **migraine** in women throughout the life span. Mayo Clin Proc. 2006 Aug;81(8):1086-91; quiz 1092.

Trenor, Cameron C., III, Chung, Richard J., Michelson, Alan D., et al. Hormonal Contraception and **Thrombotic Risk**: A Multidisciplinary Approach. Pediatrics 2011 127: 347-357.

Trussell J et al. New **estimates of the effectiveness of the Yuzpe regimen** of emergency contraception. Contraception 1998; 57:363.

Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with **ovarian cancer** risk. Am J Epidemiol. 2007 Oct 15;166(8):894-901. Epub 2007 Jul 26. Results suggest that the beneficial effect of oral contraceptives on ovarian cancer risk attenuates after 20 years since last use. Furthermore, tubal ligation, intrauterine device use, and infertility were associated with ovarian cancer risk.

van Hylckama Vlieg A, Helmerhorst F M, Vandenbroucke J P, et al. The venous **thrombotic risk** of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921, doi: 10.1136/bmj.b2921 (Published 13 August 2009)

Van Vliet HA, Grimes DA, Lopez LM, et al. **Triphasic versus monophasic** oral contraceptives for contraception. Cochrane Database Syst Rev. 2011 Nov 9;11:CD003553. The available evidence is insufficient to determine whether triphasic OCs differ from monophasic OCs in effectiveness, bleeding patterns or discontinuation rates. Therefore, we recommend monophasic pills as a first choice for women starting OC use. Large, high-quality RCTs that compare triphasic and monophasic OCs with identical progestogens are needed to determine whether triphasic pills differ from monophasic OCs.

Westhoff C, et al. Initiation of Oral Contraceptives Using a **Quick Start** Compared With a Conventional Start: A Randomized Controlled Trial. Obstet Gynecol. 2007 Jun;109(6):1270-1276. Protocols that require a woman to wait until the next menses to start hormonal contraceptives are an obstacle to contraceptive initiation. Directly observed, immediate initiation of the pill improves short-term continuation. (InfoPOEMs: The immediate start of oral contraceptives (OCs) in young women improves initiation, but not continuation of use, and does not decrease pregnancy rates. (LOE = 1b))

Westhoff CL, Torgal AH, Mayeda ER, et al. Pharmacokinetics of a combined oral contraceptive in **obese** and normal-weight women. Contraception. 2010 Jun;81(6):474-80.

Westhoff CL et al. **Body weight** does not impact pregnancy rates during use of a low-dose extended-regimen 91-day oral contraceptive. Contraception 2012 Mar; 85:235. (LoSEASONIQUE)

Wiegratz I, Kuhl H. Long-cycle treatment with oral contraceptives. Drugs. 2004;64(21):2447-62.

Wiegratz I, et al. Fertility after discontinuation of treatment with an oral contraceptive containing 30 microg of ethinyl estradiol and 2 mg of dienogest. Fertil Steril. 2006 Jun;85(6):1812-9. The present prospective study revealed only a slight delay in regaining fertility during the first three cycles after cessation of EE/DNG. Thereafter, the cumulative rate of conception did not differ from that observed in fertile women who attempted to become pregnant without prior contraception.

Wilkinson TA, Fahey N, Shields C, et al. **Pharmacy communication** to adolescents and their physicians regarding access to **emergency contraception**. Pediatrics. 2012 Apr;129(4):624-9.

Winner B, Peipert JF, Zhao Q, et al. **Effectiveness of long-acting reversible contraception**. N Engl J Med. 2012 May 24;366(21):1998-2007.

Wong CL, Farquhar C, Roberts H, et al. Oral contraceptive pill as treatment for **primary dysmenorrhoea**. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD002120. There is limited evidence for pain improvement with the use of the OCP (both low and medium dose oestrogen) in women with dysmenorrhoea. There is no evidence of a difference between different OCP preparations.

Zhang L et al. **Pregnancy outcome after levonorgestrel**-only emergency contraception failure: A prospective cohort study. Hum Reprod 2009 Mar 31; [e-pub ahead of print].

SOGC: Nov 2008 Missed Contraceptives: http://www.sogc.org/jogc/abstracts/200811_SOGCClinicalPracticeGuidelines_1.pdf

TOP

Extras:

Preventing Gaps when Switching Contraceptives. Lesnewski '11

Switching from →	Switching to	Comments
Combined OC, progestin only pill	Combined OC, progestin only pill	♦switch directly from one pill to another; do not miss a day
Combined OC	Patch or Ring	♦start patch day before last pill; start ring day after last pill ♦Do not need to complete pill cycle before switch
Patch or Ring	Combined OC	♦start pill day before scheduled to remove patch/ring; i.e. no more than 8 days after last patch (effective up to 9 days) or 34 days after ring (effective up to 35days) ♦Do not need to complete full cycle for patch/ring before pill starts
Patch	Ring	♦insert ring & remove patch on same day
Ring	Patch	♦Apply patch 2 days before ring removal
Combined OC, patch or ring	Progestin IUD or injection	♦Continue pill, patch or ring x 7days (or use barrier)
Copper IUD	Progestin IUD (i.e Mirena)	♦Use barrier x 7 days; return to fertility may be immediate
Copper IUD	Progestin injection (i.e. Depo-Provera)	♦Give injection 7 days before IUD removal; if done on same day, use barrier x 7days
Copper IUD	Combined OC, patch, or ring	♦Start new method 7 days before removal of IUD or use barrier x 7days
Progestin IUD (i.e. Mirena) or injection (i.e. Depo-Provera)	Combined OC, patch, or ring	♦Start new method 7 days before removal of IUD or next injection (i.e. may start new method up to 15 weeks after last injection)
Combined OC, patch or ring	Copper IUD	♦Can insert copper IUD up to five days after stopping pill, patch or ring
Progestin IUD (i.e. Mirena)	Copper IUD	♦Can insert copper IUD right after removing progestin IUD
Progestin injection (i.e. Depo-Provera)	Copper IUD	♦Can insert copper IUD up to 16weeks after the last shot

Consider: Abstain from sexual intercourse or use a barrier method (condoms +/- spermicide) if no overlap in methods for a minimum of 7days for most switches (see above table for exact number of days in bold print)

"Patient Friendly" Statistics for Contraceptive Failure Rates: http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118465.htm#hormonal

Out of 100 women who use the following method for 1 year:

- Injection, progestin IUD – 1 may get pregnant
- COC, POP, patch & ring – 5 may get pregnant
- Male condoms – 11 to 16 may get pregnant
- Diaphragm – 15 may get pregnant
- Sponge – 16 to 32 may get pregnant
- Female condoms – 20 may get pregnant
- Spermicide along – 30 may get pregnant

♦Study with **IMPLANON** USA found that lactogenisis not affected by early postpartum (on day 1-3) insertion.

References: Hormonal Birth Control Options – www.RxFiles.ca

[1] Black A, Francoeur D, Rowe T, et al. Canadian contraception consensus. J Obstet Gynaecol Can. 2004 Feb;26(2):143-56, 158-74.

[2] Herndon EJ, Zieman M. New contraceptive options. Am Fam Physician. 2004 Feb 15;69(4):853-60. Review. Erratum in: Am Fam Physician. 2004 Apr 15;69(8):1863.

[3] Choice of contraceptives. Treat Guidel Med Lett. 2004 Aug;2(24):55-62.

[4] Micromedex 2010

[5] Holt VL, Scholes D, Wicklund KG, et al. Body mass index, weight, and oral contraceptive failure risk. Obstet Gynecol. 2005 Jan;105(1):46-52. {If causal, this association translates to an additional 2-4 pregnancies per 100 woman-years of use among overweight women, for whom consideration of additional or effective alternative contraceptive methods may be warranted.}

[6] Wiegratz I, Kuhl H. Long-cycle treatment with oral contraceptives. Drugs. 2004;64(21):2447-62. (Pharmacists Letter. Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception, 2007. Aug 2007.)
Shrader SP, Dickerson LM. Extended- and continuous-cycle oral contraceptives. Pharmacotherapy. 2008 Aug;28(8):1033-40.

[7] Edelman AB, Koontz SL, Nichols MD, Jensen JT. Continuous oral contraceptives: are bleeding patterns dependent on the hormones given? Obstet Gynecol 2006;107:657-65. {InfoPOEMs May06. In **continuous dosing** regimens, more days of amenorrhea can be achieved with oral contraceptives (OCs) containing 1 mg norethindrone acetate (NETA) than with OCs containing 100 ug levonorgestrel (LNG). (LOE = 2b)}

[8] Johnson BA. Insertion and removal of intrauterine devices. Am Fam Physician. 2005 Jan 1;71(1):95-102.
Middleton L. J., Champaneria R., Daniels J. P., et al. on behalf of the International Heavy Menstrual Bleeding Individual Patient Data Meta-analysis Collaborative Group. Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. BMJ 2010;341:c3929, doi: 10.1136/bmj.c3929 (Published 16 August 2010)

Additional sources:

Abou-Setta AM, et al. **Levonorgestrel**-releasing intrauterine device (LNG-IUD) for symptomatic **endometriosis** following surgery. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005072.

ACOG: Practice Bulletin #121 "Long-Acting Reversible Contraception: **Implants and Intrauterine Devices**" is published in the July 2011 issue of Obstetrics & Gynecology.

Agostino H, Di Meglio G. **Low-dose** oral contraceptives in adolescents: how low can you go? J Pediatr Adolesc Gynecol. 2010 Aug;23(4):195-201.

American College of Obstetricians and Gynecologists (ACOG). **Noncontraceptive uses of hormonal contraceptives**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2010 Jan. 13 p. (ACOG practice bulletin; no. 110).

TOP

Amy JJ, Tripathi V. Contraception for women: an **evidence** based overview. BMJ. 2009 Aug 7;339:b2895. doi: 10.1136/bmj.b2895.
Bakhru A, Stanwood N. Performance of contraceptive patch compared with **oral contraceptive** pill in a high-risk population. Obstet Gynecol. 2006 Aug;108(2):378-86.
Bednarek PH et al. **Immediate versus delayed IUD insertion** after uterine aspiration. N Engl J Med 2011 Jun 9; 364:2208.
Beksinska ME, Smit JA, Kleinschmidt I, et al. Prospective study of weight change in new adolescent users of **DMPA**, NET-EN, COCs, nonusers and discontinuers of hormonal contraception. Contraception. 2010 Jan;81(1):30-4.
Blumenthal PD, Edelman A. Hormonal contraception. Obstet Gynecol. 2008 Sep;112(3):670-84.
Bonnema RA., McNamara MC., Spencer AL., **Contraception Choices in Women with Underlying Medical Conditions**. Am Fam Physician. 2010 Sep 15;82(6):621-628.
Bonny AE, et al. Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. Arch Pediatr Adolesc Med. 2006 Jan;160(1):40-5.
Berenson AB, Rahman M. Changes in weight, total fat, percent body fat, and central-to-peripheral fat ratio associated with injectable and oral contraceptive use. Am J Obstet Gynecol. 2009 Mar;200(3):329.e1-8. n=703 3yrs. Bodyweight and fat significantly increase with the use of DMPA. After discontinuation of DMPA, some decrease in bodyweight and fat occurs when NH is used.
Calhoun A. Combined hormonal contraceptives: Is it time to reassess their role in **migraine**? Headache 2011. Published online ahead of print January 6, 2012.
Camacho EM, Lunt M, Farragher TM, et al. The relationship between oral contraceptive use and functional outcome in women with recent **onset inflammatory polyarthritis**: Results from the Norfolk Arthritis Register (NOAR). Arthritis Rheum. 2011 Apr 22. doi: 10.1002/art.30416.
Campbell SJ, Cropsey KL, Matthews CA. Intrauterine device use in a high-risk population: experience from an urban university clinic. Am J Obstet Gynecol. 2007 Aug;197(2):193.e1-6; discussion 193.e6-7. IUD/IUS use appears to be safe, acceptable, and feasible in high-risk patients. The IUS (Mirena) had lower rates of complications and greater acceptability than the IUD.
Castellsagué X, Díaz M, et al. **Intrauterine device use**, cervical infection with human papillomavirus, and risk of **cervical cancer**: a pooled analysis of 26 epidemiological studies. Lancet Oncol 2011; online Sept 13.
CDC: Centers for Disease Control and Prevention (CDC). **U.S. medical eligibility criteria** for contraceptive use, 2010: adapted from the World Health Organization medical eligibility criteria for contraceptive use, 4th edition. MMWR Recomm Rep 2010 Jun 18;59(RR-4):1-86. **CDC** has released **medical eligibility criteria for contraceptive use to help U.S. healthcare providers** counsel patients about their contraceptive choices. The criteria, published in MMWR, are modified from the World Health Organization's 2009 guidance. The CDC offers modified recommendations about contraception for U.S. women who have venous thromboembolism, valvular heart disease, ovarian cancer, and uterine fibroids, as well as women who are postpartum and breast-feeding. It also gives additional guidance on contraception for women with rheumatoid arthritis, previous bariatric surgery, peripartum cardiomyopathy, endometrial hyperplasia, inflammatory bowel disease, and organ transplantation. http://www.cdc.gov/mmwr/pdf/rr/rr59e0528.pdf
CDC: 2011 **Update** to **CDC's U.S. Medical Eligibility Criteria** for Contraceptive Use, 2010: Revised Recommendations for the Use of Contraceptive Methods During the Postpartum Period. http://www.cdc.gov/mmwr/pdf/wk/mm6026.pdf
CDC **Update to CDC's U.S. Medical Eligibility Criteria** for Contraceptive Use, 2010: Revised Recommendations for the Use of Hormonal Contraception Among Women at High Risk for HIV Infection or Infected with HIV. Weekly. June 22, 2012 / 61(24);449-452. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6124a4.htm?s_cid=mm6124a4_x
CDC: Centers for Disease Control and Prevention. **Sexual experience and contraceptive use among female teens** — United States, 1995, 2002, and 2006–2010. MMWR Morb Mortal Wkly Rep 2012 May 4; 61:297.
Clark MK, et al. Bone mineral density loss and recovery during 48 months in first-time users of depot medroxyprogesterone acetate. Fertil Steril. 2006 Nov;86(5):1466-74. Epub 2006 Sep 25. Depot MPA-related BMD loss is substantial but occurs mostly during the first 2 years of DMPA use. Therefore, longer use may not substantially increase the risk of osteoporosis. The prolonged recovery time suggests the need to consider timing of use in relation to menopause or other factors that may impede bone remodeling.
Cleland K, Zhu H, Goldstuck N, et al. The efficacy of **intrauterine devices for emergency contraception**: a systematic review of 35 years of experience. Human Reproduction doi:10.1093/humrep/des140.
Clinical Effectiveness Unit. **Drug interactions** with hormonal contraception. London (UK): Faculty of Sexual and Reproductive Healthcare; 2012 Jan.
Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among **transdermal** contraceptive system users. Obstet Gynecol. 2007 Feb;109(2 Pt 1):339-46. There was a more than **two-fold increase** in the risk of venous thromboembolism associated with the transdermal contraceptive system.
Collaborative Group on Epidemiological Studies of **Ovarian Cancer**, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008 Jan 26;371(9609):303-14. Use of oral contraceptives confers long-term protection against ovarian cancer. These findings suggest that oral contraceptives have already prevented some 200,000 ovarian cancers and 100,000 deaths from the disease, and that over the next few decades the number of cancers prevented will rise to at least 30,000 per year.
Creinin MD, Meyn LA, Borgatta L, et al. Multicenter comparison of the contraceptive ring and patch: a randomized controlled trial. Obstet Gynecol. 2008 Feb;111(2 Pt 1):267-77. The majority of women who are using oral contraceptives (OCs) and try the **vaginal ring** continue with the ring rather than go back to OCs. Most women who try patches go back **to OCs**. It is uncertain whether the nonmasked nature of the trial, which was funded by the manufacturer of the vaginal ring, introduced bias into the study. (LOE = 1b-)
Culwell KR, Curtis KM. Use of contraceptive methods by women with **current venous thrombosis** on anticoagulant therapy: a systematic review. Contraception. 2009 Oct;80(4):337-45. Epub 2009 Jun 10. Levonorgestrel-IUD may be an effective treatment for menorrhagia secondary to anticoagulation or bleeding disorders & may be safer alternative to invasive treatment (hysterectomy).
Curtis KM, Martins SL. **Progestogen-only** contraception and bone mineral density: a systematic review. Contraception. 2006 May;73(5):470-87. Epub 2006 Feb 20.
Curtis KM, Ravi A, Gaffield ML. **Progestogen-only** contraceptive use in obese women. Contraception. 2009 Oct;80(4):346-54. Epub 2009 Jun 10. Adolescent DMPA users who are obese may gain more weight than normal weight users. This observation was not seen in adult DMPA users or adolescent Norplant users.
Dinger JC, et al. Oral contraceptive effectiveness according to **body mass index**, weight, age, and other factors. Am J Obstet Gynecol. 2009 Sep;201(3):263.e1-9.
Dinger JC, Heinemann LA, Kühl-Habich D. The safety of a **drospirenone**-containing oral contraceptive: final results from the **European Active Surveillance Study** on oral contraceptives based on 142,475 women-years of observation. Contraception. 2007 May;75(5):344-54.
Dinger J, Minh TD, Buttmann N, Bardenheuer K. **Effectiveness of oral contraceptive** pills in a large U.S. cohort comparing progestogen and regimen. Obstet Gynecol. 2011 Jan;117(1):33-40. There are fewer unintended pregnancies with the use of an oral contraceptive (OC) regimen with a progestogen of long half-life, such as drospirenone or norethisterone, when taken for a cycle of 24 days plus 4 days as compared with the standard 21 days plus 7 days (LOE = 2b)
Dogterom P, van den Heuvel MW, Thomsen T. Absence of pharmacokinetic interactions of the combined contraceptive vaginal ring **NuvaRing** with oral amoxicillin or doxycycline in two randomised trials. Clin Pharmacokinet. 2005;44(4):429-38.
Dunn Nick. Oral contraceptives and **venous thromboembolism**. BMJ 2009;339:b3164, doi: 10.1136/bmj.b3164 (Published 13 August 2009)
Edelman A, et al. Continuous or extended cycle vs. cyclic use of combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2005 Jul 20;3:CD004695.
Edelman A, et al. Continuous versus cyclic use of combined oral contraceptives for contraception: systematic Cochrane review of randomized controlled trials. Hum Reprod. 2006 Mar;21(3):573-8.
Etminan, Mahyar, Delaney, Joseph A.C., Bressler, Brian, et al. Oral contraceptives and the risk of **gallbladder disease**: a comparative safety study. CMAJ 2011 0: cmaj.110161.
Evra patch FDA warning Nov/05 http://www.fda.gov/bbs/topics/news/2005/NEW01262.html (& An Update on Ortho Evra & the Risk of Thromboembolism Pharmacist's Letter Dec 2005).
Health Canada Mar/06 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_14_e.html
Health Canada Nov/06 http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/evra_hpc-cps_e.html
Health Canada Jan/08 Canadian Adverse Reaction Newsletter Evra: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v18n1_e.html
FDA BCDSP VTE & PE Evra Risk Jan/08 http://www.fda.gov/bbs/topics/NEWS/2008/NEW01781.html

FDA Apr/12 has completed its review of recent observational (epidemiologic) studies regarding the risk of blood clots in women taking drospirenone-containing birth control pills.Based on this review, FDA has concluded that **drospirenone**-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills. . Report that some epidemiologic studies reported as high as a three-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or some other progestins, whereas other epidemiological studies found no additional risk of blood clots with drospirenone-containing products.

Fisher WA, Black A. Contraception in Canada: a **review** of method choices, characteristics, adherence and approaches to counselling. **CMAJ 2007**;176:953-61.

Foster DG, Hulett D, et al. Number of oral contraceptive pill **packages dispensed** and subsequent unintended pregnancies. Obstet Gynecol. 2011 Mar;117(3):566-72.

Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking **anticonvulsant therapy**. Contraception. 2011 Jan;83(1):16-29. Epub 2010 Sep 15.

Gai L, Zhang J, Zhang H, et al. The effect of depot **medroxyprogesterone acetate (DMPA) on bone mineral density** (BMD) and evaluating changes in BMD after discontinuation of DMPA in Chinese women of reproductive age. Contraception. 2011 Mar;83(3):218-22.

Gallo MF, Grimes DA, Lopez LM, Schulz KF. Non-latex versus latex male **condoms** for contraception. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003550. Although the nonlatex condoms were associated with higher rates of clinical breakage than their latex comparison condoms, the new condoms still provide an acceptable alternative for those with allergies, sensitivities, or preferences that might prevent the consistent use of latex condoms. The contraceptive efficacy of the nonlatex condoms requires more research.

Gallo M, et al. Combination injectable contraceptives for contraception. Cochrane Database Syst Rev. 2005 Jul 20;3:CD004568.

Gallo MF, Grimes DA, Schulz KF. **Cervical cap versus diaphragm** for contraception. Cochrane Database Syst Rev. 2002;(4):CD003551.

Gallo MF, Lopez LM, Grimes DA, et al. **Combination contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Sep 7;9:CD003987. Available evidence was insufficient to determine the effect of combination contraceptives on weight, but no large effect was evident.

Gemzell-Danielsson K. Mechanism of action of **emergency contraception**. Contraception. 2010 Nov;82(5):404-9.

Gomes MP, Deitcher SR. Risk of **venous thromboembolic disease** associated with hormonal contraceptives and hormone replacement therapy: a clinical review. Arch Intern Med. 2004 Oct 11;164(18):1965-76. http://archinte.ama-assn.org/cgi/reprint/164/18/1965.pdf

Guilbert ER et al. The use of **depot-medroxyprogesterone acetate** in contraception and its potential impact on skeletal health. *Contraception* 2009 Mar; 79:167.

Health Canada Mirena & uterine perforation warning 2006. http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n1_e.html#2

Greene FD, Hulett D, Bradsberry M, et al. Number of oral contraceptive pill **packages dispensed** and subsequent unintended pregnancies. Obstet Gynecol 2011;117:566-72.

Grimes DA, Lopez LM, O'Brien PA, Raymond EG. Progestin-only pills for contraception. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007541.

Grimes DA, Lopez LM, Schulz KF, et al. **Immediate post-partum insertion of intrauterine devices**. Cochrane Database Syst Rev. 2010 May 12;5:CD003036.

Gronich N, Lavi I, Rennert G. Higher risk of venous **thrombosis** associated with **drospirenone**-containing oral contraceptives: population-based cohort study. CMAJ 2011Nov 7.

Guilbert E, Boroditsky R, Black A, Kives S, Leboeuf M, Mirosh M, Senikas V, Wagner MS, Weir E, York-Lowry J, Reid R, Trussell J; Society of Obstetricians and Gynaecologists of Canada. Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception, 2007. J Obstet Gynaecol Can. 2007 Jul;29(7 Suppl 2):S1-32.

Gurtcheff SE, Turok DK, et al. **Lactogenesis** after early postpartum use of the **contraceptive implant (Implanon)**: a randomized controlled trial. Obstet Gynecol. 2011 May;117(5):1114-21. {Lactation delay, failure, and continuation were not increased among women who received the etonogestrel contraceptive implant within the first 3 days postpartum versus the standard practice of insertion at 4 weeks. Women who intended to use this form of contraception were more likely to actually receive it when the insertion was done during their postpartum hospital stay. (LOE = 1b)}

Hannaford Philip C, Iversen Lisa, Macfarlane Tatiana V, et al. **Mortality** among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. BMJ 2010

Harel Z et al. Recovery **bone mineral density** in adolescents following the use of depot **medroxyprogesterone** acetate contraceptive injections. Contraception 2010Apr; 81:281.

Health Canda June/10 **MIRENA** (Levonorgestrel-Releasing Intrauterine System) - Potential Risk of Uterine Perforation - Bayer Inc. Bayer Inc., in collaboration with Health Canada, would like to remind you of important safety information regarding reports of uterine perforation in women treated with MIRENA.

Health Canada Dec/11 has completed a safety review of drospirenone-containing oral contraceptives (marketed under the brand names Yasmin and Yaz) with respect to the risk of blood clots (venous thromboembolism, or VTE). The review determined that **drospirenone-containing birth** control pills may be associated with a risk of blood clots that is **1.5 to 3 times higher than other birth control pills**.

HHS Aug 2011.: Affordable Care Act Ensures Women Receive **Preventive Services at No Additional Cost** (incl. **contraception**). http://www.hhs.gov/news/press/2011pres/08/20110801b.html

Hicks CW, Rome ES. **Menstrual manipulation**: options for suppressing the cycle. Cleve Clin J Med. 2010 Jul;77(7):445-53.

Hidalgo MM, Hidalgo-Regina C, Bahamondes MV, et al. Serum levonorgestrel levels & endometrial thickness during extended use of the **levonorgestrel-releasing intrauterine** system. Contraception. 2009 Jul;80(1):84-9. Epub 2009 Feb 27. During extended use of the LNG-IUS, serum LNG levels were nearly half those found in the first 2 months of use (Wilcoxon signed rank test); serum E(2) levels were normal. Despite the very thin endometrium, menstrual bleeding was reinstated in many cases. At the end of its 5-year life span, there is a window for changing the LNG-IUS, and physicians and users should not be concerned about delaying replacement of the device for a short time beyond the approved life span; however, maintaining the same device long after its approved life span cannot be recommended.

Hofmeyr GJ, Singata M, Lawrie TA. **Copper containing intra-uterine devices versus depot progestogens** for contraception. Cochrane Database Syst Rev. 2010 Jun 16;6:CD007043. In the populations studied, the IUD was more effective than hormonal contraception with respect to pregnancy prevention.

Huq FY et al. Menstrual problems and contraception in women of reproductive age **receiving oral anticoagulation**. Contraception2011 Aug; 84:128.

Jick SS, Hagberg KW, Hernandez RK, Kaye JA. Postmarketing study of **ORTHO EVRA** and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous **thromboembolism**. Contraception. 2010 Jan;81(1):16-21.

Jick SS, Hernandez RK. Risk of non-fatal venous **thromboembolism** in women using oral contraceptives containing **drospirenone** compared with women using oral contraceptives containing **levonorgestrel**: case-control study using United States claims data. BMJ 2011;342:d2151.

Jones, Claire, Chan, Crystal, Farine, Dan. **Sex in pregnancy**. CMAJ 2011 0: cmaj.091580.

Kaunitz AM. Clinical practice. **Hormonal contraception in women of older reproductive age**. N Engl J Med. 2008 Mar 20;358(12):1262-70.

Kaunitz, Andrew M. "Postpartum and postabortal contraception." Up to Date. 15 Aug. 2008. 27 Feb. 2009 <http://www.utdol.com/home/index.html>.

Kaunitz AM, Meredith S, et al. **Levonorgestrel-releasing intrauterine system** and endometrial ablation in heavy menstrual bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2009 May;113(5):1104-16. Based on the meta-analysis of six randomized clinical trials, the efficacy of the levonorgestrel intrauterine system in the management of heavy menstrual bleeding appears to have similar therapeutic effects to that of endometrial ablation up to 2 years after treatment. {InfoPOEMs Jun09: The levonorgestrel-releasing intrauterine system (LNG-IUS) is as effective as endometrial ablation for the treatment of heavy menses. Its advantages include lower cost, less invasiveness, and retained fertility. (LOE = 1b)}

Kaunitz AM, Darney PD, Ross D, Wolter KD, Speroff L. **Subcutaneous DMPA** vs.intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density. Contraception. 2009 Jul;80(1):7-17. Epub 2009 Mar 27. DMPA-SC is an effective and well-tolerated contraceptive option, providing comparable efficacy and BMD safety to DMPA-IM.

Kaunitz AM, Bissonnette F, Monteiro I, et al. **Levonorgestrel**-Releasing Intrauterine System or Medroxyprogesterone for Heavy Menstrual Bleeding: A Randomized Controlled Trial. Obstet Gynecol. 2010 Sep;116(3):625-632.

Kaunitz AM, Inki P. The **levonorgestrel-releasing intrauterine system** in heavy menstrual bleeding: a benefit-risk review. Drugs. 2012 Jan 22;72(2):193-215.

Kavanaugh ML et al. Characteristics of women in the United States who use **long-acting reversible contraceptive** methods. Obstet Gynecol 2011 Jun; 117:1349.

Kroll R, et al. The efficacy and safety of a low-dose, **91-day, extended-regimen** oral contraceptive with continuous ethinyl estradiol. Contraception. 2010 Jan;81(1):41-8.

Kulier R, et al. Copper containing, framed intra-uterine devices for contraception. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005347.

Le YC, Rahman M, Berenson AB. Early weight gain predicting later **weight gain** among depot **medroxyprogesterone** acetate users. Obstet Gynecol. 2009 Aug;114(2 Pt 1):279-84. Most DMPA users who gain excessive weight experience more than a 5% weight increase within 6 months.

Legro RS, Pauli JG, Kunselman AR, et al. Effects of **Continuous versus Cyclic** Oral Contraception: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2007 Dec 4; [Epub ahead of print] Continuous oral contraception does not result in a reduction of bleeding days over a 168d period of observation, but provides greater suppression of the ovary and endometrium. These effects are associated with improved patient symptomatology.

Lesnewski R, Prine L, Ginzburg R. **Preventing Gaps when Switching** Contraceptives. Am Fam Physician. 2011 Mar 1;83(5):567-570.

Leyland N, Casper R, Laberge P, Singh SS, Allen L, Arendas K. **Endometriosis**: diagnosis and management. J Obstet Gynaecol Can 2010 Jul;32(7 Suppl 2):S1-32.

Lidegaard Øjvind, Løkkegaard Ellen, Svendsen Anne Louise, et al. Hormonal contraception and risk of venous **thromboembolism**: Denmark national follow-up study. BMJ 2009;339:b2890, doi: 10.1136/bmj.b2890 (Published 13 August 2009)

Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423.

Lidegaard O, Nielsen LH, et al. **Venous thrombosis** in users of **non-oral hormonal contraception**: follow-up study, Denmark 2001-10. BMJ. 2012 May 10;344:e2990.

Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, et al. **Thrombotic stroke and myocardial infarction** with hormonal contraception. N Engl J Med 2012;366:2257-66.

Lopez LM, et al. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003552. Effectiveness rates were similar for the methods compared. The patch group had better compliance than the COC group. Compared to COC users, patch users had more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge. The patch could lead to more discontinuation while the vaginal ring showed little difference. High losses to follow up can affect the validity of the results.

Lopez LM, Grimes DA, Gallo MF, Schulz KF. Skin patch and **vaginal ring versus combined oral contraceptives** for contraception. Cochrane Database Syst Rev. 2010 Mar 17;3:CD003552. Effectiveness was similar for the methods compared. The patch could lead to more discontinuation while the vaginal ring showed little difference. The patch group had better compliance than the COC group but more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge.

Lopez LM, Newmann SJ, Grimes DA, Nanda K, Schulz KF. **Immediate start** of hormonal contraceptives for contraception. *Cochrane Database Syst Rev.* 2008;(2):CD006260.

Lopez LM, Grimes DA, Chen-Mok M, et al. Hormonal contraceptives for **contraception in overweight or obese women**. Cochrane Database Syst Rev. 2010 Jul 7;7:CD008452. Body weight addresses overall body size, while BMI generally reflects the amount of fat. Only one of three studies using BMI found a higher pregnancy risk for overweight women. The efficacy of implants and injectable contraceptives may be unaffected by body mass. The field could use trials of contraceptive methods with groups stratified by BMI. The current evidence on effectiveness by BMI is limited. However, the contraceptive methods examined here are still among the most effective when the recommended regimen is followed.

Lopez LM, Edelman A, Chen-Mok M, et al. **Progestin-only contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Apr 13;4:CD008815. We found little evidence of weight gain when using POCs. Mean gain was less than 2 kg for most studies up to 12 months, and usually similar for the comparison group using another contraceptive. Appropriate counseling about typical weight gain may help reduce discontinuation of contraceptives due to perceptions of weight gain.

Loprinzi CL, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol. 2006 Mar 20;24(9):1409-14. Epub 2006 Feb 27.

Madden T, Proehl S, Allsworth JE, et al. **Naproxen** or estradiol for bleeding and **spotting with the levonorgestrel intrauterine system**: a randomized controlled trial. Am J Obstet Gynecol. 2012 Feb;206(2):129.e1-8.

Marions L et al. Effect of **emergency contraception** with levonorgestrel or mifepristone on ovarian function. Contraception2004 May; 69:373-7.

Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003855. Surgery, especially hysterectomy, reduces menstrual bleeding at one year more than medical treatments but LNG-IUS appears equally effective in improving quality of life. The evidence for longer term comparisons is weak and inconsistent. Oral medication suits a minority of women long term.

Margel David, Fleshner Neil E. Oral contraceptive use is associated with **prostate cancer**: an ecological study. BMJ Open 2011;1:e000311 doi:10.1136/bmjopen-2011-000311.

Medical Letter. Three new oral contraceptives. (Yaz, Seasonique, Loestrin 24 Fe) Sept 25,2006.

Medical Letter. Combination Oral Contraceptives and the Risk of **Venous Thromboembolism**. Mar 22, 2010.

Medical Letter- Treatment Guidelines: **Choice of Contraceptives**. Dec 2007; p. 101-108. (**Updated Dec 2010**)

Meier C, Brauchli YB, Jick SS, Kraenzlin ME, Meier CR. Use of Depot **Medroxyprogesterone Acetate and Fracture Risk**. J Clin Endocrinol Metab. 2010 Aug 4.

Miller L, et al. Extended Regimens of the Contraceptive Vaginal Ring: A Randomized Trial. Obstet Gynecol. 2005 Sep;106(3):473-482.

Newman, Adam. Inadvertent use of a **levonorgestrel-releasing intrauterine device as postcoital** contraception. Can Fam Physician 2010 56: 1301-1302

Noé G, Croxatto HB, Salvatierra AM, et al. Contraceptive efficacy of emergency contraception with **levonorgestrel** given before or after ovulation. Contraception. 2011 Nov;84(5):486-92. The efficacy of LNG-EC has been overestimated in studies using presumptive menstrual cycle data. Our results confirm previous similar studies and demonstrate that LNG-EC does not prevent embryo implantation and therefore cannot be labeled as abortifacient.

Odmark IS, Bixo M, Englund D, Risberg B, Jonsson B, Olsson SE. Endometrial safety and bleeding pattern during a five-year treatment with long-cycle hormone therapy. Menopause. 2005 Nov-Dec;12(6):699-707. Epub 2005 Nov 8. (InfoPOEMs: In this small study, continuous estrogen therapy combined with 14 days of progestin every 3 months (long-cycle therapy) did not result in endometrial hyperplasia or cancer. (LOE = 1b))

Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of **venous thromboembolism** in users of oral contraceptives containing **drospirenone or levonorgestrel**: nested case-control study based on UK General Practice Research Database. BMJ 2011;342:d2139.

Polonsky M. **Cancer and contraception**: Release date May 2012 SFP Guideline #20121. Contraception. 2012 Jun 7.

Prabakar I, Webb A. **Emergency contraception**. BMJ. 2012 Mar 19;344:e1492

Pederson HB, Curtis KM. Long-Acting Methods of Contraception. N Engl J Med 2005;353:2169-75.

Pharmacist's Letter: **Hormonal Contraception** July 2006

Pharmacists Letter. Canadian Consensus Guideline on **Continuous and Extended Hormonal Contraception**, 2007. Aug 2007.

Rahman M, Berenson AB. Predictors of higher **bone mineral density loss** and use of depot **medroxyprogesterone** acetate. Obstet Gynecol. 2010 Jan;115(1):35-40. The risk of higher BMD loss associated with DMPA use may be reduced by quitting smoking and increasing calcium intake. Having had a child is also protective.

Roberts T E, Tsourapas A, Middleton L J, et al. **Hysterectomy**, endometrial ablation, & levonorgestrel releasing intrauterine system (**Mirena**) for treatment of **heavy menstrual bleeding**: cost effectiveness analysis. BMJ 2011;342:doi:10.1136/bmj.d2202

Rosenberg L, Zhang Y, Constant D et al. Bone status after cessation of use of injectable **progestin** contraceptives. Contraception. 2007 Dec;76(6):425-31. Epub 2007 Nov 9. The data suggest that **bone loss during IPC use is reversible** and that this loss of bone is completely recovered several years after cessation of use.

sexualityandU.ca website (supported by **SOGC**) http://sexualityandu.ca/professionals/index.aspx

Shabaan MM, Zakherah MS, El-Nashar SA, Sayed GH. **Levonorgestrel-releasing intrauterine system** compared to low dose combined oral contraceptive pills for idiopathic **menorrhagia**: a randomized clinical trial. Contraception. 2011 Jan;83(1):48-54.

Shaamash AH, et al. A comparative study of the levonorgestrel-releasing intrauterine system Mirena(R) versus the Copper T380Aintrauterine device during lactation: breast-feeding performance, infant growth and infant development. Contraception. 2005 Nov;72(5):346-51. Epub 2005 Jul 6.

Shaarawy M, et al. Effects of the long-term use of depot medroxyprogesterone acetate as hormonal contraceptive on bone mineral density and biochemical markers of bone remodeling. Contraception. 2006 Oct;74(4):297-302. Epub 2006 Jun 16.

Speroff, Leon, and Daniel R. Mishell Jr. "The postpartum visit: it's time for a change in order to optimally initiate contraception." Contraception 78 (2008): 90-98

Shufelt CL, Bairey Merz CN. Contraceptive hormone use and **cardiovascular disease**. J Am Coll Cardiol 2009; 53:221-231.

SOGC: Nov 2008 **Missed Contraceptives**: http://www.sogc.org/jogc/abstracts/200811_SOGCClinicalPracticeGuidelines_1.pdf

Steiner MJ, Kwok C, Stanback J, et al. Injectable contraception: what should the longest interval be for reinjections? Contraception. 2008 Jun;77(6):410-4. Epub 2008 Apr 10. Extending the current WHO **grace period for DMPA reinjection from 2 to 4 weeks** does not increase pregnancy risk and could increase contraceptive continuation.

Stewart FH, Kaunitz AM, Laguardia KD, et al. Extended use of transdermal norelgestromin/ethinyl estradiol: a randomized trial. Obstet Gynecol. 2005 Jun;105(6):1389-96.

Sulak PJ, Kuehl TJ, Coffee A, Willis S. Prospective analysis of occurrence and management of breakthrough bleeding during an **extended oral contraceptive** regimen. Am J Obstet Gynecol. 2006 Apr 27; [Epub ahead of print]

Sulak PJ, et al. Frequency and management of breakthrough bleeding with **continuous use of the transvaginal** contraceptive **ring**: a randomized controlled trial. Obstet Gynecol. 2008 Sep;112(3):563-71.

Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and management of **abnormal uterine bleeding** in premenopausal women. Am Fam Physician. 2012

Jan 1;85(1):35-43.
Templeton A, Grimes DA. A **Request for Abortion**. N Engl J Med 2011; 365:2198-2204.
Thonneau P, et al. Risk factors for **IUD failure**: results of a large multicentre case-control study. Hum Reprod. 2006 Oct;21(10):2612-6. Epub 2006 Jun 14. Only a history of previous IUD expulsion was found to be a risk factor for failure, indicating that these women should have regular medical and echographical follow-up. Comparing the efficacy rate of various types of IUDs, we found a clear advantage for levonorgestrel-releasing devices.
Trenor, Cameron C, Chung, Richard J., Michelson, Alan D., et al. Hormonal Contraception and **Thrombotic Risk**: A Multidisciplinary Approach. Pediatrics 2011 127: 347-357.
Trussell J. Contraceptive failure in the United States. Contraception. 2004 Aug;70(2):89-96.
Tsai R, Schaffir J. Effect of depot **medroxyprogesterone** acetate on **postpartum depression**. Contraception. 2010 Aug;82(2):174-7. Epub 2010 Apr 13. Administration of DMPA in the immediate postpartum period does not appear to predispose women to PPD.
Van Houdenhoven K, et al. Uterine perforation in women using a levonorgestrel-releasing intrauterine system. Contraception. 2006 Mar;73(3):257-60. Epub 2005 Oct 21.
van Hylckama Vlieg A, Helmerhorst F M, Vandenbroucke J P, et al. Venous **thrombotic risk** of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study**.** BMJ 2009;339:b2921, doi: 10.1136/bmj.b2921 (Published 13 August 2009)
Van Vliet HA, Grimes DA, Lopez LM, et al. **Triphasic versus monophasic** oral contraceptives for contraception. Cochrane Database Syst Rev. 2011 Nov 9;11:CD003553.
The available evidence is insufficient to determine whether triphasic OCs differ from monophasic OCs in effectiveness, bleeding patterns or discontinuation rates. Therefore, we recommend monophasic pills as a first choice for women starting OC use. Large, high-quality RCTs that compare triphasic and monophasic OCs with identical progestogens are needed to determine whether triphasic pills differ from monophasic OCs.
Westhoff CL, Torgal AH, Mayeda ER, et al. Pharmacokinetics of a combined oral contraceptive in **obese** and normal-weight women. Contraception. 2010 Jun;81(6):474-80.
Westhoff CL et al. **Body weight** does not impact pregnancy rates during use of a low-dose extended-regimen 91-day oral contraceptive. Contraception 2012 Mar; 85:235. (LoSEASONIQUE)
Wiegratz I, Kuhl H. Long-cycle treatment with oral contraceptives. Drugs. 2004;64(21):2447-62.
Wilailak S, Vipupinyo C, Suraseranivong V, et al. **Depot medroxyprogesterone** acetate and epithelial **ovarian cancer**: a multicentre case-control study. BJOG. 2012 May;119(6):672-7.
Winner B, Peipert JF, Zhao Q, et al. **Effectiveness of long-acting reversible contraception**. N Engl J Med. 2012 May 24;366(21):1998-2007.

References: *The Rx Files* Postmenopausal & Herbal Pharmacotherapy

[1] Pepping J. Black cohosh: Cimicifuga racemosa. Am.J Health Syst.Pharm. 1999;56:1400-02.

[2] Jacobson JS, Troxel AB, Evans J et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19:2739-45. (Pockaj BA, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. J Clin Oncol. 2006 Jun 20;24(18):2836-41.)

[3] The Canadian consensus conference on menopause and osteoporosis. J Obstet Gynaecol Can 2001;23:1-90.

[4] Therapeutic Research Faculty. Natural Database Monographs. Natural Database . 2002. Ref Type: Electronic Citation.

[5] Amato P, Christophe S, Mellon P. Estrogenic activity of herbs commonly used as remedies fo menopausal symptoms. Menopause 2002;9:145-50.

[6] Liske E, Hanggi W, et al. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): a 6-month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based.Med 2002;11:163-74.

[7] Shuster J. Black cohosh root? Chasteberry tree? Seizures! Hospital Pharmacy 1996;31:1553-4.

[8] Facts and comparisons. The review of natural products (formerly the Lawrence Review of natural products). In: DerMarderosian A, editor. St. Louis MO, 2002.

[9] Morelli V, Naquin C. Alternative therapies for traditional disease states: menopause. Am.Fam.Physician 2002;66:129-34.
Jurgens T, Whelan AM. Advising patients on the use of natural health products to treat premenstrual syndrome. Can Pharm J 2009;142:228-233.

[10] Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. Fertil.Steril. 1997;68:981-6.

[11] Scott GN, Elmer GW. Update on natural product--drug interactions. Am.J Health Syst.Pharm 2002;59:339-47.

[12] Chandler F. Herbs: everyday reference for health professionals. Ottawa, Canadian Pharmacists Association & Canadian Medical Association. 2000.

[13] Page RL, Lawrence JD. Potentiation of warfarin by dong quai. Pharmacotherapy 1999;19:870-876.

[14] Fugh-Berman A. Herb-drug interactions. Lancet 2000;355:134-8.

[15] Chenoy R, Hussain S, Tayob Y, O'Brien PMS, Moss MY, Morse PF. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. BMJ 1994;308:501-3.

[16] Clifton-Bligh PB, Baber RJ, Fulcher GR, Nery ML, Moreton T. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. Menopause. 2001;8:259-65.

[17] Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes. Obstet.Gynecol 1998;91:6-11.

[18] Quella SK, Loprinzi CL, Barton DL et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. J Clin Oncol 2000;18:1068-74.
Levis S, Strickman-Stein N, Ganjei-Azar P, et al. Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial. Arch Intern Med. 2011;171 (15):1363-1369. Soy isoflavone supplementation had no effect on bone mineral density over the 2 years of this study, but increased the percentage of women reporting hot flashes. (LOE = 1b-)

[19] Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995;333:276-82.

[20] Potter SM, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman JW, Jr. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. Am.J Clin Nutr. 1998;68:1375S-1379S.
Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. JAMA. 2004 Jul 7;292(1):65-74.
Wong WW, Lewis RD, Steinberg FM, et al. **Soy** isoflavone supplementation and bone mineral density in menopausal women: a 2-y multicenter clinical trial. Am J Clin Nutr. 2009 Sep 16. Daily supplementation with 120 mg soy hypocotyl isoflavones reduces whole-body bone loss but does not slow bone loss at common fracture sites in healthy postmenopausal women.

[21] Alexandersen P, Toussaint A, Christiansen C, et al. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. JAMA. 2001 Mar 21;285(11):1482-8.

[22] Duncan AM, Underhill KE, Xu X, Lavalleur J, Phipps WR, Kurzer MS. Modest hormonal effects of soy isoflavones in postmenopausal women. J Clin frinol.Metab 1999;84:3479-84.

[23] Balk J, Whiteside D, Naus, G et al. A pilot study of the effects of phytoestrogen supplementation on postmenopausal endometrium. J Soc Gynecol Invest 2002;9:238-42.
Steinberg FM, Murray MJ, Lewis RD, et al.Clinical outcomes of a 2-y soy isoflavone supplementation in menopausal women. Am J Clin Nutr. 2010 Dec 22.
Kang, Xinmei, Zhang, Qingyuan, Wang, Shuhuai, et al. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. CMAJ 2010 182: 1857-1862.
Ollberding NJ, Lim U, Wilkens LR, et al. Legume, soy, tofu, and isoflavone intake and endometrial cancer risk in postmenopausal women in the multiethnic cohort study. J Natl Cancer Inst. 2012 Jan 4;104(1):67-76.

[24] Brinker F. Herb contraindications and drug interactions, 3rd ed. Eclectic Medical Publishing. 2001. 177-178.

[25] O'Hara M, Kiefer D, Farrell K, Kemper K. A review of 12 commonly used medicinal herbs. Arch.Fam.Med 1998;7:523-36.

[26] Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies. Am.J Health Syst.Pharm 1999;56:125-38.

[27] Garges HP, Varia I, Doraiswamy PM. Cardiac complications and delirium associated with valerian root withdrawal. JAMA 1998;280:1566-7.

[28] Bedard M. Dong quai for women. Canadian Pharmaceutical Journal 2002;135:20-1.

[29] Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 2002;288:835-40.

[30] Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Intern Med. 2002 Nov 19;137(10):805-13. (Nedrow A, et al **Complementary and alternative** therapies for the management of menopause-related symptoms: a systematic evidence review. Arch Intern Med. 2006 Jul 24;166(14):1453-65. (InfoPOEMs: There is no evidence of benefit of acupuncture, magnet therapy, stress reduction, exercise, progressive muscle relaxation, or traditional Chinese herbal therapy on menopausal symptoms. Black cohosh, which has been associated with liver toxicity, and soy supplements may decrease hot flashes in some patients, and osteopathic manipulation was effective in one study. (LOE = 1a-)))

[31] Micromedex 2010

[32] Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, et al.; **WHI** Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA. 2003 May 28;289(20):2673-84.

[33] Rapp SR, Espeland MA, et al.; **WHIMS**. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003 May 28;289(20):2663-72.
Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM, Ockene J, Davatzikos C. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. Neurology. 2009 Jan 13;72(2):135-42. Conjugated equine estrogens with or without MPA are associated with greater brain atrophy among women aged 65 years and older; however, the adverse effects are most evident in women experiencing cognitive deficits before initiating hormone therapy.
Coker LH, Hogan PE, Bryan NR, et al. Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. Neurology. 2009 Jan 13;72(2):125-34. Conjugated equine estrogen-based hormone therapy was not associated with a significant increase in ischemic brain lesion volume relative to placebo. This finding was consistent within each trial and in pooled analyses across trials.

[34] Shumaker SA, Legault C, et al.; **WHIMS**. Estrogen plus progestin & the incidence of dementia & mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003 May 28;289(20):2651-62. Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In addition, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women. (Shumaker SA, et al.; Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2947-58. Estrogen therapy alone did not reduce dementia or MCI incidence and increased the risk for both end points combined.) (Maki PM, Gast MJ, Vieweg AJ, Burriss SW, Yaffe K. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. Neurology. 2007 Sep 25;69(13):1322-30. n=180. Cognitive Complaints in Early Menopause Trial (COGENT-stopped beause of WHI). There were no differences between groups on any cognitive or QoL measures, except for an increase in sexual interest and thoughts with HT. With the power to detect an effect size of >or=0.45, this study suggests potential modest negative effects on verbal memory that are consistent with previous hormone therapy trials in older women.) Petitti DB, Crooks VC, Chiu V, Buckwalter JG, Chui HC. Incidence of dementia in long-term hormone users. Am J Epidemiol. 2008 Mar 15;167(6):692-700. Epub 2008 Jan 23. After adjustment for age, education, and medical history, hazard ratios for incident dementia were 1.34 (95% confidence interval: 0.95, 1.89) in estrogen/progestin users and 1.23 (95% confidence interval: 0.94, 1.59) in estrogen users. These findings do not provide support for an effect of estrogen or estrogen/progestin use in preventing dementia.

[35] Khan MA, Hlatky MA, Liu MW, Lin F, ET AL. **HERS** Investigators. Effect of postmenopausal hormone therapy on coronary heart disease events after percutaneous transluminal coronary angioplasty. Am J Cardiol. 2003 Apr 15;91(8):989-91, A7.

[36] Hays J, Ockene JK, Brunner RL, Kotchen JM, et al.; **WHI** Investigators. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med. 2003 May 8;348(19):1839-54. Epub 2003 Mar 17

[37] Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. Am J Med. 2002 Nov;113(7):543-8.

[38] Byington RP, Furberg CD, et al.; Heart and Estrogen/Progestin Replacement Study Research Group. Effect of estrogen plus progestin on progression of carotid atherosclerosis in postmenopausal women with heart disease: **HERS B-mode substudy**. Arterioscler Thromb Vasc Biol. 2002 Oct 1;22(10):1692-7.

[39] Hulley S, Furberg C, Barrett-Connor E, Cauley J, et al.; HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (**HERS II**). JAMA. 2002 Jul 3;288(1):58-66.

[40] Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA; Heart and Estrogen/Progestin Replacement Study (**HERS**) Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. JAMA. 2002 Feb 6;287(5):591-7.

[41] Simon JA, Hunninghake DB, et al. Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2001 Oct 2;135(7):493-501.

[42] Cauley JA, Black DM, Barrett-Connor E, Harris F, et al. Effects of hormone replacement therapy on clinical fractures and height loss: The Heart and Estrogen/Progestin Replacement Study (**HERS**). Am J Med. 2001 Apr 15;110(6):442-50.

[43] Chelebowski R, Hendrix S, Langer R, Stefanick M, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. The Women's Health Initiative (**WHI**) Randomized Trial. JAMA 2003;2
(Stefanick ML, et al. WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006 Apr 12;295(14):1647-57. (InfoPOEMs: Estrogen therap

TOP

increase the risk of breast cancer in postmenopausal women with prior hysterectomy. Women receiving estrogen are more likely to require further testing as a result of questionably abnormal mammogram results, potentially leading to heightened anxiety and a reduced quality of life. The decision to use estrogen in postmenopausal women after hysterectomy should be individualized on the basis of overall potential risks and benefits. Women most likely to benefit from estrogen therapy include those with disabling hot flashes and an increased risk of osteoporotic fractures. Treatment should be limited whenever possible to the first 5 years (or less) after menopause. (LOE = 1b)))

[44] Treatment Guidelines: **Drugs for Prevention & Treatment of Postmenopausal Osteoporosis**. **The Medical Letter**: November, **2002**; (3) pp. 13-18, & **October 2005, & REVISED Oct 2008**..

[45] Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004 Jan 7;291(1):47-53.

[46] Holmberg L., Anderson H., for the HABITS steering and data monitoring committees; **HABITS** (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped; Published online February 3, 2004.

[47] Johnston SL, Farrell SA, Bouchard C, et al.; SOGC Joint Committee-Clinical Practice Gynaecology and Urogynaecology. The detection and management of vaginal atrophy. J Obstet Gynaecol Can. 2004 May;26(5):503-15.

[48] Women's Health Initiative (**WHI**). Effects of Conjugated Equine **Estrogen** in Postmenopausal Women with Hysterectomy. Principal results from the Womens Health Initiative Randomized Controlled Trial. JAMA 2004;291:1701-1712.(Brunner RL, Gass M, Aragaki A, et al. Effects of Conjugated Equine Estrogen on Health-Related **Quality of Life** in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Clinical Trial. Arch Intern Med. 2005 Sep 26;165(17):1976-86).(Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease: The Women's Health Initiative. Arch Intern Med. 2006 Feb 13;166(3):357-65. CONCLUSIONS: Conjugated equine estrogens provided no overall protection against myocardial infarction or coronary death in generally healthy postmenopausal women during a 7-year period of use. There was a suggestion of lower coronary heart disease risk with CEE among women 50 to 59 years of age at baseline.)

Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol* 2012; online March 7.

[49] Women's Health Initiative (**WHI**). Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Womens Health Initiative Randomized Controlled Trial. JAMA 2002;288:321-33.

Manson JE, Hsia J, Johnson KC, Rossouw JE, et al; Women's Health Initiative Investigators (**WHI**). Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003 Aug 7;349(6):523-34.

Wathen CN, Feig DS, Feightner JW, et al. Hormone replacement therapy for the primary prevention of chronic diseases: recommendation statement from the Canadian Task Force on Preventive Health Care. CMAJ. 2004 May 11;170(10):1535-1537.

Dominic J. Cirillo, BS; Robert B. Wallace, MD, MSc; Rebecca J. Rodabough, MS; Philip Greenland, MD; Andrea Z. LaCroix, PhD; Marian C. Limacher, MD; Joseph C. Larson, MS. Effect of Estrogen Therapy on Gallbladder Disease. JAMA. 2005;293:330-339.

Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, Aragaki A, Naughton MJ, Wallace RB, McNeeley SG. Effects of estrogen with and without progestin on urinary incontinence. JAMA. 2005 Feb 23;293(8):935-48.

Espeland MA, Rapp SR, Shumaker SA, et al.; Women's Health Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2959-68.

(Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007; 297:1465-1477. Women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion for statistical significance. A similar nonsignificant trend was observed for total mortality but the risk of stroke was elevated regardless of years since menopause.)

Ravdin PM, Cronin KA, Howlader N, et al. The **decrease in breast-cancer incidence** in 2003 in the United States. N Engl J Med 2007:356; 1670-1674. The decrease in breast-cancer incidence seems to be temporally related to the first report of the Women's Health Initiative and the ensuing drop in the use of hormone-replacement therapy among postmenopausal women in the United States.

Beral V, Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet 2007; DOI:10.1016/S0140-6736(07)60534-0.

Beral V; Million Women Study Collaborators; Bull D, Green J, Reeves G. Ovarian cancer and hormone replacement therapy in the **Million Women Study**. Lancet. 2007 May 19;369(9574):1703-10. Women who use HRT are at an increased risk of both incident and fatal ovarian cancer. Since 1991, use of HRT has resulted in some 1300 additional ovarian cancers and 1000 additional deaths from the malignancy in the UK.

Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, Kuller LH, Cochrane BB, Hunt JR, Ludlam SE, Pettinger MB, Gass M, Margolis KL, Nathan L, Ockene JK, Prentice RL, Robbins J, Stefanick ML; WHI and WHI-CACS Investigators. Estrogen therapy and **coronary-artery calcification**. N Engl J Med. 2007 Jun 21;356(25):2591-602. n=1064 Among women 50 to 59 years old at enrollment, the calcified-plaque burden in the coronary arteries after trial completion was lower in women assigned to estrogen only than in those assigned to placebo.

Vickers MR, MacLennan AH, Lawton B, et al. Main morbidities recorded in the Women's International Study of Long Duration Oestrogen After Menopause (**WISDOM**): a randomized controlled trial of hormone replacement therapy in postmenopausal women. BMJ 2007; DOI:10.1136/bmj.39266.425069 Hormone replacement therapy increases cardiovascular and thromboembolic risk when started many years after the menopause. The results are consistent with the findings of the women's health initiative study and secondary prevention studies. Research is needed to assess the long term risks and benefits of starting hormone replacement therapy near the menopause, when the effect may be different.

Kerlikowske K, Miglioretti DL, Buist DS, Walker R, Carney PA. **Declines in Invasive Breast Cancer** and Use of Postmenopausal Hormone Therapy in a Screening Mammography Population. J Natl Cancer Inst. 2007 Aug 14; [Epub ahead of print] Our finding of a statistically significant decline in the rate of ER-positive invasive breast cancer in a screening mammography population after the start of a concomitant substantial decline in postmenopausal hormone therapy use suggests that a decline in screening mammography rates is unlikely to account for the recent decline in US breast cancer incidence.

Li CI, Malone KE, Porter PL, et al. Relationship between Menopausal Hormone Therapy and Risk of Ductal, Lobular, and Ductal-Lobular Breast Carcinomas. Cancer Epidemiol Biomarkers Prev. 2008 Jan;17(1):43-50. Current CHT users for **>/=3 years have a substantially increased risk of lobular carcinomas**. Although lobular carcinomas are less common than ductal carcinomas (approximately 16% versus 70% of all invasive breast cancers in the United States), this duration is shorter than the 5 years of use widely cited to be needed to confer an increased risk of breast cancer overall.

Chlebowski RT, Anderson G, Pettinger M, et al. for the Women's Health Initiative Investigators. Estrogen Plus Progestin and **Breast Cancer Detection by Means of Mammography and Breast Biopsy**. Arch Intern Med. 2008 Feb 25;168(4):370-377. Use of conjugated equine estrogens plus medroxyprogesterone acetate for approximately 5 years resulted in more than 1 in 10 and 1 in 25 women having otherwise avoidable mammogram abnormalities and breast biopsies, respectively, and compromised the diagnostic performance of both. This adverse effect on breast cancer detection should be incorporated into risk-benefit discussions with women considering even short-term combined hormone therapy.

Heiss G, Wallace R, Anderson GL, et al. WHI Investigators. Health risks and benefits **3 years after stopping** randomized treatment with estrogen and progestin. JAMA. 2008 Mar 5;299(9):1036-45. The increased cardiovascular risks in the women assigned to CEE plus MPA during the intervention period were not observed after the intervention. A greater risk of fatal & nonfatal malignancies occurred after intervention in the CEE plus MPA group & the global risk index was 12% higher in women randomly assigned to receive CEE plus MPA compared with placebo.

Rohan TE, Negassa A, Chlebowski RT, et al.Conjugated Equine Estrogen and Risk of **Benign Proliferative Breast Disease**: WHI - A Randomized Controlled Trial. J Natl Cancer Inst. 2008 Apr 8; [Epub ahead of print] Use of 0.625 mg/d of CEE was associated with a statistically significant increased risk of benign proliferative breast disease.

Bray PF, Larson JC, Lacroix AZ, et al. Women's Health Initiative Investigators. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. Am J Cardiol. 2008 Jun 1;101(11):1599-1605. Epub 2008 Apr 2. In conclusion, postmenopausal women with **undesirable lipid levels** had excess coronary heart disease risk when using CEE with or without MPA. However, women with favorable lipid levels, especially LDL/HDL cholesterol ratio <2.5, did not have increased risk of coronary heart disease with CEE with or without MPA irrespective of hs-CRP.

Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM Ockene J, Davatzikos C. Postmenopausal hormone therapy and regional **brain volumes**: the WHIMS-MRI Study. Neurology. 2009 Jan 13;72(2):135-42. Conjugated equine estrogens with or without MPA are associated with greater brain atrophy among women aged 65 years and older; however, the adverse effects are most evident in women experiencing cognitive deficits before initiating hormone therapy.

Coker LH, Hogan PE, Bryan NR, et al. Postmenopausal hormone therapy and **subclinical cerebrovascular disease**: the WHIMS-MRI Study. Neurology. 2009 Jan 13;72(2):125-34. Conjugated equine estrogen-based hormone therapy was not associated with a significant increase in ischemic brain lesion volume relative to placebo. This finding was consistent within each trial and in pooled analyses across trials.

Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, et al. WHI Investigators. **Breast cancer** after use of estrogen plus progestin in postmenopausal women. N Engl J Med. 2009 Feb 5;360(6):573-87. The increased risk of breast cancer associated with the use of estrogen plus progestin declined markedly soon after discontinuation of combined hormone therapy and was unrelated to changes in frequency of mammography.

Shetty KD, Vogt WB, Bhattacharya J. Hormone replacement therapy and cardiovascular health in the United States. Med Care. 2009 May;47(5):600-6. Decreased HRT use was not associated with reduced acute stroke rate but was associated with a decreased **acute myocardial infarction** rate among women. Our results suggest that observational data can provide correct inferences on clinical outcomes in the overall population if a suitable natural experiment is identified.

Prentice RL, Manson JE, Langer RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated **soon after menopause**. (WHI) Am J Epidemiol. 2009 Jul 1;170(1):12-23. Epub 2009 May 25. These analyses provide little support for the hypothesis of favorable effects among women who initiate postmenopausal estrogen use soon after menopause, either for coronary heart disease or for health benefits versus risk indices considered.

Chlebowski RT, Schwartz AG, Wakelee H, et al. for the Women's Health Initiative Investigators. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet. 2009 Sep 18.

Espeland MA, Tindle HA, Bushnell CA, et al. for the Women's Health Initiative Memory Study. Brain Volumes, Cognitive Impairment, and Conjugated Equine Estrogens. J Gerontol A Biol Sci Med Sci. 2009 Sep 3.

Crandall Carolyn J.; Aragaki Aaron K.; Chlebowski Rowan T.; et al. New-Onset **Breast Tenderness** After Initiation of Estrogen Plus Progestin Therapy and Breast Cancer Risk. Arch Intern Med. 2009;169(18):1684-1691.

Toh Sengwee, Hernández-Díaz Sonia, Logan Roger, Et al. **Coronary Heart Disease** in Postmenopausal Recipients of Estrogen Plus Progestin Therapy: Does the Increased Risk Ever Disappear?: A Randomized Trial. Ann Intern Med February 16, 2010.

Manson JE, Allison MA, Carr JJ, et al. for the Women's Health Initiative and Women's Health Initiative-**Coronary Artery Calcium** Study Investigators. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause. 2010 Jun 14.

Harman S. Mitchell. Therapeutics: Women's Health Initiative (WHI) randomised ontrolled trial: Combined estrogen plus progestin may reduce coronary heart disease risk after 5 years of use in postmenopausal women starting treatment within 10 years of menopause, Evid Based Med 2010;15:69-70 doi:10.1136/ebm1079

Chlebowski RT., Anderson GL., Manson JE., et al. **Lung Cancer** Among Postmenopausal Women Treated With Estrogen Alone in the Women's Health Initiative (WHI) Randomized Trial. Journal of the National Cancer Institute Advance Acc

13, 2010.
Chlebowski Rowan T.; Anderson Garnet L.; Gass Margery; et al. for the WHI Investigators Estrogen Plus Progestin and **Breast Cancer Incidence and Mortality** in Postmenopausal Women. JAMA. 2010;304(15):1684-1692.
LaCroix AZ, Chlebowski RT, Manson JE, et al; WHI Investigators. Health outcomes **after stopping conjugated equine estrogens** among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA. 2011;305(13): 1305-1314.
De P, Neutel CI, Olivotto I, Morrison H. **Breast cancer incidence and hormone replacement therapy in Canada**. J Natl Cancer Inst. 2010 Oct 6;102(19):1489-95.
Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine **oestrogen and breast cancer** incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol* 2012; online March 7.

[50] Ockene JK, Barad DH, Cochrane BB, Larson JC, et al. Symptom experience after discontinuing use of estrogen plus progestin. JAMA. 2005 Jul 13;294(2):183-93. (Haimov-Kochman R, et al. **Gradual discontinuation** of hormone therapy does not prevent the reappearance of climacteric symptoms: a randomized prospective study. Menopause. 2006 May 25; [Epub ahead of print]

[51] Hodis HN, Mack WJ, Azen SP, ET AL. Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial Research Group (**WELL-HART**). Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med. 2003 Aug 7;349(6):535-45.

[52] Gruber DM, Sator MO, Kirchengast S. Effect of percutaneous androgen replacement therapy on body composition and body weight in postmentopausal women. Maturitas 1998;29:253-9.

[53] Utiger RD. The need for more vitamin D. N Eng J Med 1998;338:828-9.
Hanley DA, Cranney A, Jones G, et al. **Vitamin D in adult** health & disease: a review and **guideline statement from Osteoporosis Canada**–summary.CMAJ 2010 0: cmaj.091062.
Vitamin D supplementation: Recommendations for Canadian mothers and infants. Paediatr Child Health 2007;12(7):583-9. Reference No. FNIM07-01.
http://www.cps.ca/english/statements/ii/fnim07-01.htm
IOM (Institute of Medicine): Dietary Reference Intakes for **Calcium and Vitamin D** Nov,2010. http://www.iom.edu/~/media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf
Rosen Clifford J. **Vitamin D Insufficiency**. N Engl J Med 2011; 364:248-254.
Bosomworth, N.J. Mitigating epidemic vitamin D deficiency: The agony of evidence. Can Fam Physician 2011 57: 16-20.

[54] Boucher M, Murphy G, Goyle D, et al. Bisphosphonates and teriparatide of r the prevention of osteoporotic fractures in postmenopausal women [Technology overview no 22]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/660

[55] Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996;23:259-63.

Additional references:

Goodman NF, Cobin RH, Ginzburg SB, Katz IA, Woode DE. **AACE**- American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of **menopause**. Endocr Pract 2011 Nov-Dec;17(Suppl 6):1-25.
https://www.aace.com/files/menopause.pdf

Agarwal A, Deepinder F, Cocuzza M, Short RA, Evenson DP. Effect of vaginal **lubricants on sperm motility** and chromatin integrity: a prospective comparative study. Fertil Steril. 2008 Feb;89(2):375-9. Epub 2007 May 16.

Agha-Hosseini M, Kashani L, Aleyaseen A, et al. Crocus sativus L. (**saffron**) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG. 2008 Mar;115(4):515-9. Saffron was an effective treatment for premenstrual syndrome (PMS) in this well-designed but small and short-term study. Consider recommending saffron, if cost is not an obstacle. Larger and longer studies are needed to confirm this result. (LOE = 1b)

Akhila V, Pratapkumar. A comparison of **transdermal and oral HRT** for menopausal symptom control. Int J Fertil Womens Med. 2006 Mar-Apr;51(2):64-9.

Alhola P, Polo-Kantola P, Erkkola R, Portin R. **Estrogen** therapy and **cognition**: **a 6-year** single-blind follow-up study in postmenopausal women. Neurology. 2006 Aug 22;67(4):706-9.

Aromatase Inhibitors and Vaginal Estrogen, Pharmacist's Letter May 2006

Bachmann GA, Schaefers M, Uddin A, Utian WH. Lowest Effective Transdermal 17{beta}-Estradiol Dose for Relief of Hot Flushes in Postmenopausal Women: A Randomized Controlled Trial. Obstet Gynecol. 2007 Oct;110(4):771-779. **Micro-dose E2 (0.014 mg/d) was clinically and statistically significantly more effective** than placebo in reducing the number of moderate and severe hot flushes, with a 41% responder rate, supporting the concept of the lowest effective dose. Many women complaining of menopausal hot flushes will get relief from ultra-low-dose hormone therapy patches, so it makes sense to start low in the effort to minimize dosing. (LOE = 1b)

Barakat RR, et al.; Gynecologic Oncology Group Study. Randomized double-blind trial of **estrogen replacement therapy** versus placebo in **stage I or II endometrial cancer**: a Gynecologic Oncology Group Study. J Clin Oncol. 2006 Feb 1;24(4):587-92.

Basson R. Clinical practice. **Sexual desire** and arousal disorders in women. N Engl J Med. 2006 Apr 6;354(14):1497-506.

Beral V, Reeves G, Bull D, Green J; for the **Million Women Study Collaborators**. **Breast Cancer Risk** in Relation to the Interval Between Menopause and Starting Hormone Therapy. J Natl Cancer Inst. 2011 Jan 28.

Beresford SA, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial.JAMA. 2006 Feb 8;295(6):643-54.

Berry DA, et al.; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators Effect of **screening and adjuvant** therapy on mortality from **breast cancer**. N Engl J Med. 2005 Oct 27;353(17):1784-92. (InfoPOEMs: Almost half of the reduction in breast cancer mortality over the past decade can be attributed to the increased use of screening mammography; the remainder appears to be due to improvements in therapy. (LOE = 1b))

Brandes JL. The influence of estrogen on **migraine**: a systematic review. JAMA. 2006 Apr 19;295(15):1824-30.

Briggs GE, Freeman RK, Yaffe SJ, editors. Drugs in Pregnancy and Lactation. 9th ed. Williams and Wilkins; Philadelphia, PA: 2011

Buist D. S., MAnderson, ,et al. Short-Term **Hormone Therapy Suspension and Mammography** Recall: A Randomized Trial. Ann Intern Med 2009; 752-765.

Buyon JP, Petri MA, Kim MY, et al. The effect of **combined estrogen and progesterone** hormone replacement therapy on disease activity in systemic **lupus** erythematosus: a randomized trial. Ann Intern Med. 2005 Jun 21;142(12 Pt 1):953-62.

Canonico M, Oger E, Plu-Bureau G, et al; Estrogen and Thromboembolism Risk (**ESTHER**) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study.Circulation. 2007 Feb 20;115(7):840-5. **Oral but not transdermal estrogen** is associated with an increased **VTE risk**. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. If confirmed, these findings could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogens.

Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and **risk of venous thromboembolism** in postmenopausal women: systematic review and meta-analysis. BMJ. 2008 May 20. [Epub ahead of print] Oral oestrogen increases the risk of venous thromboembolism, especially during the first year of treatment. **Transdermal oestrogen may be safer** with respect to thrombotic risk.

Carroll DG, Kelley KW. Use of **antidepressants for management of hot flashes**. Pharmacotherapy. 2009 Nov;29(11):1357-74.

Casini ML, et al. Psychological assessment of the effects of treatment with **phytoestrogens** on postmenopausal women: a randomized, double-blind, crossover, placebo-controlled study. Fertil Steril. 2006 Apr;85(4):972-8. (InfoPOEMs: Isoflavone treatment enhanced **mood** in healthy postmenopausal women, but did not improve scores on cognitive measures. The overall risks and benefits of long-term treatment remain uncertain. (LOE = 1b))

Cheong JL. Retinal vein thrombosis associated with a herbal **phytoestrogen** preparation (black cohosh, dong quai, red clover & wold Mexican yam) in a susceptible patient. Postgrad Med J. 2005 Apr;81(954):266-7.

Chlebowski RT., Anderson GL., Manson JE., et al. **Lung Cancer** Among Postmenopausal Women Treated With Estrogen Alone in the Women's Health Initiative (WHI) Randomized Trial. Journal of the National Cancer Institute Advance Access published Aug 13, 2010.

Chotirmall SH, Smith SG, Gunaratnam C, et al. Effect of **Estrogen on Pseudomonas Mucoidy and Exacerbations in Cystic Fibrosis**. N Engl J Med. 2012 May 20.

Cody JD, Richardson K, Moehrer B, et al. Oestrogen therapy for **urinary incontinence** in post-menopausal women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD001405.

Col NF, Fairfield KM, Ewan-Whyte C, Miller H. **In the clinic. Menopause**. Ann Intern Med. 2009 Apr 7;150(7):ITC4-1-15; quiz ITC4-16,.

Cranney A, et al.; Clinical Guidelines Committee of Osteoporosis Canada. **Parathyroid hormone** for the treatment of osteoporosis: a systematic review. CMAJ. 2006 Jul 4;175(1):52-9.

Cummings SR, Ettinger B, Delmas PD, et al. **LIFT** Trial Investigators. The effects of **tibolone** in older postmenopausal women. N Engl J Med. 2008 Aug 14;359(7):697-708. Tibolone reduced the risk of fracture and breast cancer and possibly colon cancer but increased the risk of stroke in older women with osteoporosis. For every 1000 women treated for 1 year with tibolone, there will be approximately 9 fewer vertebral fractures, 7 fewer nonvertebral fractures, 2 fewer breast cancers, 1 fewer colon cancer, 2 more strokes, and 1 additional endometrial cancer. Although the authors recommend that tibolone not be used in women older than 70 years or in those who have risk factors for stroke, it is hard to see a compelling advantage of this drug for any group of women since bisphosphonates provide a safer way to prevent fracture. (LOE = 1b)

Cunha EP, Azevedo LH, Pompei LM, et al. Effect of **abrupt discontinuation versus gradual dose reduction** of postmenopausal hormone therapy on hot flushes. Climacteric. 2010 Feb 12.

Curb JD, et al. **Venous thrombosis and conjugated equine estrogen** in women without a uterus. Arch Intern Med. 2006 Apr 10;166(7):772-80. During a mean of 7.1 years, VT occurred in 111 women randomly assigned to receive estrogen (3.0 per 1000 person-years) and 86 randomly assigned to receive placebo (2.2 per 1000 person-years; hazard ratio, 1.32; 95% confidence interval, 0.99-1.75). Deep venous thrombosis was reported in 85 women randomly assigned to receive estrogen (2.3 per 1000 person-years) and 59 randomly assigned to receive placebo (1.5 per 1000 person-years; hazard ratio, 1.47; 95% confidence interval, 1.06-2.06).An early increased VT risk is associated with use of estrogen, especially within the first 2 years, but this risk increase is less than that for estrogen plus progestin.

Dekosky ST, Williamson JD, Fitzpatrick AL, et al.; for the Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for Prevention of Dementia: A Randomized Controlled Trial. JAMA. 2008 Nov 19;300(19):2253-2262. (n=3,069 6.1yrs) In this study, G biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.

Dodd JM, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004947.

Dickson G. Gynescomastia. Am Fam Physician. 2012 Apr 1;85(7):716-722.

Eliassen A. Heather; Hankinson Susan E.; Rosner Bernard; et al. **Physical Activity and Risk of Breast Cancer** Among Postmenopausal Women. Arch Intern Med. 2010;170(19):1758-1764.

Ensrud KE, Joffe H, Guthrie KA, et al. Effect of **escitalopram on insomnia** symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes: a randomized controlled trial. Menopause. 2012 Mar 19.

Farquhar CM, et al., the Cochrane HT Study Group. **Long term hormone therapy** for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2005 Jul 20;3:CD004143.

TOP

FDA Concern over Bio-Identicals Jan/08: **Bio-Identicals: Sorting Myths from Facts** http://www.fda.gov/consumer/updates/bioidenticals010908.html.
Freedman RR, Kruger ML, Tancer ME. **Escitalopram** treatment of menopausal hot flashes. Menopause. 2011 Apr 30. (not effective)
Freeman Ellen W., Guthrie Katherine A., Caan Bette, et al. Efficacy of **Escitalopram for Hot Flashes** in Healthy Menopausal Women: A Randomized Controlled Trial. JAMA. 2011;305(3):267-274.doi:10.1001/jama.2010.2016.
Freeman EW et al. **Duration of menopausal hot flushes** and associated risk factors. Obstet Gynecol 2011 May; 117:1095.
Ford O, Lethaby A, et al. **Progesterone** for Premenstrual Syndrome. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD003415. We could not say that progesterone helped women with PMS, nor that it was ineffective. Neither trial distinguished a subgroup of women who benefited.
Gast GCM, Pop VJM, Samsioe GN, et al. **Vasomotor menopausal symptoms** are associated with **increased risk of coronary heart disease**. Menopause 2011; 18:146-151.
Geller SE, Shulman LP, van Breemen RB, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. Menopause. 2009 Jul 15. [Epub ahead of print] Compared with placebo, black cohosh and red clover did not reduce the number of vasomotor symptoms. Safety monitoring indicated that chemically and biologically standardized extracts of black cohosh and red clover were safe during daily administration for 12 months.
Genazzani AR et al. Effect of 1-year, low-dose **DHEA** therapy (10mg daily) on climacteric symptoms and female sexuality. Climacteric. 2011 Dec;14(6):661-8.
Genistein: Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2007 Aug;92(8):3068-75. Epub 2007 May 22. These results suggest that 54 mg genistein plus calcium, vitamin D(3), and a healthy diet was associated with favorable effects on both glycemic control and some cardiovascular risk markers in a cohort of osteopenic, postmenopausal women. D'Anna R, Cannata ML, Atteritano M, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause. 2007 Jul-Aug;14(4):648-55. The phytoestrogen genistein has been shown to be effective on vasomotor symptoms without an adverse effect on endometrium. Marini H, Minutoli L, Polito F, et al. Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):839-47. Summary for patients in: Ann Intern Med. 2007 Jun 19;146(12):I34. Twenty-four months of tx with genistein has positive effects on BMD in osteopenic postmenopausal women.
Geukes M et al. The impact of **menopausal symptoms on work** ability. Menopause 2012 Mar; 19:278.
Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. Arch Intern Med. 2004 Oct 11;164(18):1965-76.
Goodwin JW, Green SJ, et al Phase III randomized placebo-controlled trial of two doses of **megestrol** acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. J Clin Oncol. 2008 Apr 1;26(10):1650-6. MA significantly reduced vasomotor symptoms with durable benefit over 6 months. MA 20 mg/d is the preferred dose. There was no significant impact on other menopausal symptoms.
Gordon PR, et al. **Sertraline** to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population. Menopause. 2006 Jul-Aug;13(4):568-75.
Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of **Raynaud's phenomenon**. BMJ. 2012 Feb 7;344:e289.
Grady D. Clinical practice. **Management of menopausal symptoms**. N Engl J Med. 2006 Nov 30;355(22):2338-47.
Grady D, Cohen B, Tice J, et al. **Ineffectiveness of sertraline** for treatment of menopausal hot flushes: a randomized controlled trial. N=99 6weeks. Obstet Gynecol. 2007 Apr;109(4):823-30. Treatment with sertraline did not improve hot flush frequency or severity in generally healthy perimenopausal and postmenopausal women, but was associated with bothersome side effects. (InfoPOEMs: Sertraline is no better than placebo for the treatment of menopausal hot flushes. (LOE = 1b))
Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. Arch Intern Med. 2008 Apr 28;168(8):861-6. (Nurses' Health Study) Hormone therapy is associated with an increased **risk of stroke**, and this increased risk does not appear to be related to the timing of the initiation of HT. In younger women, with lower stroke risk, the attributable risk of stroke owing to hormone use is modest and might be minimized by lower doses and shorter treatment duration.
Guimaraes P, et al. **Progestin** negatively affects hearing in aged women. Proc Natl Acad Sci U S A. 2006 Sep 19;103(38):14246-9. Epub 2006 Sep 7.
Haimov-Kochman R, et al. **Gradual discontinuation** of hormone therapy does not prevent the reappearance of climacteric symptoms: a randomized prospective study. Menopause. 2006 May 25; [Epub ahead of print]
Haimov-Kochman R, Hochner-Celnikier D. Hot flashes revisited: pharmacological and herbal options for hot flashes management. What does the evidence tell us? Acta Obstet Gynecol Scand. 2005 Oct;84(10):972-9. CONCLUSIONS: A critical review of the literature shows that progesterone may have an independent effect on relieving hot flashes. New nonhormonal agents such as selective serotonin-uptake-inhibitor anti-depressants and a new anti-convulsant gabapentin yielded promising results on small well-conducted studies. Isoflavone's effect on hot flashes is variable and inconsistent, and only modest and delayed improvement of symptoms could be expected by BC and vitamin E. There are insufficient data on the other herbal alternative therapies at this time. Well-designed large studies are needed to further explore new modalities of treatment.
Hall E, Frey BN, Soares CN. **Non-hormonal treatment strategies for vasomotor symptoms**: a critical review. Drugs. 2011 Feb 12;71(3):287-304. doi: 10.2165/11585360-000000000-00000.
Hayes Laura P, Carroll Dana G, Kelley Kristi W. Use of **Gabapentin for the Management of Natural or Surgical Menopausal** Hot Flashes. Articles Ahead of Print published 22 February 2011, DOI 10.1345/aph.1P366.
He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of **soybean** protein on blood pressure: a randomized, controlled trial. Ann Intern Med. 2005 Jul 5;143(1):1-9. Summary for patients in: Ann Intern Med. 2005 Jul 5;143(1):I11.
Health Canada Dec/05 Notice to Discontinue **Climacteron** http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/climacteron_hpc-cps_e.pdf
Health Canada Aug/06 & Jan/10 is advising consumers about a possible link between health products containing herbal medicine **black cohosh** and liver damage. A number of international case reports of liver damage suspected to be associated with the use of black cohosh, including three case reports in Canada and one published case of death in the United States. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html , http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v20n1-eng.php#_Black_cohosh_products
Health Canada Jan/08 is warning Canadians not to use the unauthorized product **RGC-RMC Rheumax Capsule** (batch number REM1-SI93016N). This batch of RGC-RMC Rheumax Capsule has been found to contain **progesterone**, a steroid hormone that can have adverse effects on the brain, breast and skin and should only be taken if prescribed by a health professional.
Henderson VW, St John JA, Hodis HN, et al; For the **WISH** Research Group. Long-term **soy isoflavone supplementation** and cognition in women: A randomized, controlled trial. Neurology. 2012 Jun5;78(23):1841-1848.
Hickey M, Elliott J, Davison SL. Hormone replacement therapy. BMJ. 2012 Feb 16;344:e763.
Hill DA, Hill SR. Counseling patients about **hormone therapy and alternatives for menopausal symptoms**. Am Fam Physician. 2010 Oct 1;82(7):801-7.
Holmberg L, Iversen OE, Rudenstam CM, et al. On behalf of the **HABITS** Study Group. **Increased Risk of Recurrence After Hormone Replacement Therapy in Breast Cancer Survivors**. J Natl Cancer Inst. 2008 Mar 25; [Epub ahead of print]. After extended follow-up, there was a clinically and statistically significant increased risk of a new breast cancer event in survivors who took HT.
Howard BV, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006 Feb 8;295(6):655-66.
Howard BV, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. JAMA. 2006 Jan 4;295(1):39-49.
Huang Alison J.; Subak Leslee L.; Wing Rena et al; for the Program to Reduce Incontinence by Diet and Exercise Investigators An **Intensive Behavioral Weight Loss** Intervention and Hot Flushes in Women. Arch Intern Med. 2010;170(13):1161-1167.
Huang AJ, Grady D, Jacoby VL, Blackwell TL, Bauer DC, Sawaya GF. **Persistent hot flushes** in older postmenopausal women. Arch Intern Med. 2008 Apr 28;168(8):840-6. For a substantial minority of women, hot flushes are a persistent source of discomfort into the late postmenopausal years. Identification of risk factors for hot flushes may help guide evaluation and treatment in this population.
Ismail SI, Bain C, Hagen S. Oestrogens for treatment or prevention of **pelvic organ prolapse** in postmenopausal women. Cochrane Database Syst Rev. 2010 Sep 8;9:CD007063. There was limited evidence from randomised controlled trials regarding the use of oestrogens for the prevention and management of pelvic organ prolapse. The use of local oestrogen in conjunction with pelvic floor muscle training before surgery may reduce the incidence of post-operative cystitis within four weeks after surgery.
Jacobson BC, Moy B, Colditz GA, Fuchs CS. Postmenopausal hormone use and symptoms of gastroesophageal reflux. Arch Intern Med. 2008 Sep 8;168(16):1798-804. Postmenopausal use of estrogens, selective estrogen receptor modulators, or OTC hormone preparations is associated with a greater likelihood of symptoms of **GERD**.
Jing Z, Yang X, Ismail KM, Chen X, Wu T. Chinese herbal medicine for premenstrual syndrome. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006414. It is rare in PMS management that efficacy claims are substantiated by clinical trials. One of the identified trials was well designed and reported on the effectiveness of **Jingqianping** in the treatment of premenstrual syndrome Qiao 2002. However, currently there is insufficient evidence to support the use of chinese herbal medicine for PMS and further, well controlled, trials are needed before any final conclusions could be drawn.
Jurgens T, Whelan AM. Advising patients on the use of **natural health products to treat premenstrual** syndrome. Can Pharm J 2009;142:228-233.
Kaya C, Dincer Cengiz S, Cengiz B, Akgun G. The long-term effects of low-dose 17beta-**estradiol** and dydrogesterone hormone replacement therapy on 24-h ambulatory **blood pressure** in hypertensive postmenopausal women: a 1-year randomized, prospective study. Climacteric. 2006 Dec;9(6):437-45.
Kerlikowske K, Cook AJ, Buist DS, et al. **Breast Cancer Risk by Breast Density**, Menopause, and Postmenopausal Hormone Therapy Use. J Clin Oncol. 2010 Jul 19.
Korhonen K, Auvinen A, Lyytinen H, et al. A nationwide cohort study on the incidence of **meningioma** in women using postmenopausal hormone therapy in Finland. Am J Epidemiol. 2012 Feb 15;175(4):309-14.
Kornstein SG, Jiang Q, Reddy S, Musgnung JJ, Guico-Pabia CJ. Short-term efficacy and safety of **desvenlafaxine** in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder. J Clin Psychiatry. 2010 Aug;71(8):1088-96.
Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. **JAMA. 2004** Jul 7;292(1):65-74.
Lacey JV Jr, et al. Menopausal hormone therapy and **ovarian cancer risk** in the National Institutes of Health-AARP Diet and Health Study Cohort. J Natl Cancer Inst. 2006 Oct 4;98(19):1397-405. Long durations of use of unopposed estrogen and of estrogen plus progestin, especially sequential regimens, are associated with increased ovarian cancer risk.
Lee S, Kolonel L, Wilkens L, Wan P, Henderson B, Pike M. Postmenopausal hormone therapy and **breast cancer** risk: The multiethnic cohort. Int J Cancer. 2005 Sep 16; [Epub ahead of print]
Lemaitre RN, Weiss NS, Smith NL, Psaty BM, Lumley T, Larson EB, Heckbert SR. **Esterified estrogen and conjugated equine estrogen** and the risk of incident myocardial infarction and stroke. Arch Intern Med. 2006 Feb 27;166(4):399-404.
Lenart BA, Lorich DG, Lane JM. **Atypical fractures of the femoral diaphysis** in postmenopausal women taking alendronate.N Engl J Med. 2008 Mar 20;358(12):1304-6.
Lethaby A, Suckling J, Barlow D, et al. Hormone replacement therapy in postmenopausal women: **endometrial hyperplasia and irregular bleeding**. Cochrane Database Syst Rev. 2004;(3):CD000402.
Lethaby A, Hogervorst E, Richards M, Yesufu A, Yaffe K. Hormone replacement therapy for **cognitive function** in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003122. There is good evidence that both ERT and HRT do not prevent cognitive decline in older postmenopausal women when given as short term or longer term (up to five years) therapy. It is not known whether either specific types of ERT or HRT have specific effects in subgroups of women, although there was evidence that combined hormone therapy in similarly aged women was associated with a decrement in a number of verbal memory tests and a small improvement in a test of figural memory.
Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. **Phytoestrogens** for vasomotor menopausal symptoms. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD001395.
Levis S, Strickman-Stein N, Ganjei-Azar P, et al. **Soy isoflavones** in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial. (SPARE) Arch Intern Med. 2011;171 (15):1363-1369. (200mg for 2yrs did not prevent bone loss or menopausal symptoms)
Lindblad BE, Håkansson N, Philipson B, Wolk A. Hormone Replacement Therapy in Relation to Risk of **Cataract** Extraction A Prospective Study of Women. Ophthalmology. 2010 Mar;117(3):424-430. Epub 2010 Jan 4.
Lindh-Åstrand L et al. A randomized controlled study of **taper-down or abrupt discontinuation** of hormone therapy in women treated for vasomotor symptoms. Menopause 2010 Jan/Feb; 17:72.

TOP

Loibl S, Schwedler K, von Minckwitz G, Strohmeier R, Mehta K, Kaufmann M. **Venlafaxine** 37.5mg bid is superior to clonidine 0.075 mg twice a day (n=64, 4 weeks) as treatment of hot flashes in breast cancer patients--a double-blind, randomized study. Ann Oncol. 2007 Apr;18(4):689-93. Epub 2007 Jan 17. Venlafaxine is significantly more effective in reducing the frequency of hot flashes in breast cancer patients than clonidine.

Loprinzi CL, Sloan J, Stearns V, et al. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol. 2009 Jun 10;27(17):2831-7. Epub 2009 Mar 30. Some newer antidepressants and gabapentin, within 4 weeks of therapy initiation, decrease hot flashes more than placebo.

Low Dog T. Menopause: a review of **botanical** dietary supplements. Am J Med. 2005 Dec 19;118(12 Suppl 2):98-108.

Liu B, Beral V, Balkwill A, Green J, Sweetland S, Reeves G; for the Million Women Study Collaborators. **Gallbladder disease and use of transdermal** versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. BMJ. 2008 Jul 10;337:a386. doi: 10.1136/bmj.a386. Gallbladder disease is common in postmenopausal women and use of hormone replacement therapy increases the risk. Use of transdermal therapy rather than oral therapy over a five year period could **avoid one cholecystectomy in every 140 users**.

Løkkegaard E, Andreasen AH, Jacobsen RK, Nielsen LH, Agger C, Lidegaard O. Hormone therapy and risk of myocardial infarction: a national register study. Eur Heart J. 2008 Sep 30. [Epub ahead of print] In a National cohort study, we found that HT **regimen and route** of application could modify the influence of HT on the risk of MI.

Lyytinen H, Pukkala E, Ylikorkala O. **Breast cancer** risk in postmenopausal women using **estrogen-only** therapy. Obstet Gynecol. 2006 Dec;108(6):1354-60. Estradiol for 5 years or more, either orally or transdermally, means 2-3 extra cases of breast cancer per 1,000 women who are followed for 10 years. Oral estradiol use for less than 5 years, oral estriol, or vaginal estrogens were not associated with a risk of breast cancer.

Maalouf Naim M.; Sato Alicia H.; Welch Brian J.; et al. Postmenopausal Hormone Use and the Risk of **Nephrolithiasis**: Results From the Women's Health Initiative Hormone Therapy Trials. Arch Intern Med. 2010;170(18):1678-1685.

Mackenzie R, et al. **Progesterone** for the prevention of **preterm birth** among women at increased risk: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2006 May;194(5):1234-42. Epub 2006 Apr 21. InfoPOEMS – July 28, 2006: Bottom Line: Second-trimester progestational agents significantly reduce the risk of birth before 37 weeks' gestation for women at increased risk of preterm birth. Reduction in perinatal mortality or serious morbidity has not yet been established. (LOE = 1a-)

Madalinska JB, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women **after prophylactic salpingo-oophorectomy**. J Clin Oncol. 2006 Aug 1;24(22):3576-82.

Maki PM, Rubin LH, Fornelli D, et al. Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. Menopause. 2009 Jul 8. [Epub ahead of print] PubMed PMID: 19590458. Results indicate that a **red clover** (phytoestrogen) supplement or **black cohosh** has no effects on cognitive function. CEE/MPA reduces objective hot flashes but worsens some aspects of verbal memory.

Mann E, Smith MJ, Hellier J, et al. **Cognitive behavioural treatment** for women who have menopausal symptoms after breast cancer treatment (**MENOS 1**): a randomised controlled trial. Lancet Oncol 2012

McClung MR. Osteopenia: to treat or not to treat? Ann Intern Med. 2005 May 3;142(9):796-7.

McTiernan A, Martin CF, Peck JD, ET AL.; WHI Mammogram Density Study Investigators. Estrogen-plus-progestin use and mammographic density in postmenopausal women: women's health initiative randomized trial. J Natl Cancer Inst. 2005 Sep 21;97(18):1366-76. CONCLUSIONS: Use of up to 2 years of estrogen plus progestin was associated with increases in mammographic density.

Medical Letter. Low dose **Transdermal Estrogens**. Aug 27,2007.

Medical Letter. Bioidentical Hormones. May 31, 2010.

Medical Letter. **Drugs for Menopausal Symptoms**. May 28, 2012.

MHRA Dec/11 In response to an urgent notice issued by the MHRA, **Bee Health Ltd has agreed to stop marketing FSC Black Cohosh 1000 mg** due to concerns about the high dosage of black cohosh in the product. The MHRA advises consumers not to take the FSC Black Cohosh product as it equates to 50 times the dose approved for traditional herbal medicinal products used to relieve menopausal symptoms. It is not known what the risks or effects on the body could be associated with such a high level of Black Cohosh.

Mishra GD, Kuh D. **Health symptoms during midlife** in relation to menopausal transition: British prospective cohort study. BMJ 2012;344:e402.

Morch Lina Steinrud; Lokkegaard Ellen; Andreasen Anne Helms; et al. Hormone Therapy and **Ovarian Cancer**. JAMA. 2009;302(3):298-305.

Motivala A, Pitt B. **Drospirenone** for oral contraception and hormone replacement therapy : are its cardiovascular risks and benefits the same as other progestogens? Drugs. 2007;67(5):647-55. Our review of the literature suggests that because of its anti-mineralocorticoid effects, drospirenone in conjunction with estrogen may prevent the development of cardiovascular disease in both pre- and post-menopausal women.

National Institutes of Health. National Institutes of Health State-of-the-Science Conference statement: **management of menopause-related** symptoms. Ann Intern Med. 2005 Jun 21;142(12 Pt 1):1003-13. Epub 2005 May 27.

Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. **Complementary and alternative** therapies for the management of menopause-related symptoms: a systematic evidence review. Arch Intern Med. 2006 Jul 24;166(14):1453-65.

Nelson HD, et al. **Nonhormonal therapies for menopausal hot flashes: systematic review** and meta-analysis. JAMA. 2006 May 3;295(17):2057-71. The SSRIs or SNRIs, clonidine, and gabapentin trials provide evidence for efficacy; however, effects are less than for estrogen, few trials have been published and most have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict use for many women. These therapies may be most useful for highly symptomatic women who cannot take estrogen but are not optimal choices for most women. (InfoPOEMs: Evidence supports the nonhormonal treatment of menopausal hot flashes with paroxetine (Paxil), clonidine (Catapres), gabapentin (Neurontin), and soy isoflavone extract. The overall effect size of all nonhormonal treatments is less than that of estrogen. Treatment should be individualized according to symptom severity and risk profiles. (LOE = 1a-)) (Reddy SY, et al. Gabapentin, Estrogen, and Placebo for Treating Hot Flushes: A Randomized Controlled Trial. Obstet Gynecol. 2006 Jul;108(1):41-48. Despite the small scale of this study, (12 week n=60) gabapentin appears to be as effective as estrogen in the treatment of postmenopausal hot flushes. (InfoPOEMs: In this small study, high-dose gabapentin (Neurontin) was as effective as the usual dose of conjugated equine estrogens (Premarin) for the treatment of menopausal vasomotor symptoms. Larger studies are needed to confirm this result. (LOE = 1b))) (Loprinzi CL, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol. 2006 Mar 20;24(9):1409-14. Epub 2006 Feb 27.)(Butt DA, Lock M, Lewis JE, Ross S, Moineddin R. Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause. 2007 Oct 2; [Epub ahead of print]) Loprinzi CL, Sloan J, Stearns V, et al. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol. 2009 Jun 10;27(17):2831-7. Epub 2009 Mar 30. Some newer antidepressants and gabapentin, within 4 weeks of therapy initiation, decrease hot flashes more than placebo.

Nelson HD. **Menopause**. Lancet. 2008 Mar 1;371(9614):760-70.

Nelson HD, Walker M, Zakher B, Mitchell J. **Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions**: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendations (**USPSTF**). Ann Intern Med. 2012 May 28.

Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo. Ann Intern Med 2006;145:869-879. {InfoPOEMS-Feb07: Neither soy, black cohosh, or a naturopathic multibotanical was effective in decreasing the duration or severity of vasomotor symptoms. These results are similar to other research findings. (LOE = 1b) }

Njor SH, Hallas J, Schwartz W, Lynge E, Pedersen AT. Type of hormone therapy and risk of **misclassification at mammography** screening. Menopause. 2010 Aug 19.

North American Menopause Society. Recommendations for **estrogen and progestogen use** in peri-and postmenopausal women: October 2004 position statement of The North American Menopause Society. Menopause. 2004 Nov-Dec;11(6 Pt 1):589-600. **North American Menopause Society Management of osteoporosis** in postmenopausal women: 2006 position statement of The North American Menopause Society. Menopause. 2006 May-Jun;13(3):340-67; quiz 368-9. (Utian WH, Archer DF, Bachmann GA, et al. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. (**NAMS**) Menopause. **2008** Jul-Aug;15(4 Pt 1):584-602. http://www.menopause.org/PSHT08.pdf Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable close to menopause but decreases with aging and with time since menopause in previously untreated women.)

North American Menopause Society. **NAMS**: Management of **osteoporosis in postmenopausal women**: **2010** position statement of The North American Menopause Society. Menopause. **2010** Jan-Feb;17(1):25-54.

North American Menopause Society. The role of **local vaginal estrogen for treatment of vaginal atrophy** in postmenopausal women: **2007 position statement** of The North American Menopause Society. Menopause. 2007 May-Jun;14(3):370-1. The choice of therapy should be guided by clinical experience and patient preference. Progestogen is generally not indicated when low-dose estrogen is administered locally for vaginal atrophy. Data are insufficient to recommend annual endometrial surveillance in asymptomatic women using vaginal ET. Vaginal ET should be continued for women as long as distressful symptoms remain. For women treated for non-hormone-dependent cancer, management of vaginal atrophy is similar to that for women without a cancer history. For women with a history of hormone-dependent cancer, management recommendations are dependent upon each woman's preference in consultation with her oncologist.

North American Menopause Society. **NAMS**: Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause. **2010** Feb 12. [Epub ahead of print] Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable for women who initiate HT close to menopause but decreases in older women and with time since menopause in previously untreated women. http://www.menopause.org/PSht10.pdf

Osmers R, Friede M, et al. Efficacy and safety of isopropanolic **black cohosh** extract for climacteric symptoms. Obstet Gynecol 2005; 105:1074-83. (InfoPOEMs: This study reports that isopropanolic black cohosh extract (Remifemin) at a dose of 20 mg twice daily is statistically more effective than placebo for the treatment of menopausal vasomotor symptoms. These results will probably be used to promote its use. However, the authors did not supply sufficient data to determine the extent of benefit or the number needed to treat. This evidence is insufficient to determine whether black cohosh has a clinically relevant effect in treating menopausal symptoms. (LOE = 1b-)) CONCLUSION: This isopropanolic extract of black cohosh root stock is effective in relieving climacteric symptoms, especially in early climacteric women.

Ouyang P, et al.; for the Estrogen And Graft Atherosclerosis Research (**EAGAR**) investigators. Randomized trial of hormone therapy in women after coronary bypass surgery Evidence of differential effect of hormone therapy on angiographic progression of disease in saphenous vein grafts and native coronary arteries. Atherosclerosis. 2006 Jan 23; [Epub ahead of print]

Palmert Mark R, Dunkel Leo. **Delayed Puberty**. N Engl J Med 2012; 366:443-453.

Pandya KJ, Morrow GR, Roscoe JA, et al. **Gabapentin** for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. Lancet. 2005 Sep 3-9;366(9488):818-24. Gabapentin is effective in the control of hot flashes at a dose of 900 mg/day, but not at a dose of 300 mg/day. This drug should be considered for treatment of hot flashes in women with breast cancer. (InfoPOEMs: Women with a history of breast cancer may obtain some relief from hot flashes with 900 mg gabapentin daily. The 300 mg daily dose was not effective. (LOE = 1b-))

Pattimakiel L, Thacker HL. Bioidentical hormone therapy: Clarifying the misconceptions. Cleve Clin J Med. 2011 Dec;78(12):829-36.

Pharmacist's Letter. **Angeliq** (Estradiol & Drospirenone) Dec 2008.

Phillips TJ, Symons J, Menon S; HT Study Group. Does hormone therapy improve age-related skin changes in postmenopausal women? A randomized, double-blind, double-dummy, placebo-controlled multicenter study assessing the effects of norethindrone acetate and ethinyl estradiol in the improvement of mild to moderate age-related skin changes in postmenopausal women. J Am Acad Dermatol. 2008 Jul 12. [Epub ahead of print] Low-dose hormone therapy for 48 weeks in postmenopausal women did not significantly alter mild to moderate age-related facial skin changes. This study found **no benefit** for hormone replacement therapy (HRT) with progesterone and estrogen in reducing age-related adverse **skin changes** (ie, wrinkling and crows' feet) in postmenopausal women. (LOE = 1b-)

Pockaj B ; Gallagher J ; Loprinzi C et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: J Clin Oncol. 2006; 24:2836-41. CONCLUSION: This trial failed to provide any evidence that black cohosh reduced hot flashes more than Pl.

Politi MC, et al. Revisiting the **duration of vasomotor symptoms** of menopause: a meta-analysis. J Gen Intern Med. 2008 Sep;23(9):1507-13. Epub 2008 Jun 3. Our findings suggest a median symptom duration of about 4 years among symptomatic women. A longer symptom duration may affect treatment decisions and clinical guidelines. Further prospective, longitudinal studies of menopausal symptoms should be conducted to confirm these results.

Rada G, Capurro D, Pantoja T, et al. **Non-hormonal interventions for hot flushes in women with a history of breast cancer**. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004923. DOI: 10.1002/14651858.CD004923.pub2. Clonidine, SSRIs

TOP

and relaxation therapy showed a mild to moderate effect on reducing hot flushes in women with a history of breast cancer.
Reddy SY, Warner H, Guttuso T, et al. Gabapentin, estrogen, and placebo for treating hot flashes: a randomized controlled trial. Obstet Gynecol 2006;108:41-48. InfoPoems: In this small study, high-dose gabapentin (Neurontin) was as effective as the usual dose of conjugated equine estrogens (Premarin) for the treatment of menopausal vasomotor symptoms. Larger studies are needed to confirm this result. (LOE = 1b)
Reed SD, Newton KM, Garcia RL, et al. Complex **hyperplasia** with and without atypia: clinical outcomes and implications of **progestin therapy**. Obstet Gynecol. 2010 Aug;116(2 Pt 1):365-73.
Reed SD, Newton KM, LaCroix AZ, et al. Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of **black cohosh**, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (**HALT**) Study. Menopause. 2008 Jan-Feb;15(1):51-8.
Renoux Christel, Dell'Aniello Sophie, Garbe Edeltraut, et al. **Transdermal and oral hormone replacement therapy** and the risk of stroke: a nested case-control study. BMJ 2010;340:c2519, doi: 10.1136/bmj.c2519 (Published 3 June 2010)
Reynolds K, et al. A meta-analysis of the effect of **soy protein** supplementation on serum lipids. Am J Cardiol. 2006 Sep 1;98(5):633-40. Epub 2006 Jul 12.
Roberts H. **Managing the menopause**. BMJ. 2007 Apr 7;334(7596):736-41.
Rogines-Velo MP et al. Effect of **medroxyprogesterone on depressive symptoms** in depressed and nondepressed perimenopausal and postmenopausal women after discontinuation of transdermal estradiol therapy. Menopause2012 Apr; 19:471.
Romieu I, Fabre A, Fournier A, Kauffmann F, Varraso R, Mesrine S, Leynaert B, Clavel-Chapelon F. Postmenopausal hormone therapy and **asthma onset** in the E3N cohort. Thorax. 2010 Feb 8.
Rosenberg L, Palmer JR, Wise LA, Adams-Campbell LL. A prospective study of female **hormone use** and breast cancer among **black women**. Arch Intern Med. 2006 Apr 10;166(7):760-5.
Royal College of Obstetricians and Gynaecologists (**RCOG**). **Venous thromboembolism and hormone replacement therapy**. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 May
Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M. **Soy** Protein, Isoflavones, and Cardiovascular Health. An **American Heart Association** Science Advisory for Professionals From the Nutrition Committee. Circulation. 2006 Jan 17; [Epub ahead of print]
Salpeter SR, et al. Brief report: **Coronary heart disease** events associated with hormone therapy in **younger and older** women. A meta-analysis. J Gen Intern Med. 2006 Apr;21(4):363-6. Hormone therapy reduces the risk of CHD events in younger postmenopausal women. In older women, HT increases, then decreases risk over time.(Alexandersen P, et al. The long-term impact of 2-3 years of hormone replacement therapy on cardiovascular mortality and atherosclerosis in healthy women. Climacteric. 2006 Apr;9(2):108-18.)
Samsioe G, et al. Estalis 50/140 Study Group. **Endometrial safety**, overall safety and tolerability of transdermal continuous combined hormone replacement therapy over 96 weeks: a randomized open-label study. Climacteric. 2006 Oct;9(5):368-79. Continuous combined transdermal HRT with E2/NETA shows no evidence of an increased endometrial hyperplasia or endometrial cancer risk over a 96-week period.
Santen RJ, Allred DC, Ardoin SP, et al. **Postmenopausal Hormone Therapy**: An **Endocrine Society** Scientific Statement. J Clin Endocrinol Metab. **2010** Jun 21. http://www.endo-society.org/journals/ScientificStatements/upload/jc-2009-2509v2.pdf
Schabath MB, Hernandez LM, Wu X, Pillow PC, Spitz MR. Dietary **phytoestrogens** and lung cancer risk. JAMA. 2005 Sep 28;294(12):1493-504.
Sestak I, et al. Influence of hormone replacement therapy on **tamoxifen-induced vasomotor** symptoms. J Clin Oncol. 2006 Aug 20;24(24):3991-6.
Shah NR, Jones JB, Aperi J, Shemtov R, Karne A, Borenstein J. **Selective Serotonin Reuptake Inhibitors** for Premenstrual Syndrome and Premenstrual Dysphoric Disorder: A Meta-Analysis. Obstet Gynecol. 2008 May;111(5):1175-1182. Selective serotonin reuptake inhibitors were found to be effective in treating premenstrual symptoms, with continuous dosing regimens favored for effectiveness.
Shapley M, Blagojevic M, Jordan K, Croft P. The **spontaneous resolution of heavy menstrual** bleeding in the perimenopausal years. BJOG. 2012 Feb 8.
Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. Obstet Gynecol. 2008 Nov;112(5):1053-60. After 12 weeks of treatment, an ultra-low-dose **10-microgram E2 vaginal tablet (Vagifem),** compared with placebo, demonstrated significant improvement for the primary endpoints: vaginal cytology and pH and most bothersome urogenital symptoms score. In this study a 10-mcg estradiol vaginal tablet used twice weekly was better than placebo for the reduction of bothersome postmenopausal vaginal symptoms. The tablet currently on the market (Vagifem, by the same manufacturer) is 25 mcg. Perhaps once weekly use of the available tablet would be equivalent to twice weekly use of the lower dose, but that would require another study that the manufacturer is unlikely to fund. (LOE = 2b)
SOGC 2009 Menopause and Osteoporosis Update 2009-SOGC Jan 2009. http://www.sogc.org/media/pdf/advisories/Meno-Osteo-Update_JOGC-Jan_09.pdf
Star Trial (Study of Tamoxifen and Raloxifene) for Breast Cancer Prevention Medical Letter May 8, 2006 & Pharmacist's Letter May 2006. InfoPOEMs: Tamoxifen (Nolvadex, Tamofen) and raloxifene (Evista) are similarly effective for reducing the risk of invasive breast cancer in postmenopausal women. Although women taking tamoxifen are at an increased risk of thromboembolic events and cataracts, they report improved sexual function compared with women taking raloxifene. All-cause mortality and overall quality-of-life were similar in both treatment groups. (LOE = 1b-).
Stefanick ML, et al. WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006 Apr 12;295(14):1647-57. (InfoPOEMs: Estrogen therapy alone does not increase the risk of breast cancer in postmenopausal women with prior hysterectomy. Women receiving estrogen are more likely to require further testing as a result of questionably abnormal mammogram results, potentially leading to heightened anxiety and a reduced quality of life. The decision to use estrogen in postmenopausal women after hysterectomy should be individualized on the basis of overall potential risks and benefits. Women most likely to benefit from estrogen therapy include those with disabling hot flashes and an increased risk of osteoporotic fractures. Treatment should be limited whenever possible to the first 5 years (or less) after menopause. (LOE = 1b))
Shah NR, Borenstein J, Dubois RW. Postmenopausal hormone therapy and **breast cancer**: a systematic review and meta-analysis. Menopause. 2005 Nov-Dec;12(6):668-78. (InfoPOEMs: This meta-analysis of 13 large observational studies found that combined estrogen and progestin hormone therapy (CHT) for postmenopausal women is more likely than estrogen-only hormone therapy (ET) to be associated with breast cancer. This result is concondant with clinical trial data from the Women's Health Initiative (WHI). There is still uncertainty about whether ET increases the risk of breast cancer, based on the heterogeneity found in this meta-analysis and the discordance of these results with those from the WHI. (LOE = 2a))
Snitz Beth E.; O'Meara Ellen S.; Carlson Michelle C.; et al. for the **Ginkgo** Evaluation of Memory (**GEM**) Study Investigators. Ginkgo biloba for Preventing Cognitive Decline in Older Adults: A Randomized Trial. JAMA. 2009;302(24):2663-2670. Compared with placebo, the use of G biloba, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment.
Somunkiran A, Erel CT, Demirci F, Senturk ML. The effect of **tibolone** versus 17beta-estradiol on climacteric symptoms in women with surgical menopause: A randomized, cross-over study. Maturitas. 2006 Jul 8; [Epub ahead of print]
Stearns V, Slack R, Greep N, et al. **Paroxetine** is an effective treatment **for hot flashes**: results from a prospective randomized clinical trial. J Clin Oncol. 2005 Oct 1;23(28):6919-30.
Steinauer JE, Waetjen LE, Vittinghoff E, Subak LL, Hulley SB, Grady D, Lin F, Brown JS. Postmenopausal hormone therapy: does it cause incontinence? Obstet Gynecol. 2005 Nov;106(5 Pt 1):940-5.
Shu XO, Zheng Y, Cai H, Gu K, Chen Z, Zheng W, Lu W. **Soy food intake and breast cancer** survival. JAMA. 2009 Dec 9;302(22):2437-43.
Suckling J, Lethaby A, Kennedy R. **Local oestrogen for vaginal atrophy** in postmenopausal women. Cochrane Database Syst Rev. 2003;(4):CD001500. (see also Pharmacist's Letter May 2006)
Suckling J, Lethaby A, Kennedy R. **Local oestrogen for vaginal atrophy** in postmenopausal women. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD001500.
Svejme O, Ahlborg H, et al. **Early menopause** and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. BJOG. 2012 Apr 25.
Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA. Combined **estrogen and testosterone** use and risk of breast cancer in postmenopausal women. Arch Intern Med. 2006 Jul 24;166(14):1483-9.
Trock BJ, Meta-analysis of **soy intake and breast cancer risk**. J Natl Cancer Inst. 2006 Apr 5;98(7):459-71. Soy intake may be associated with a small reduction in breast cancer risk. However, this result should be interpreted with caution due to potential exposure misclassification, confounding, and lack of a dose response. Given these caveats and results of some experimental studies that suggest adverse effects from soy constituents, recommendations for high-dose isoflavone supplementation to prevent breast cancer or prevent its recurrence are premature. (InfoPOEMs: If the existing research results are true, high soy intake is associated with a small protective effect against breast cancer. However, the published studies have enough flaws to make me question this effect. (LOE = 3a-))
Uebelhack R, et al. **Black cohosh and St. John's wort** for climacteric complaints: a randomized trial. (n=301 16weeks) Obstet Gynecol. 2006 Feb;107(2 Pt 1):247-55.
Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. **Endometrial effects** of long-term treatment with **phytoestrogens**: a randomized, double-blind, placebo-controlled study. Fertil Steril. 2004 Jul;82(1):145-8, quiz 265.
U.S. Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. Ann Intern Med. 2005 May 17;142(10):855-60. (InfoPOEMS: Estrogen/progestin therapy should not routinely be used to prevent chronic disease in postmenopausal women. The Task Force making this recommendation did not address short-term (1-2 years) treatment of symptoms of menopause. The risks with chronic therapy are minimal, but so are the benefits to chronic disease prevention. (LOE = 1a))
Vaidya D, Becker DM, Bittner V, et al. **Ageing, menopause, and ischaemic heart disease** mortality in England, Wales, and the United States: modeling study of national mortality data. BMJ 2011; 343: DOI:10.1136/bmj.d5170.
Visvanathan K, et al. American society of clinical oncology clinical practice guideline update on pharmacologic interventions including **tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction**. J Clin Oncol. 2009 Jul 1;27(19):3235-58. Epub 2009 May 26.
Vogel VG, Costantino JP, Wickerham DL, et al. (NSABP). Effect of **tamoxifen vs raloxifene** on the risk of developing invasive breast cancer and other disease outcomes. The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA 2006;295:2727-2741 (InfoPOEMs: Tamoxifen (Nolvadex, Tamofen) and raloxifene (Evista) are similarly effective for reducing the risk of invasive breast cancer in postmenopausal women. Although women taking tamoxifen are at an increased risk of thromboembolic events and cataracts, they report improved sexual function compared with women taking raloxifene. All-cause mortality and overall quality-of-life were similar in both treatment groups. (LOE = 1b-))
Waetjen LE, Brown JS, Vittinghoff E, et al. The Effect of Ultralow-Dose Transdermal Estradiol on **Urinary Incontinence** in Postmenopausal Women. Obstet Gynecol. 2005 Nov;106(5):946-952.
Welton AJ, Vickers MR, Kim J, et al. for the **WISDOM** team. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ. 2008 Aug 21;337:a1190. doi: 10.1136/bmj.a1190. Combined HRT started many years after the menopause can improve health related quality of life.
Yaffe K, Vittinghoff E, Ensrud KE, Johnson KC, Diem S, Hanes V, Grady D. Effects of ultra-low-dose transdermal estradiol on **cognition** and health-related quality of life. Arch Neurol. 2006 Jul;63(7):945-50.
Zhu X, Proctor M, Bensoussan A, Wu E, Smith CA. **Chinese herbal medicine** for primary dysmenorrhoea. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005288. The review found promising evidence supporting the use of Chinese herbal medicine for primary dysmenorrhoea; however, results are limited by the poor methodological quality of the included trials.

Osteoporosis:

AAOS- Guideline on the Treatment of Symptomatic Osteoporotic Spinal Compression Fractures- **Vertebroplasty** 2010 Recommendations http://www.aaos.org/Research/guidelines/SCFsummary.pdf
Abrahamsen B. **Bisphosphonate adverse effects**, lessons from large databases. Curr Opin Rheumatol. 2010 Jul;22(4):404-9.
Abrahamsen B. **Adverse effects of bisphosphonates**. Calcif Tissue Int. 2010. Jun;86(6):421-35. Epub 2010 Apr 21.
Alibhai SM, Duong-Hua M, et al. Impact of **androgen deprivation therapy** on cardiovascular disease and diabetes. J Clin Oncol. 2009 Jul 20;27(21):3452-8. Epub 2009 Jun 8.
Aloia JF, Talwar SA, Pollack S, Yeh J. A randomized controlled trial of **vitamin D3** supplementation in African American women. Arch Intern Med. 2005 Jul 25;165(14):1618-23.

TOP

Alonso-Coello P, García-Franco AL, Guyatt G, Moynihan R. Drugs for **pre-osteoporosis: prevention or disease mongering**? BMJ. 2008 Jan 19;336(7636):126-9.

Amin S, et al. **Estradiol, testosterone**, and the risk for hip fractures in **elderly men** from the Framingham Study. Am J Med. 2006 May;119(5):426-33.

Armingeat T, et al. **Intravenous pamidronate** for **pain relief** in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. Osteoporos Int. 2006 Aug 8; [Epub ahead of print]

Avenell A, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD000227& ACP Journal Club . AUTHORS' CONCLUSIONS: Frail older people confined to institutions may sustain fewer hip and other non-vertebral fractures if given vitamin D with calcium supplements. Effectiveness of vitamin D alone in fracture prevention is unclear. There is no evidence of advantage of analogues of vitamin D compared with vitamin D. Calcitriol may be associated with an increased incidence of adverse effects. Dose, frequency, and route of administration of vitamin D in older people require further investigation.

Barrett-Connor E, Grady D, et al.; **MORE** Investigators (Multiple Outcomes of Raloxifene Evaluation). Raloxifene and **cardiovascular** events in osteoporotic postmenopausal women: four-year results from the MORE randomized trial. JAMA. 2002 Feb 20;287(7):847-57.

Bashutski JD, Eber RM, Kinney JS, et al. **Teriparatide and Osseous Regeneration** in the Oral Cavity. N Engl J Med. 2010 Oct 16. (n=40, 6 weeks, 1yr follow up)

Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, et al. Upper gastrointestinal tract safety profile of **alendronate**: the Fracture Intervention Trial. Arch Intern Med 2000;160:517-25.

Baxter NN, Habermann EB, Tepper JE, Durham SB, eta l. Risk of pelvic fractures in older women following **pelvic irradiation**. JAMA. 2005 Nov 23;294(20):2587-93. (InfoPOEMs: Pelvic irradiation significantly increases the risk of pelvic fractures in older women. Treatment for anal cancer is associated with the highest risk of pelvic fracture. (LOE = 2b-))

Bean GR, Kimler BF, Seewaldt VL. Long-term **raloxifene** in a woman at high risk for **breast cancer**. N Engl J Med. 2006 Oct 12;355(15):1620-2.

Bell Katy J L, Hayen Andrew, Macaskill Petra, et al. Value of routine **monitoring of bone mineral density** after starting bisphosphonate treatment: secondary analysis of trial data**.** BMJ 2009;338:b2266, doi: 10.1136/bmj.b2266 (Published 23 June 2009)

Berger C, Langsetmo L, Joseph L, Hanley DA, et al. Canadian Multicentre Osteoporosis Study Research Group. Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. CMAJ. 2008 Jun 17;178(13):1660-8. (CaMos) The period of accelerated loss of bone mineral density in the hip bones occurring among women and men older than 65 may be an important contributor to the increased incidence of hip fracture among patients in that age group. The extent of bone loss that we observed in both sexes indicates that, in the absence of additional risk factors or therapy, repeat testing of bone mineral density to diagnose osteoporosis could be delayed to every 5 years.

Berry SD, Samelson EJ, Hannan MT, et al. **Second hip fracture** in older men and women: the framingham study. Arch Intern Med. 2007 Oct 8;167(18):1971-6. Following a first hip fracture, 2.5% of subjects experienced a second hip fracture within 1 year, and 8.2% of subjects (9.7% of women) experienced a second hip fracture within 5 years. One-year mortality following an initial hip fracture was 15.9% compared with 1-year mortality following a second hip fracture of 24.1%.Among survivors of an initial hip fracture, the incidence of a second hip fracture is substantial. Older age and functional status may be important predictors of a second hip fracture.

Berry S, Waldron T, Winquist E, Lukka H. The use of **bisphosphonates** in men with hormone-refractory **prostate cancer**: a systematic review of randomized trials. Can J Urol. 2006 Aug;13(4):3180-8.

Bhasin S, et al. **Testosterone therapy** in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006 Jun;91(6):1995-2010. Epub 2006 May 23. Erratum in: J Clin Endocrinol Metab. 2006 Jul;91(7):2688.

Bilezikian JP. **Osteonecrosis of the jaw**--do bisphosphonates pose a risk? N Engl J Med. 2006 Nov 30;355(22):2278-81.

Bingham CO 3rd, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with **medial compartment osteoarthritis** of the knee: Results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum. 2006 Oct 30;54(11):3494-3507 [Epub ahead of print]

Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005 May 11;293(18):2257-64 & ACP Journal Club . (Oral vitamin D supplementation between 700 to 800 IU/d appears to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons. An oral vitamin D dose of 400 IU/d is not sufficient for fracture prevention.)(InfoPOEMs: Supplementation with calcium 1000 mg and vitamin D3 800 IU daily decreases the likelihood that older people will experience a first hip fracture or other nonvertebral fracture. The dose of calcium is lower than the 1500 mg daily that is recommended and usually used; the vitamin D dose is higher than the dose usually used in comparison studies with other drugs. These results conflict with 2 large studies in patients at high risk or with a previous osteoporotic fracture for whom these doses did not decrease the rate of fracture (BMJ 2005; 330:1003-06 and Lancet 2005; 365:1621-28). (LOE = 1a))

Bischoff-Ferrari HA, et al. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Arch Intern Med. 2006 Feb 27;166(4):424-30. (InfoPOEMs: Treating older women with vitamin D and calcium decreases their likelihood of experiencing a fall, although the change in fall rate does not occur quickly. The effect is more pronounced in inactive women. (LOE = 1b))

Bisphosphonate-associated **jaw osteonecrosis.** Pharmacist's Letter August 2006. (Bilezikian JP. Osteonecrosis of the jaw--do bisphosphonates pose a risk? N Engl J Med. 2006 Nov 30;355(22):2278-81. Woo SB, Hellstein JW, Kalmar JR. Bisphosphonates and osteonecrosis of the jaw. Ann Intern Med. 2006 Nov 21;145(10):792. (50 cases in those receiving po bisphosphonates for osteoporosis))

Bjelakovic G, Gluud LL, Nikolova D, et al. **Vitamin D supplementation for prevention of mortality** in adults. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD007470. DOI: 10.1002/14651858.CD007470.pub2. Vitamin D in the form of vitamin D3 seems to decrease mortality in predominantly elderly women who are mainly in institutions and dependent care. Vitamin D2, alfacalcidol, and calcitriol had no statistically significant effect on mortality. Vitamin D3 combined with calcium significantly increased nephrolithiasis. Both alfacalcidol and calcitriol significantly increased hypercalcaemia.

Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of **alendronate** on risk of fracture in women with **existing vertebral fractures**. Fracture Intervention Trial Research Group (**FIT**). Lancet 1996;348:1535-41.

Black DM, Bilezikian JP, Ensrud KE, et al. PaTH Study Investigators. One year of alendronate after one year of **parathyroid** hormone (1-84) for osteoporosis. N Engl J Med. 2005 Aug 11;353(6):555-65.

Black DM, Greenspan SL, Ensrud KE, et al.; PaTH Study Investigators. The effects of **parathyroid hormone and alendronate** alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003 Sep 25;349(13):1207-15. Epub 2003 Sep 20.

Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. **FIT** Research Group [published correction appears in J Clin Endocrinol Metab 2001;86:938]. J Clin Endocrinol Metab 2000;85:4118-24.

Black DM, Delmas PD, Eastell R, et al. **HORIZON** Pivotal Fracture Trial. **Once-yearly zoledronic** acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007 May 3;356(18):1809-22. Treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% during a 3-year period, as compared with placebo (3.3% in the zoledronic-acid group vs. 10.9% in the placebo group; relative risk, 0.30; 95% confidence interval [CI], 0.24 to 0.38) and reduced the risk of hip fracture by 41% (1.4% in the zoledronic-acid group vs. 2.5% in the placebo group; hazard ratio, 0.59; 95% CI, 0.42 to 0.83). Nonvertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively (P<0.001 for all comparisons). Zoledronic acid was also associated with a significant improvement in bone mineral density and bone metabolism markers. Adverse events, including change in renal function, were similar in the two study groups. However, serious atrial fibrillation occurred more frequently in the zoledronic acid group 1.3 vs 0.5% (in 50 vs. 20 patients, P<0.001). A once-yearly infusion of zoledronic acid during a 3-year period significantly reduced the risk of vertebral, hip, and other fractures.

Black, Dennis M., Kelly, Michael P., Genant, Harry K., et al. the Fracture Intervention Trial (FIT,FLEX) and HORIZON Pivotal Fracture Trial Steering Committees, Bisphosphonates and Fractures of the **Subtrochanteric or Diaphyseal Femur**. N Engl J Med 2010 0: NEJMoa1001086.

Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. **Mortality risk** associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA. 2009 Feb 4;301(5):513-21. In a sample of older women and men, all low-trauma fractures were associated with increased mortality risk for 5 to 10 years. Subsequent fracture was associated with increased mortality risk for an additional 5 years.

Bolland MJ, Barber PA, Doughty RN, et al.. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ. 2008 Jan 15; [Epub ahead of print] Calcium supplementation in healthy postmenopausal women is associated with upward trends in cardiovascular event rates.

Bolland Mark J, Avenell Alison, Baron John A, et al, Effect of **calcium** supplements on risk of **myocardial infarction** and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.

Boonen S, et al. Effect of osteoporosis treatments on risk of **non-vertebral fractures**: review and meta-analysis of intention-to-treat studies. Osteoporos Int. 2005 Oct;16(10):1291-8. Epub 2005 Jun 29.

Boonen S, Sellmeyer DE, Lippuner K, Orlov-Morozov A, Abrams K, Mesenbrink P,Eriksen EF, Miller PD. **Renal safety of annual zoledronic** acid infusions in osteoporotic postmenopausal women. Kidney Int. 2008 May 28. [Epub ahead of print] We found that transient changes in renal function can occur following an annual zoledronic acid infusion but, in the long term, renal function was not different from control patients.

Bonnick S, et al. Comparison of **weekly** treatment of postmenopausal osteoporosis with **alendronate versus risedronate** over two years. J Clin Endocrinol Metab. 2006 Jul;91(7):2631-7. Epub 2006 Apr 24.

Bordeleau L, Pritchard KI, Loprinzi CL, et al. Multicenter, Randomized, Cross-Over Clinical Trial of **Venlafaxine Versus Gabapentin** {venlafaxine (37.5 mg daily for 7 days followed by 75 mg daily for 21 days) versus gabapentin (300 mg once per day for 3 days, then 300 mg twice per day for 3 days, then 300 mg three times per day for 22 days)} for the Management of Hot Flashes in Breast Cancer Survivors. J Clin Oncol. 2010 Nov 8.

Brown JP, et al. **Canadian consensus conference on osteoporosis, 2006 update**. J Obstet Gynaecol Can. 2006 Feb;28(2 Suppl 1):S95-S112. http://sogc.org/guidelines/documents/JOGC-suppl-1eng-osteoporosis.pdf

Brown JP, Josse RG; Scientific Advisory Council of the Osteoporosis Society of Canada. **2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada**. CMAJ. 2002 Nov 12;167(10 Suppl):S1-34. Review. Erratum in: CMAJ. 2003 Feb 18;168(4):400. CMAJ. 2003 Mar 18;168(6):676.. CMAJ. 2003 Mar 4;168(5):544. http://www.cmaj.ca/cgi/content/full/167/10_suppl/s1

Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71:103-11.

Buchbinder, Rachelle, Osborne, Richard H., Ebeling, Peter R., et al.. A Randomized Trial of **Vertebroplasty** for Painful Osteoporotic Vertebral Fractures. N Engl J Med 2009 361: 557-568.

Cadarette SM, Katz JN, Brookhart MA, Stürmer T, Stedman MR, Solomon DH. **Relative effectiveness of osteoporosis drugs** for preventing nonvertebral fracture. Ann Intern Med. 2008 May 6;148(9):637-46. Differences in fracture risk between risedronate or raloxifene and alendronate were small. Nasal calcitonin recipients may have a higher risk for nonvertebral fractures compared with alendronate recipients.

Calle EE, Feigelson HS, Hildebrand JS, Teras LR, Thun MJ, Rodriguez C. Postmenopausal hormone use and **breast cancer** associations differ by hormone regimen and histologic subtype. Cancer. 2009 Jan 20. [Epub ahead of print] Use of E + P is more detrimental to the breast than E-only use, in terms of both ductal and lobular cancer. The findings from the current study suggest a window of 2 to 3 years for the risks of E + P both to become apparent after initial use and to attenuate after cessation.

Canalis E, Giustina A, Bilezikian JP. Mechanisms of **anabolic therapies** for osteoporosis. N Engl J Med. 2007 Aug 30;357(9):905-16.

Casele H, et al. **Bone density** changes in women who receive **thromboprophylaxis** in pregnancy. Am J Obstet Gynecol. 2006 Oct;195(4):1109-13. In this study, the incidence of clinically significant bone loss (> or = 10%) in the femur in women who received thromboprophylaxis in pregnancy is approximately 2% to 2.5% and appears to be similar, regardless of whether the patient receives low molecular weight heparin therapy or unfractionated heparin therapy.

Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of **estrogen plus progestin** on risk of fracture and bone mineral density: the Women's Health Initiative (**WHI**) randomized trial. JAMA 2003;290:1729-38.

Cauley JA, Hochberg MC, Lui LY, Palermo L, Ensrud KE, Hillier TA, Nevitt MC,

Cauley JA, Lacroix AZ, Wu L, Horwitz M, et al. Serum 25-hydroxyvitamin D concentrations and risk for **hip fractures**. Ann Intern Med. 2008 Aug 19;149(4):242-50. Low serum 25(OH) vitamin D concentrations are associated with a higher risk for hip fracture.

Cummings SR. **Long-term risk of incident vertebral fractures**. JAMA. 2007 Dec 19;298(23):2761-7. Low BMD and prevalent vertebral fractures are independently related to new vertebral fractures over 15 years of follow-up. Women with a prevalent vertebral fracture have a substantially increased absolute risk of an incident fracture, especially if they have osteoporosis diagnosed by BMD.

Cummings, Steven R., Martin, Javier San, McClung, Michael R., et al., the **FREEDOM** Trial, **Denosumab** for Prevention of Fractures in Postmenopausal Women with Osteoporosis. N Engl J Med 2009 0: NEJMoa0809493

Center JR, Bliuc D, Nguyen TV, Eisman JA. **Risk of subsequent fracture after low-trauma fracture** in men and women. JAMA. 2007 Jan 24;297(4):387-94. After an initial low-trauma fracture, absolute risk of subsequent fracture was similar for men and women. This increased risk occurred for virtually all clinical fractures and persisted for up to 10 years.

Che M, Ettinger B, Nguyen MT, Pressman AR, Johnston J. High-dose **corticosteroid** exposure and osteoporosis intervention in adults. Ann Allergy Asthma Immunol. 2006 Oct;97(4):497-501.

TOP

Chesnut CH 3d, Silverman S, Andriano K, Genant H, et al. A randomized trial of nasal spray salmon **calcitonin** in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. **PROOF** Study Group. Am J Med 2000;109:267-76. CONCLUSION: Salmon calcitonin nasal spray at a dose of 200 IU daily significantly reduces the risk of new vertebral fractures in postmenopausal women with osteoporosis The reductions in vertebral fractures in the 100-IU (RR = 0.85, 95% CI: 0.60- to 1.21) and the **400-IU** (RR = 0.84, 95% CI: 0.59- to 1.18) groups were not significantly different from placebo. .

Cheung AM, Tile L, Lee Y, et al. **Vitamin K Supplementation** in Postmenopausal Women with Osteopenia (ECKO Trial): A Randomized Controlled Trial. PLoS Med. 2008 Oct 14;5(10):e196. [Epub ahead of print] Daily 5 mg of vitamin K1 supplementation for 2 to 4 y does not protect against age-related decline in BMD, but may protect against fractures and cancers in postmenopausal women with osteopenia. More studies are needed to further examine the effect of vitamin K on fractures and cancers.

Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. **Vitamin K and the Prevention of Fractures:** Systematic Review and Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2006 Jun 26;166(12):1256-61.

Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, et al. **Risedronate** therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999;42:2309-18.

Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. **Daily and cyclic parathyroid** hormone in women receiving alendronate. N Engl J Med. 2005 Aug 11;353(6):566-75.

Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV, Krege JH. Effects of **Teriparatide** in Postmenopausal Women with Osteoporosis on **Prior Alendronate or Raloxifene**: Differences between Stopping and Continuing the Antiresorptive Agent.J Clin Endocrinol Metab. 2009 Jul 7. [Epub ahead of print] In women with osteoporosis treated with antiresorptives, greater bone turnover increases were achieved by switching to teriparatide, while greater BMD increases were achieved by adding teriparatide.

Cranney A, Adachi JD. Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. Drug Saf. 2005;28(8):721-30.

Cranney A, et al. Clinical Guidelines Committee of **Osteoporosis Canada**. **Parathyroid hormone** for the treatment of osteoporosis: a systematic review. CMAJ. 2006 Jul 4;175(1):52-9. (InfoPOEMs: There is consistent evidence that human parathyroid hormone (hPTH) reduces the risk of recurrent fracture in very high-risk women with osteoporosis and a history of fracture. An accompanying guideline reports that the number needed to treat (NNT) with hPTH 34 (teriparatide [Forteo]) for 21 months to prevent one vertebral fracture is 11 and the NNT for 21 months to prevent one nonvertebral fracture is 34. This compares with NNTs of 9 and 34, respectively, for 36 months of alendronate. Given the much lower cost and greater convenience of alendronate and other bisphosphonates, teriparatide should be reserved for a very select group of very osteoporotic patients. (LOE = 1a))

Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of **alendronate** on risk of fracture in women with **low bone density** but without vertebral fractures: results from the Fracture Intervention Trial (**FIT**). JAMA 1998;280:2077-82. CONCLUSIONS: In women with low BMD but without vertebral fractures, 4 years of alendronate safely increased BMD and decreased the risk of first vertebral deformity. Alendronate significantly reduced the risk of clinical fractures among women with osteoporosis but not among women with higher BMD. Alendronate increased BMD at all sites studied (P<.001) and reduced clinical fractures from 312 in the placebo group to 272 in the intervention group, but not significantly so (14% reduction; relative hazard [RH], 0.86; 95% confidence interval [CI], 0.73-1.01).

Cummings SR. **A 55-year-old woman with osteopenia**. JAMA. 2006 Dec 6;296(21):2601-10. (Khosla S, Melton LJ 3rd. Clinical practice. **Osteopenia**. N Engl J Med. 2007 May 31;356(22):2293-300.)

Cummings SR, Schwartz AV, Black DM. **Alendronate and atrial fibrillation**. N Engl J Med. 2007 May 3;356(18):1895-6. Serious atrial fibrillation: 1.5% alendronate vs 1% placebo during an average of 4 years of the FIT trial.

Cummings SR et al. **Lasofoxifene** in postmenopausal women with osteoporosis. N Engl J Med 2010 Feb 25; 362:686.

De Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D, et al. Esophagitis associated with the use of **alendronate**. N Engl J Med 1996;335:1016-21.

de Nijs RN, et al. STOP Investigators. **Alendronate or alfacalcidol** in **glucocorticoid-induced** osteoporosis. N Engl J Med. 2006 Aug 17;355(7):675-84.

Delmas PD, et al. **Intravenous ibandronate** injections in postmenopausal women with osteoporosis: One-year results from the dosing intravenous administration study. Arthritis Rheum. 2006 Jun;54(6):1838-46. As assessed by BMD, intravenous injections of ibandronate (2 mg every 2 months or 3 mg every 3 months) are at least as effective as the regimen of 2.5 mg orally daily, which has proven antifracture efficacy, and are well tolerated.

Dormuth CR, Carney G, Carleton B, et al. **Thiazolidinediones** and fractures in men and women. *Arch Intern Med*. 2009; 169:1395-1402.

Downey TW, et al. **Adherence and persistence** associated with the pharmacologic treatment of osteoporosis in a managed care setting. South Med J. 2006 Jun;99(6):570-5. (InfoPOEMs: Approximately half the women initially prescribed a bisphosphonate -- daily or weekly treatment -- will not be taking it after 3 months, and only 1 in 5 will be taking it after a year. Since this short duration is unlikely to provide them with meaningful benefit, the money spent on bone mineral density testing and the rest of the diagnostic work-up and follow-up, along with the cost of the initial drug therapy, is essentially wasted on 4 of 5 women diagnosed with osteoporosis. (LOE = 1b))

Ebeling PR. Clinical practice. **Osteoporosis in men**. N Engl J Med. 2008 Apr 3;358(14):1474-82.

Eneroth M, Olsson UB, Thorngren KG. **Nutritional Supplementation** Decreases Hip Fracture-related Complications. Clin Orthop Relat Res. 2006 Oct;451:212-7.

Ensrud K, et al Effect of **raloxifene** on **cardiovascular adverse events** in postmenopausal women with osteoporosis. Am J Cardiol. 2006 Feb 15;97(4):520-7. Epub 2006 Jan 4. Conclusion, we found no evidence of a beneficial or harmful effect of raloxifene on the incidence of cardiovascular events overall, or coronary or cerebrovascular events, in postmenopausal osteoporotic women at relatively low risk of cardiovascular events.

Ensrud KE, Ewing SK, Taylor BC, et al.; for the Study of Osteoporotic Fractures Research Group. Comparison of 2 Frailty Indexes for Prediction of Falls, Disability, Fractures, and Death in Older Women. Arch Intern Med. 2008 Feb 25;168(4):382-389. The simple SOF index (components of weight loss, inability to rise from a chair 5 times without using arms, and reduced energy level) predicts risk of falls, disability, fracture, and death as well as the more complex CHS index and may provide a useful definition of frailty to identify older women at risk of adverse health outcomes in clinical practice.

Etminan M, et al. Use of Oral Bisphosphonates and the Risk of Aseptic **Osteonecrosis**: A Nested Case-Control Study. J Rheumatol. 2008 Jan 15; [Epub ahead of print] In this cohort of elderly cardiovascular patients, an association was observed between oral bisphosphonate use and aseptic osteonecrosis.

Ettinger B, et al. Reduction of vertebral fracture risk in postmenopausal women with **osteoporosis** treated with **raloxifene**: a 3-yr randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (**MORE**) Investigators [correction JAMA 1999;282:2124]. JAMA 1999;282:637-45. CONCLUSIONS: In postmenopausal women with osteoporosis, raloxifene increases bone mineral density in the spine and femoral neck and reduces risk of vertebral fracture.

Ettinger B, Pressman A, Schein J, Chan J, Silver P, Connolly N. **Alendronate** use among 812 women: prevalence of gastrointestinal complaints, noncompliance with patient instructions, and discontinuation. J Managed Care Pharm 1998;4:488-92.

Favus Murray J., **Bisphosphonates for Osteoporosis**. N Engl J Med 2010; 363:2027-2035.

FDA July/11 notified healthcare professionals and patients about its ongoing review of data from published studies to evaluate whether use of **oral bisphosphonate** drugs is associated with an increased risk of cancer of the esophagus. FDA has not concluded that taking an oral bisphosphonate drug increases the risk of **esophageal cancer**. There are insufficient data to recommend endoscopic screening of asymptomatic patients.

Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of **parathyroid hormone, alendronate, or both** in men with osteoporosis. N Engl J Med. 2003 Sep 25;349(13):1216-26. Epub 2003 Sep 20.

Fogelman I, Ribot C, Smith R, et al. **Risedronate** reverses bone loss in postmenopausal women with **low bone mass**: results from a multinational, double-blind, placebo-controlled trial. **BMD-MN** Study Group. J Clin Endocrinol Metab. 2000 May;85(5):1895-900.

Formoso G, Perrone E, Maltoni S, et al. Short and long term effects of **tibolone** in postmenopausal women. Cochrane Database Syst Rev. 2012 Feb 15;2:CD008536. Tibolone, used at the daily dose of 2.5 mg, may be less effective than combined HT in alleviating menopausal symptoms although it reduced the incidence of vaginal bleeding. There was evidence that treatment with combined HT was more effective in managing menopausal symptoms than was tibolone. Available data on the long term safety of tibolone is concerning given the increase in the risk of breast cancer in women who had already suffered from breast cancer in the past and in a separate trial the increase in the risk of stroke in women whose mean age was over 60 years.

Freeman EW, Rickels K, Sammel MD, Lin H, Sondheimer SJ. Time to relapse after short- or long-term treatment of severe premenstrual syndrome with **sertraline**. Arch Gen Psychiatry. 2009 May;66(5):537-44.

Gafni RI, et al. **Tenofovir** disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. Pediatrics. 2006 Sep;118(3):e711-8. Epub 2006 Aug 21.

Gallagher JC, Levine JP. **Preventing osteoporosis** in symptomatic postmenopausal women. Menopause. 2010 Aug 5.

Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A. Hormone replacement therapy is associated with decreased survival in women with **lung cancer.** J Clin Oncol. 2006 Jan 1;24(1):59-63. Epub 2005 Nov 28.

Gaudio A, Morabito N. Pharmacological management of severe postmenopausal osteoporosis. Drugs Aging. 2005;22(5):405-17.

Gillespie WJ, Gillespie LD, Parker MJ. **Hip protectors for preventing hip fractures** in older people. Cochrane Database Syst Rev. 2010 Oct 6;10:CD001255. The effectiveness of the provision of hip protectors in reducing the incidence of hip fracture in older people is still not clearly established, although they may reduce the rate of hip fractures if made available to frail older people in nursing care.

Gnant M, Mlineritsch B, Schippinger W, et al. ABCSG-12 Trial Investigators, Marth C. Endocrine therapy plus **zoledronic acid in premenopausal breast cancer**. N Engl J Med. 2009 Feb 12;360(7):679-91. The addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival in premenopausal patients with estrogen-responsive early breast cancer.

Grant AM, Avenell A, Campbell MK, et al.; Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of **Calcium Or vitamin D**, **RECORD**): a randomised placebo-controlled trial. Lancet. 2005 May;365(9471):1621-8 & ACP Journal Club. (InfoPOEMs: The combination of calcium 1000 mg and vitamin D3 800 IU was ineffective in preventing fractures in 2 studies enrolling a total of more than 8500 participants, almost all of whom were female and at least 70 years old and either had a previous osteoporotic fracture or were at high risk. The dose of calcium is lower than the 1500 mg commonly recommended and used. These results conflict with a meta-analysis that found that the combination therapy reduced fracture rate, including hip fracture, in older patients who have not had a previous hip or nonvertebral fracture (JAMA 2005; 293:2257-64). (LOE = 1b))

Greenblatt D. Treatment of postmenopausal osteoporosis. Pharmacotherapy. 2005 Apr;25(4):574-84.

Greenspan SL, Resnick NM, Parker RA. Combination therapy with **hormone replacement and alendronate** for prevention of bone loss in elderly women: a randomized controlled trial. JAMA. 2003 May 21;289(19):2525-33.

Greenspan SL, Emkey RD, Bone HG, et al. Significant differential effects of **alendronate, estrogen, or combination** therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002 Dec 3;137(11):875-83. Summary for patients in: Ann Intern Med. 2002 Dec 3;137(11):I31.

Grey A, Bolland MJ, Wattie D, Horne A, Gamble G, Reid IR. The antiresorptive effects of a single dose of zoledronate persist for two years: a randomized, placebo-controlled trial in osteopenic postmenopausal women. J Clin Endocrinol Metab. 2009 Feb;94(2):538-44. Epub 2008 Dec 2. n=50. Antiresorptive effects of a single 5-mg dose of **zoledronate** are sustained for at least 2 yr. The magnitudes of the effects on markers of bone turnover and bone mineral density are comparable at 12 and 24 months. Administration of zoledronate at intervals of up to 2 yr may be associated with antifracture efficacy; clinical trials to investigate this possibility are justified.

Grossman JM, Gordon R, Ranganath VK, et al. **American College of Rheumatology (ACR) 2010** recommendations for the prevention and treatment of **glucocorticoid-induced osteoporosis**. Arthritis Care Res (Hoboken). 2010 Jul 26.

Hanley DA, Cranney A, Jones G, et al. **Vitamin D in adult** health & disease: a review and **guideline statement from Osteoporosis Canada**–summary.CMAJ 2010 0: cmaj.091062.

Harris ST, Watts NB, Genant HK, et al. Effects of **risedronate** treatment on vertebral and nonvertebral fractures in women with postmenopausal **osteoporosis**: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (**VERT**) Study Group. JAMA 1999;282:1344-52. Treatment with 5 mg/d of risedronate, compared with placebo, decreased the cumulative incidence of new vertebral fractures by 41 % (95% confidence interval [CI], 18%-58%) over 3 years (11.3 % vs 16.3%; P= .003). A fracture reduction of 65% (95% CI, 38%-81 %) was observed after the first year (2.4% vs 6.4%; P<.001). The cumulative incidence of nonvertebral fractures over 3 years was reduced by 39% (95% CI, 6%-61 %) (5.2 % vs 8.4%; P = .02). Bone mineral density increased significantly compared with placebo at the lumbar spine (5.4% vs 1.1 %), femoral neck (1.6% vs -1.2%), femoral trochanter (3.3% vs -0.7%), and midshaft of the radius (0.2% vs -1.4%). Bone formed during risedronate treatment was histologically normal. The overall safety profile of risedronate, including gastrointestinal safety, was similar to that of placebo. CONCLUSIONS: These data suggest that risedronate therapy is effective and well tolerated in the treatment of women with established postmenopausal osteoporosis who had at least 1 **vertebral fracture at baseline**.

Health Canada May 2006: The **RUTH** study demonstrated an **increase in mortality due to stroke** for Evista compared to placebo. The incidence of stroke mortality was 1.5 per 1,000 women per year for placebo versus 2.2 per 1,000 women per year for Evista (p=0.0499). The incidence of stroke, myocardial infarction, hospitalized acute coronary syndrome, cardiovascular mortality, or overall mortality (all causes combined) was comparable for Evista and placebo. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/evista_hpc-cps_e.html Barrett-Connor E, et al.; Raloxifene Use for The Heart (**RUTH**) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N=10,101 5.6yrs N Engl J Med. 2006 Jul 13;355(2):125-37. (InfoPOEMs: For every 1000 wome

TOP

for 5 years, we can expect 4 to 5 additional strokes, 6 additional episodes of venous thromboembolism (VTE), 6 fewer invasive breast cancers, and 6 to 7 fewer clinical vertebral fractures. The cost for this mixed bag of benefits and harms would be approximately $1000 per woman per year, for a total cost of $5,000,000 at current drug prices. (LOE = 1b))

Health Canada May/12: Cases of severe, sometimes **fatal, symptomatic hypocalcemia associated with XGEVA (denosumab)** treatment have been reported in cancer patients with bone metastases

Heaney RP, Zizic TM, Fogelman I, Olszynski WP, et al. **Risedronate** reduces the risk of **first vertebral fracture in osteoporotic women**. Osteoporos Int. 2002;13(6):501-5.

Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident **atrial fibrillation** in women. Arch Intern Med. 2008 Apr 28;168(8):826-31. Ever use of alendronate was associated with an increased risk of incident AF in clinical practice.

Hippisley-Cox Julia, Coupland Carol, Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of **QFractureScores.** BMJ 2009;339:b4229, doi: 10.1136/bmj.b4229 (Published 19 November 2009)

Hippisley-Cox J, Coupland C. Derivation and validation of **updated QFracture algorithm** to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ. 2012 May 22;344:e3427.

Hoes JN, et al. EULAR evidence-based management of systemic **glucocorticoid therapy** in rheumatic diseases. Ann Rheum Dis. 2007 Dec;66(12):1560-7. Epub 2007 Jul 27. **Algorithm** provided

Holder KK, Kerley SS. Alendronate for fracture prevention in postmenopause. Am Fam Physician. 2008 Sep 1;78(5):579-81. For vertebral fractures, a 45 percent relative risk reduction was found (relative risk [RR] = 0.55; 95% confidence interval [CI], 0.45 to 0.67). This was significant for primary prevention, with a 45 percent relative risk reduction (RR = 0.55; 95% CI, 0.38 to 0.80) and 2 percent absolute risk reduction; and for secondary prevention, with 45 percent relative risk reduction (RR = 0.55; 95% CI, 0.43 to 0.69) and 6 percent absolute risk reduction. For nonvertebral fractures, a 16 percent relative risk reduction was found (RR = 0.84; 95% CI, 0.74 to 0.94). This was significant for secondary prevention, with a 23 percent relative risk reduction (RR = 0.77; 95% CI, 0.64 to 0.92) and a 2 percent absolute risk reduction, but not for primary prevention (RR = 0.89; 95% CI, 0.76 to 1.04). There was a 40 percent relative risk reduction in hip fractures (RR = 0.60; 95% CI, 0.40 to 0.92), but only secondary prevention was significant, with a 53 percent relative risk reduction (RR = 0.47; 95% CI, 0.26 to 0.85) and a 1 percent absolute risk reduction. At 10 mg of alendronate per day, clinically important and statistically significant reductions in vertebral, nonvertebral, hip, and wrist fractures were observed for secondary prevention. The authors found no statistically significant results for primary prevention, with the exception of vertebral fractures, for which the reduction was clinically important.

Howe TE, Shea B, Dawson LJ, et al. **Exercise for preventing and treating osteoporosis** in postmenopausal women. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD000333. DOI: 10.1002/14651858.CD000333.pub2. Our results suggest a relatively small statistically significant, but possibly important, effect of exercise on bone density compared with control groups. Exercise has the potential to be a safe and effective way to avert bone loss in postmenopausal women.

Ing-Lorenzini K, Desmeules J, Plachta O, Suva D, Dayer P, Peter R. **Low-energy femoral fractures** associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital. Drug Saf. 2009;32(9):775-85. doi: 10.2165/00002018-200932090-00002.

Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between **fractures and mortality**: results from the Canadian Multicentre Osteoporosis Study. CMAJ. 2009 Aug 4. [Epub ahead of print]

Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, **medroxyprogesterone** acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. Lancet Oncol. 2009 Dec 4.

Jaakkola S, Lyytinen H, Pukkala E, Ylikorkala O. **Endometrial cancer** in postmenopausal women using estradiol-progestin therapy. Obstet Gynecol. 2009 Dec;114(6):1197-204. Use of a continuous rather than a sequential estradiol-progestin regimen decreases the risk of endometrial cancer, whereas the route of administration or type of progestin does not differ in terms of endometrial cancer risk.

Jackson RD, LaCroix AZ, Gass M, et al.; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006 Feb 16;354(7):669-83.
Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones. (InfoPOEMs: The ability of a small dose of calcium and vitamin D to prevent fractures in healthy community-dwelling women is modest at best. This study used a relatively low dose of vitamin D (less than the 700 IU to 800 IU found most beneficial in previous studies), and the patients were generally at low risk of fracture. Perhaps that explains the discordance of these findings with the bulk of the literature on this topic. (LOE = 1b))

Jacoby Vanessa L.; Grady Deborah; Wactawski-Wende Jean; et al. **Oophorectomy vs Ovarian Conservation With Hysterectomy**: Cardiovascular Disease, Hip Fracture, and Cancer in the Women's Health Initiative Observational Study. Arch Intern Med. 2011;171(8):760-768.

Järvinen TL, Sievänen H, Khan KM, Heinonen A, Kannus P. Shifting the focus in fracture prevention **from osteoporosis to falls**. BMJ. 2008 Jan 19;336(7636):124-6.

Jones GL, Ledger W, Mitchell C. Suspected **premature menopause**. BMJ. 2008 Apr 12;336(7648):833.

Kakaria PJ, Nashel DJ, Nylen ES. Debilitating muscle cramps after **teriparatide** therapy. Ann Intern Med. 2005 Feb 15;142(4):310.

Kallmes, David F., Comstock, Bryan A., Heagerty, Patrick J., et al. A Randomized Trial of **Vertebroplasty** for Osteoporotic Spinal Fractures. N Engl J Med 2009 361: 569-579.

Karim R, Dell RM, Greene DF, et al. Hip fracture in postmenopausal women **after cessation of hormone therapy**: results from a prospective study in a large health management organization. Menopause. 2011 Nov;18(11):1172-7.

Kelly R, Taggart H. Incidence of gastrointestinal side effects due to **alendronate** is high in clinical practice. BMJ 1997;315:1235.

Kahn SE, et al. **Rosiglitazone-associated fractures** in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008 May;31(5):845-51. Epub 2008 Jan 25. Further investigation into the risk factors and underlying pathophysiology for the increased fracture rate in women taking rosiglitazone is required to relate them to preclinical data and better understand the clinical implications of and possible interventions for these findings.

Kemmler Wolfgang; von Stengel Simon; Engelke Klaus; et al. **Exercise** Effects on Bone Mineral Density, Falls, Coronary Risk Factors, and Health Care Costs in Older Women: The Randomized Controlled Senior Fitness and Prevention (**SEFIP**) Study. Arch Intern Med. 2010;170(2):179-185.

Khan AA, Sándor GK, Dore E, et al. Canadian Association of Oral and Maxillofacial Surgeons. **Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw**. J Rheumatol. 2008 Jul;35(7):1391-7. Epub 2008 Jun 1. Erratum in: J Rheumatol. 2008 Aug;35(8):1688. J Rheumatol. 2008 Oct;35(10):2084.

Khosla S. Update in **male osteoporosis**. J Clin Endocrinol Metab. 2010 Jan;95(1):3-10.

Khosla S, Burr D, Cauley J, Dempster DW,et al.; **American** Society for Bone and Mineral Research. **Bisphosphonate-associated osteonecrosis** of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007 Oct;22(10):1479-91.

Knox SS, Jackson T, Javins B, et al. Implications of **Early Menopause** in Women Exposed to **Perfluorocarbons**. J Clin Endocrinol Metab. 2011 Mar 16.

Korownyk, Christina, Allan, G. Michael, Kolber, Michael R. **Bone mineral density testing**: Too much of a good thing? Can Fam Physician 2010 56: 1299.

Korpelainen Raija; Keinanen-Kiukaanniemi Sirkka; Nieminen Pentti; et al. Long-term Outcomes of **Exercise**: Follow-up of a Randomized Trial in Older Women With Osteopenia. Arch Intern Med. 2010;170(17):1548-1556.

Lacy MQ, et al. Mayo clinic consensus statement for the use of **bisphosphonates in multiple myeloma**. Mayo Clin Proc. 2006 Aug;81(8):1047-53.

Langsetmo L, Nguyen TV, Nguyen D, et al. Independent external validation of **nomograms for predicting risk of low-trauma fracture and hip fracture** CMAJ 2010 0: cmaj.100458.

Lenart BA, Lorich DG, Lane JM. **Atypical fractures** of the femoral diaphysis in postmenopausal women taking **alendronate**. N Engl J Med. 2008 Mar 20;358(12):1304-6.

Leslie WD, Berger C, Langsetmo L, et al. Construction and validation of a simplified fracture risk assessment tool for Canadian women and men: results from the CaMos and Manitoba BMD cohorts. Osteoporos Int. (**CAROC** 2010) In press.
h ttp://osteoporosis.bluerush.ca/www/pdf/caroc_oct_2010.pdf

Leslie WD., Morin S, Lix LM. A Before-and-After Study of **Fracture Risk Reporting** and Osteoporosis treatment Initiation. *Ann Intern Med* November 2, 2010 153:580-586.

Levis S, Strickman-Stein N, Ganjei-Azar P, et al. Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial. Arch Intern Med. 2011;171 (15):1363-1369. Soy isoflavone supplementation had no effect on bone mineral density over the 2 years of this study, but increased the percentage of women reporting hot flashes. (LOE = 1b-)

Li Kuanrong, Kaaks R, Linseisen J, et al. Associations of **dietary calcium intake and calcium supplementation** with **myocardial infarction** and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart 2012. (In press)

Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral **alendronate** on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The **Alendronate Phase III** Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437-43.

Liberman UA. **Long-term safety of bisphosphonate** therapy for osteoporosis : a review of the evidence. Drugs Aging. 2006;23(4):289-98.

Lim LS, Fink HA, Kuskowski MA, Taylor BC, Schousboe JT, Ensrud KE; for the Osteoporotic Fractures in Men (MrOS) Study Group. Loop Diuretic Use and Increased Rates of Hip Bone Loss in Older Men: The Osteoporotic Fractures in Men Study. Arch Intern Med. 2008 Apr 14;168(7):735-740. We conclude that loop diuretic use in older men is associated with increased rates of hip bone loss. These results suggest that the potential for bone loss should be considered when **loop diuretics** are prescribed to older patients in clinical practice.

Lim LS, Hoeksema LJ, Sherin K; **ACPM** Prevention Practice Committee. **Screening** for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. Am J Prev Med. 2009 Apr;36(4):366-75.

Lippman ME, et al. Effect of **raloxifene** on the incidence of **invasive breast cancer** in postmenopausal women with osteoporosis categorized by breast cancer risk. (From MORE & CORE trials)Clin Cancer Res. 2006 Sep 1;12(17):5242-7.

Liu RH, Albrecht J, Werth VP. Cross-sectional study of bisphosphonate use in dermatology patients receiving **long-term oral corticosteroid** therapy. Arch Dermatol. 2006 Jan;142(1):37-41.

Liu H, Michaud K, et al. The **Cost-effectiveness** of Therapy With **Teriparatide** and Alendronate in Women With Severe Osteoporosis. Arch Intern Med. 2006 Jun 12;166(11):1209-17.

Liu H, Paige NM, Goldzweig CL, Wong E, et al. **Screening for osteoporosis in men**: a systematic review for an American College of Physicians guideline. Ann Intern Med. 2008 May 6;148(9):685-701. Review. Summary for patients in: Ann Intern Med. 2008 May 6;148(9):I35. Key risk factors for low BMD-mediated fracture include increased age, low body weight, weight loss, physical inactivity, prolonged corticosteroid use, previous osteoporotic fracture, and androgen deprivation therapy. Non-DXA tests either are too insensitive or have insufficient data to reach conclusions.

Long CY, Liu CM, Hsu SC, Wu CH, Wang CL, Tsai EM. A randomized comparative study of the effects of oral and **topical** estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. Menopause. 2006 Sep-Oct;13(5):737-43.

Lopez LM, Edelman A, Chen-Mok M, Trussell J, Helmerhorst FM. **Progestin-only contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Apr 13;4:CD008815. We found little evidence of weight gain when using POCs.
Mean gain was less than 2 kg for most studies up to 12 months, and usually similar for the comparison group using another contraceptive.

Luckey M, Kagan R, Greenspan S, Bone H, Kiel RD, Simon J, Sackarowitz J, Palmisano J, Chen E, Petruschke RA, de Papp AE. Once-weekly **alendronate 70 mg and raloxifene 60 mg** daily in the treatment of postmenopausal osteoporosis. Menopause. 2004 Jul-Aug;11(4):405-15.

Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C,et al. the **HORIZON** Recurrent Fracture Trial. **Zoledronic** Acid and Clinical Fractures and Mortality after Hip Fracture. N Engl J Med. 2007 Sep 17; [Epub ahead of print] An annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a **reduction in the rate of new clinical fractures and improved survival**.

Mackey DC, Lui LY, Cawthon PM, et al. Study of Osteoporotic Fractures (SOF) and Osteoporotic Fractures in Men Study (MrOS) Research Groups. **High-trauma fractures** and low bone mineral density in older women and men. JAMA. 2007 Nov 28;298(20):2381-8. Similar to low-trauma nonspine fractures, high-trauma nonspine fractures are associated with low BMD and increased risk of subsequent fracture in older adults. High-trauma nonspine fractures should be included as outcomes in osteoporosis trials and observational studies.

Maclean C, Newberry S, Maglione M, et al. **Systematic Review**: Comparative Effectiveness of Treatments to **Prevent Fractures** in Men & Women with Low Bone Density or Osteoporosis. Ann Intern Med. 2007 Dec 17; [Epub ahead of print] Although good eviden
agents are effective in preventing osteoporotic fractures, data are insufficient to determine the relative efficacy or safety of these agents.

TOP

Magliano DJ, Rogers SL, Abramson MJ, Tonkin AM. Hormone therapy and **cardiovascular disease**: a systematic review and meta-analysis. BJOG. 2006 Jan;113(1):5-14.

Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista (**CORE**): **breast cancer incidence** in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004; 96:1751-61.

Martino S, Disch D, Dowsett SA, Keech CA, Mershon JL. Safety assessment of **raloxifene over eight years** in a clinical trial setting. Curr Med Res Opin. 2005 Sep;21(9):1441-52.

Mauck KF, Cuddihy MT, Atkinson EJ, Melton LJ 3rd. Use of clinical prediction rules in detecting osteoporosis in a population-based sample of postmenopausal women. Arch Intern Med 2005;165:530-36. (InfoPOEMs: Clinical prediction rules for low bone mineral density have limited usefulness in postmenopausal women. They may be most useful in selecting women to screen who are between 60 and 65 years old. Universal screening is already advocated for women 65 and older. For women younger than 60 the usefulness is limited by a combination of poor specificity of the rules and poor correlation of bone density with fracture risk. However, a low prediction rule score might assure a few women that they don't need to be tested. (LOE = 1b))

Mazziotti G, Canalis E, Giustina A. **Drug-induced osteoporosis**: mechanisms and clinical implications. Am J Med. 2010 Oct;123(10):877-84.

McClung MR, Geusens P, Miller PD, et al. Effect of **risedronate** on the risk of hip fracture in elderly women. Hip Intervention Program Study Group (**HIP**). N Engl J Med 2001;344:333-40. CONCLUSIONS: Risedronate significantly reduces the risk of hip fracture among elderly women with confirmed **osteoporosis** but not among elderly women selected primarily on the basis of risk factors other than low bone mineral density. RESULTS: Overall, the incidence of hip fracture among all the women assigned to risedronate was 2.8%, as compared with 3.9 % among those assigned to placebo (relative risk, 0.7; 95 percent confidence interval, 0.6 to 0.9; P=0.02). In the group of women with osteoporosis (those 70 to 79 years old), the incidence of hip fracture among those assigned to risedronate was 1.9 percent, as compared with 3.2 percent among those assigned to placebo (relative risk, 0.6; 95 percent confidence interval, 0.4 to 0.9; P=0.009). In the group of women selected primarily on the basis of nonskeletal risk factors (those at least 80 years of age), the incidence of hip fracture was 4.2 percent among those assigned to risedronate and 5.1 percent among those assigned to placebo (P=0.35).

McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of **teriparatide** and **alendronate** in increasing bone mass. Arch Intern Med. 2005 Aug 8-22;165(15):1762-8.

McClung MR, Lewiecki EM, Cohen SB, et al. AMG 162 Bone Loss Study Group. **Denosumab** in postmenopausal women with low bone mineral density. N Engl J Med. 2006 Feb 23;354(8):821-31.

McKague M, Jorgenson D, Buxton KA. **Ocular side effects of bisphosphonates**: A case report and literature review. Can Fam Physician. 2010 Oct;56(10):1015-7.

Medical Letter Aug 14/28,2006. **Intravenous Ibandronate** (Boniva)

Medical Letter - Treatment Guidelines. **Drugs for Postmenopausal Osteoporosis**. **Oct 2008**.

Menopause: The Journal of The North American Menopause Society Vol. 17, No. 2, pp. 242/255 DOI: 10.1097/gme.0b013e3181d0f6b9. {tapering estrogen when stopping results in similar side effects to just stopping without taper.}

Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of **thiazolidinediones and fracture risk**. Arch Intern Med. 2008 Apr 28;168(8):820-5. This analysis provides further evidence of a possible association between long-term use of thiazolidinediones and fractures, particularly of the hip and wrist, in patients with diabetes mellitus.

Michaelsson K, Bergstrom R, Mallmin H, Holmberg L, Wolk A, Ljunghall S. Screening for osteopenia and osteoporosis: selection by body composition. Osteoporos Int 1996;6:120-6.

Michalska D, et al. The effect of **raloxifene after discontinuation** of long-term **alendronate** treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2006 Mar;91(3):870-7. Epub 2005 Dec 13.

Mok Chi Chiu, Ying King Yee, To Chi Hung, et al. **Raloxifene for prevention of glucocorticoid-induced bone loss**: a 12-month randomised double-blinded placebo-controlled trial. Ann Rheum Dis 2011;70:778-784 Published Online First: 27 December 2010.

National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Accessed June 21, 2004, at: http://www.nof.org/professionals/clinical/clinical.htm.

Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: a review of the evidence for the **U.S. Preventive Services Task Force**. Ann Intern Med 2002;137:529-41.

Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of **parathyroid hormone** (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.RESULTS: New vertebral fractures occurred in 14 percent of the women in the placebo group and in 5 percent and 4 percent, respectively, of the women in the 20-microg and 40-microg parathyroid hormone groups; the respective relative risks of fracture in the 20-microg and 40-microg groups, as compared with the placebo group, were 0.35 and 0.31 (95 percent confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). New nonvertebral fragility fractures occurred in 6 percent of the women in the placebo group and in 3 percent of those in each parathyroid hormone group (relative risk, 0.47 and 0.46, respectively [95 percent confidence intervals, 0.25 to 0.88 and 0.25 to 0.861). As compared with placebo, the 20-microg and 40-microg doses of parathyroid hormone increased bone mineral density by 9 and 13 more percentage points in the lumbar spine and by 3 and 6 more percentage points in the femoral neck; the 40-microg dose decreased bone mineral density at the shaft of the radius by 2 more percentage points. Both doses increased total-body bone mineral by 2 to 4 more percentage points than did placebo. Parathyroid hormone had only minor side effects (occasional nausea and headache). CONCLUSIONS: Treatment of postmenopausal osteoporosis with parathyroid hormone (1-34) decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body bone mineral density; and is well tolerated. The 40-microg dose increased bone mineral density more than the 20-microg dose but had similar effects on the risk of fracture and was more likely to have side effects.

Nevitt MC, Chen P, Dore RK, Reginster JY, Kiel DP, Zanchetta JR, Glass EV, Krege JH. Reduced risk of back pain following **teriparatide** treatment: a meta-analysis. Osteoporos Int. 2005 Sep 2; [Epub ahead of print]

Nice Oct 2008: Primary Prevention http://guidance.nice.org.uk/TA160 & Secondary Prevention of Osteoporosis http://guidance.nice.org.uk/TA161 **Guidelines**

North American Menopause Society. **NAMS**: Management of **osteoporosis in postmenopausal women**: **2010** position statement of The North American Menopause Society. Menopause. **2010** Jan-Feb;17(1):25-54.

North American Menopause Society. **Management of osteoporosis in postmenopausal women: 2006** position statement of The North American Menopause Society. Menopause. 2006 May-Jun;13(3):340-67; quiz 368-9.

Obermayer-Pietsch BM, Marin F, McCloskey EV, et al.; for the EUROFORS Investigators. Effects of **Two Years of Daily Teriparatide** Treatment on Bone Mineral Density in Postmenopausal Women with Severe Osteoporosis with and without Prior Antiresorptive Treatment. J Bone Miner Res. 2008 May 27. [Epub ahead of print] Nausea (13.3%) and arthralgia (11.7%) were the most commonly reported adverse events. Asymptomatic hypercalcemia was reported in 5.0% of patients. Teriparatide treatment for 24 months is associated with a significant increase in BMD in patients with and without previous AR use. Prior AR treatment modestly blunted the BMD response to teriparatide. Safety was consistent with current prescribing label information.

O'donnell S, Cranney A, Wells G, Adachi J, Reginster J. Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005326.

Orwoll E, Alendronate for the treatment of **osteoporosis in men**. N Engl J Med. 2000 Aug 31;343(9):604-10.

Orwoll E, et al. Osteoporotic Fractures in **Men** Study Group. Endogenous **testosterone** levels, physical performance, and fall risk in older men. Arch Intern Med. 2006 Oct 23;166(19):2124-31. Falls were common among older men. Fall risk was higher in men with lower bioavailable testosterone levels. The effect of testosterone level was independent of poorer physical performance, suggesting that the effect of testosterone on fall risk may be mediated by other androgen actions.

Quandt SA, Thompson DE, et al. Fracture Intervention Trial Research Group. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of-1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. (**FIT**). Mayo Clin Proc. 2005 Mar;80(3):343-9.

Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Forciea MA, Owens DK; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. **Screening for osteoporosis in men**: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008 May 6;148(9):680-4. Summary for patients in: Ann Intern Med. 2008 May 6;148(9):I35.

Pack AM, Morrell MJ, Randall A, et al. Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. Neurology. 2008 Apr 29;70(18):1586-93. In contrast, those treated with carbamazepine, lamotrigine, and valproate did not have detectable adverse effects on bone turnover or bone mineral density. These results raise **concerns about the long-term effects of phenytoin monotherapy on bone** in young women with epilepsy.

Palmieri C, Macgregor T, Girgis S, Vigushin D. Serum 25 **hydroxyvitamin D** levels in early and advanced **breast cancer**. J Clin Pathol. 2006 Oct 17; [Epub ahead of print]

Pham AN, Datta SK, Weber TJ, et al. **Cost-Effectiveness of Oral Bisphosphonates** for Osteoporosis at Different Ages and Levels of **Life Expectancy**. J Am Geriatr Soc. 2011 Aug 30. doi: 10.1111/j.1532-5415.2011.03571.x.

Papaioannou, Alexandra, Morin, Suzanne, Cheung, Angela M., et al. **2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada**: summary CMAJ 2010 0: cmaj.100771.

Parker M, Johansen A. **Hip fracture**. BMJ. 2006 Jul 1;333(7557):27-30.

Pharmacists Letter. **New Developments with Bisphosphonate** Therapy. June 2007.

Planas J, Trilla E, Raventós C, et al. Alendronate decreases the fracture risk in patients with prostate cancer on **androgen-deprivation therapy** and with severe osteopenia or osteoporosis. BJU Int. 2009 Jun 22. [Epub ahead of print]

Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of **calcium** and supplementation with **cholecalciferol (vitamin D3)** for prevention of fractures in primary care. BMJ. 2005 Apr 30;330(7498):1003 & ACP Journal Club.

Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. Arch Intern Med. 2008 Jan 14;168(1):103-8. Patients with a history of falling and vitamin D insufficiency living in sunny climates benefit from ergocalciferol supplementation in addition to calcium, which is associated with a 19% reduction in the relative risk of falling, mostly in winter.

Prince RL, et al. Effects of **calcium** supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Supplementation with calcium carbonate tablets supplying 1200 mg/d is ineffective as a public health intervention in preventing clinical fractures in the ambulatory elderly population owing to poor long-term compliance, but it is effective in those patients who are compliant. Arch Intern Med. 2006 Apr 24;166(8):869-75. (InfoPOEMs: In women older than 70 years, calcium supplementation does not decrease fracture risk. In women who took at least 80% of their dosage, however, fractures were significantly decreased. There were not enough hip fractures in the study groups to determine whether calcium had any effect on hip fracture. (LOE = 1b-))

Prithwish De, C. Ineke Neutel, Ivo Olivotto, et al. **Breast Cancer Incidence and Hormone Replacement Therapy in Canada**. JNCI J Natl Cancer Inst first published online September 23, 2010 doi:10.1093/jnci/djq345.

Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Forciea MA, Owens DK; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. **Pharmacologic treatment** of low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008 Sep 16;149(6):404-15.

QFractureScore http://www.qfracture.org/

Rad M, et al. Comparative effects of a contraceptive **vaginal ring** delivering a nonandrogenic progestin & **continuous ethinyl estradiol** & a **combined oral contraceptive** containing levonorgestrel on **hemostasis** variables. Am J Obstet Gynecol. 2006 Jul;195(1):72-7. Epub 2006 Mar 20.

Rahmani, Poupak, Morin, Suzanne. **Prevention of osteoporosis**-related fractures among postmenopausal women and older men. CMAJ 2009 0: cmaj.080709

Raisz LG. Clinical practice. **Screening for osteoporosis**. N Engl J Med. 2005 Jul 14;353(2):164-71.

Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on **Glucocorticoid-Induced Osteoporosis**. Arthritis Rheum 2001;44:1496-503.

Reginster JY, Felsenberg D, Boonen S, et al. Effects of long-term **strontium** ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum. 2008 May 31;58(6):1687-1695. [Epub ahead of print] Our findings indicate that treatment of postmenopausal osteoporosis with strontium ranelate results in a sustained reduction in the incidence of osteoporotic nonvertebral fractures, including hip fractures, and vertebral fractures over 5 years.

Reginster J, Minne HW, Sorensen OH, Hooper M, et al. Randomized trial of the effects of **risedronate** on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (**VERT**) Study Group. Osteoporos Int 2000;11:83-91.

Reid IR, Brown JP, Burckhardt P, et al. Intravenous **zoledronic** acid in postmenopausal women with **low bone mineral density**. N Engl J Med. 2002 Feb 28;346(9):653-61.

Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily **risedronate** in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res 2000;15:1006-13.

Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of **zoledronic** acid with risedronate for Paget's disease. N Engl J Med. 2005 Sep 1;353(9):898-908.

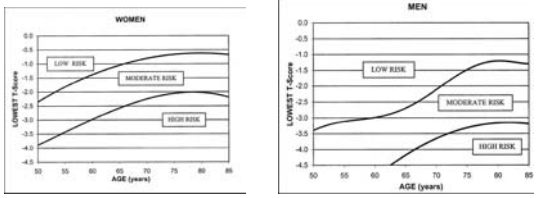
Reid IR, Mason B, et al. Randomized controlled trial of **calcium** in healthy older women. Am J Med. 2006 Sep;119(9):777-85.

Reid DM, et al.; HORIZON investigators. **Zoledronic acid and risedronate** in the prevention and treatment of **glucocorticoid-induced** osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2009 Apr 11;373(967

Ringe JD, Faber H, Fahramand P, Schacht E. **Alfacalcidol** versus plain vitamin D in the treatment of **glucocorticoid/inflammation-induced osteoporosis**. J Rheumatol Suppl. 2005 Sep;76:33-40.

TOP

Rizzoli R, Greenspan SL, Bone G 3d, Schnitzer TJ, Watts NB, Adami S, et al. Two-year results of **once-weekly** administration of **alendronate** 70 mg for the treatment of postmenopausal osteoporosis. J Bone Miner Res 2002;17:1988-96.
Robbins J, Aragaki AK, Kooperberg C, et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. JAMA. 2007 Nov 28;298(20):2389-98. This **algorithm, based on 11 clinical factors**, may be useful to predict the 5-year risk of hip fracture among postmenopausal women of various ethnic backgrounds.
Rosen CJ. Clinical practice. Postmenopausal osteoporosis. N Engl J Med. **2005** Aug 11;353(6):595-603.
Rosen CJ, et al. **Fosamax** Actonel Comparison Trial Investigators. Treatment with once-weekly alendronate 70 mg vs once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study.J Bone Miner Res.2005 Jan;20(1):141-51.Epub 2004 Sep29.
Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related **osteonecrosis** of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Oct;102(4):433-41. Epub 2006 Jul 31.
Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on **bisphosphonate-related osteonecrosis of the jaws**--2009 update. J Oral Maxillofac Surg. 2009 May;67(5 Suppl):2-12.
Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. **Alendronate** for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med 1998;339:292-9.
Saag KG, Shane E, Boonen S, Marín F, et al. **Teriparatide** or Alendronate in **Glucocorticoid-Induced Osteoporosis**. N Engl J Med. 2007 Nov 15;357(20):2028-2039. Among patients with osteoporosis who were at high risk for fracture, bone mineral density increased more in patients receiving teriparatide than in those receiving alendronate.
Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of **teriparatide versus alendronate** for treating **glucocorticoid**-induced osteoporosis: Thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009 Oct 29;60(11):3346-3355.
Sainz M., et al. **Strontium ranelate may cause alopecia** BMJ 2009;338:b1494, doi: 10.1136/bmj.b1494
Salpeter SR, Cheng J, Thabane L, et al. Bayesian meta-analysis of **hormone therapy** and **mortality** in **younger** postmenopausal women. Am J Med. 2009 Nov;122(11):1016-1022.e1.
Sanders Kerrie M.; Stuart Amanda L.; Williamson Elizabeth J.; et al. **Annual High-Dose Oral Vitamin D (500,000IU x1/yr for 3-5yrs**: increased falls & fractures) and Falls and Fractures in Older Women: A Randomized Controlled Trial. JAMA. 2010;303(18):1815-1822.
Sato Y, Iwamoto J, Kanoko T, Satoh K. **Risedronate** sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Arch Intern Med. 2005 Aug 8-22;165(15):1743-8.
Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with **risedronate** and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med. 2005 Aug 8-22;165(15):1737-42.
Schousboe JT, Nyman JA, Kane RL, Ensrud KE. **Cost-effectiveness** of alendronate therapy for **osteopenic** postmenopausal women. Ann Intern Med. 2005 May 3;142(9):734-41.
Schousboe JT, Ensrud KE, Nyman JA, Melton LJ 3rd, Kane RL. **Universal bone densitometry screening** combined with alendronate therapy for those diagnosed with osteoporosis is highly cost-effective for elderly women. J Am Geriatr Soc. 2005 Oct;53(10):1697-704.
Schwartz AV, et al. **Thiazolidinedione** use and **bone loss** in older diabetic adults. J Clin Endocrinol Metab. 2006 Sep;91(9):3349-54. Epub 2006 Apr 11.
Sedghizadeh PP, Stanley K, Caligiuri M, Hofkes S, Lowry B, Shuler CF. Oral bisphosphonate use and the prevalence of **osteonecrosis of the jaw**: An institutional inquiry. J Am Dent Assoc. 2009 Jan;140(1):61-6. These patients represented one in 23 of the patients receiving alendronate, or approximately **4 percent of the population**. The findings from this study indicated that even short-term oral use of alendronate led to ONJ in a subset of patients after certain dental procedures were performed.
Seeman E, Delmas PD. **Bone quality**--the material and structural basis of bone strength and fragility. N Engl J Med. 2006 May 25;354(21):2250-61.
Shane E, Burr D, Ebeling PR, Abrahamsen B, et al. **Atypical subtrochanteric and diaphyseal femoral fractures**: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. (ASBMR) 2010 Sep 14.
Sharpe KH, McClements P, Clark DI, et al. Reduced risk of oestrogen receptor positive **breast cancer** among peri- and post-menopausal women in **Scotland following a striking decrease** in use of hormone replacement therapy. Eur J Cancer. 2010 Jan 30.
Shimon I, Eshed V, Doolman R, Sela BA, Karasik A, Vered I. Alendronate for osteoporosis in men with androgen-repleted hypogonadism. Osteoporos Int. 2005 Dec;16(12):1591-6. Epub 2005 Mar 15.
Siffledeen JS, Fedorak RN, Siminoski K, et al. Randomized trial of etidronate plus calcium and vitamin D for treatment of low bone mineral density in **Crohn's disease**. Clin Gastroenterol Hepatol. 2005 Feb;3(2):122-32. Low bone mineral density is frequently associated with Crohn's disease. Supplementation with daily calcium and vitamin D is associated with increases in bone mineral density. The addition of oral etidronate does not further enhance bone mineral density.
Siminoski K, Leslie WD, Frame H, Hodsman A, Josse RG, Khan A, Lentle BC,Lévesque J, Lyons DJ, Tarulli G, Brown JP; Canadian Association of Radiologists. **Recommendations for bone mineral density reporting in Canada**. Can Assoc Radiol J. 2005 Jun;56(3):178-88.



Zones of fracture risk for women & men. (See also **WHO 10yr Probability of Fracture Algorithm called FRAX** http://www.shef.ac.uk/FRAX/index.htm)

Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA 2001;286:2815-22.
Siris ES, Harris ST, Eastell R, et al.; Continuing Outcomes Relevant to Evista (**CORE**) Investigators. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005 Sep;20(9):1514-24. Epub 2005 May 16.
Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007 Dec;46(12):1852-7. An **annual i.m. injection of 300 000 IU vitamin D(2)** is not effective in preventing non-vertebral fractures among elderly men and women resident in the general population.
Smith, Matthew R., Egerdie, Blair, Toriz, Narciso Hernandez, et al., the Denosumab **HALT** Prostate Cancer Study Group, **Denosumab** in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer. N Engl J Med 2009 0: NEJMoa0809003
SOGC 2006 Menopause Consensus Report. A Journalist's Menopause Handbook: A companion guide to the Society of Obstetricians and Gynaecologists of Canada Menopause Consensus Report. http://www.sogc.org/media/pdf/advisories/Menopause-journalists-guide_e.pdf (2006 Menopause Consensus Report. Pharmacist's Letter Mar 2006)
SOGC 2009 Menopause and Osteoporosis Update 2009-SOGC Jan 2009. http://www.sogc.org/media/pdf/advisories/Meno-Osteo-Update_JOGC-Jan_09.pdf
Solomon DH, Avorn J, Katz JN, Finkelstein JS, Arnold M, Polinski JM, Brookhart MA. **Compliance** with osteoporosis medications. Arch Intern Med. 2005 Nov 14;165(20):2414-9.
Sørensen HT, et al. Use of bisphosphonates among women & risk of **atrial fibrillation & flutter**: population based case-control study. BMJ. 2008Mar 11; [Epub ahead of print] No evidence was found that use of bisphosphonates increases the risk of atrial fibrillation & flutter.
Stoch SA, Saag KG, Greenwald M, et al. Once-weekly oral alendronate 70 mg in patients with **glucocorticoid-induced** bone loss: a 12-month randomized, placebo-controlled clinical trial. J Rheumatol. 2009 Aug;36(8):1705-14.
Sweet MG, Sweet JM, Jeremiah MP, Galazka SS. **Diagnosis and treatment of osteoporosis**. Am Fam Physician. 2009 Feb 1;79(3):193-200.
Szmuilowicz ED, Manson JE, Rossouw JE et al. **Vasomotor symptoms and cardiovascular events** in postmenopausal women. Menopause 2011; DOI: 10.1097/gme.0b013e3182014849.
Taggart H, Bolognese MA, Lindsay R, Ettinger MP, Mulder H, Josse RG, et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials [published correction appears in Mayo Clin Proc 2002;77:601]. Mayo Clin Proc 2002;77:262-70.
The role of **calcium** in peri- and postmenopausal women: 2006 position statement of The North American Menopause Society. Menopause. 2006 Nov-Dec;13(6):862-77.
U.S. Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Ann Intern Med 2002;137:526-8.
Uitterlinden AG, et al.; APOSS Investigators; EPOS Investigators; EPOLOS Investigators; FAMOS Investigators; LASA Investigators; Rotterdam Study Investigators; GENOMOS Study. The association between common **vitamin D receptor gene** variations and osteoporosis: a participant-level meta-analysis. Ann Intern Med. 2006 Aug 15;145(4):255-64.
Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and **osteonecrosis** of the jaw: cause and effect or a post hoc fallacy? Ann Oncol. 2006 Aug;17(8):1197-204.
Van Poznak CH, Temin S, Yee GC, et al. American Society of Clinical Oncology (**ASCO**) Executive Summary of the Clinical Practice Guideline Update on the Role of **Bone-Modifying Agents in Metastatic Breast Cancer**. J Clin Oncol. 2011 Feb 22.
Villar J, Abdel-Aleem Het al.; World Health Organization Calcium Supplementation for the Prevention of Preeclampsia Trial Group. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol. 2006 Mar;194(3):639-49. CONCLUSION: A 1.5-g calcium/day supplement did not prevent preeclampsia but did reduce its severity, maternal morbidity, and neonatal mortality, albeit these were secondary outcomes.
Vis M, Bultink IE, Dijkmans BA, Lems WF. The effect of **intravenous pamidronate** versus oral alendronate on bone mineral density in patients with osteoporosis. Osteoporos Int. 2005 May 10; [Epub ahead of print]
Vogel VG, et al. Effects of Tamoxifen vs Raloxifene on the Risk of Developing Invasive Breast Cancer and Other Disease Outcomes: The NSABP Study of Tamoxifen and Raloxifene (**STAR**) P-2 Trial. JAMA. 2006 Jun 5; [Epub ahead of print] Raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and has a lower risk of thromboembolic events and cataracts but a nonstatistically significant higher risk of noninvasive breast cancer. The risk of other cancers, fractures, ischemic heart disease, and stroke is similar for both drugs. (Land SR, et al. Patient-Reported Symptoms and Quality of Life During Treatment With Tamoxifen or Raloxifene for Breast Cancer Prevention: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA. 2006 Jun 5; [Epub ahead of print] No significant differences existed between the tamoxifen and raloxifene groups in patient-reported outcomes for physical health, mental health, and depression, although the tamoxifen group reported better sexual function. Although mean symptom severity was low among these postmenopausal women, those in the tamoxifen group reported more gynecological problems, vasomotor symptoms, leg cramps, and bladder control problems, whereas women in the raloxifene group reported more musculoskeletal problems, dyspareunia, and weight gain.)
Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of **risedronate** treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 2000;67:277-85.
Wactawski-Wende J, et al.; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006 Feb 16;354(7):684-96. Erratum in: N Engl J Med. 2006 Mar 9;354(10):1102. (InfoPOEMs: A modest dose of calcium and vitamin D does not alter the risk of colorectal cancer in healthy, normal-risk women. (LOE = 1b))
Walter C, Al-Nawas B, du Bois A, Buch L, Harter P, Grötz KA. Incidence of bisphosphonate-associated **osteonecrosis of the jaws in breast cancer** patients. Cancer. 2009 Jan 20. [Epub ahead of print] With a prevalence of 5.3%, BP-ONJ in breast cancer patients has become a relevant disease that should be discussed with patients for whom bisphosphonates have been recommended. Appropriate dental care before bisphosphonate therapy commences has been advised to reduce the occurrence of BP-ONJ.
Walter C, Al-Nawas B, Grötz KA, Thomas C, Thüroff JW, Zinser V, Gamm H, Beck J, Wagner W. Prevalence and Risk Factors of Bisphosphonate-Associated **Osteonecrosis of the Jaw in Prostate Cancer** Patients with Advanced Disease Treated with Zoledronate. Eur Urol. 2008 Jun 26. [Epub ahead of print] Eight of 43 patients developed BP-ONJ (18.6%). The reason for this relatively high incidence compared to other studies might be the prospective study design and thorough dental examination. In studies with such small numbers as l to date, nondetection or nonreported cases of BP-ONJ have an influence on the outcome. The incidence of BP-ONJ in patients with pCA might be an underestimated problem.

TOP

Warensjö Eva, Byberg Liisa, Melhus Håkan, et al. **Dietary calcium intake** and risk of fracture and osteoporosis: prospective longitudinal cohort study. BMJ 2011;342:doi:10.1136/bmj.d1473 (Published 24 May 2011)

Weinstein RS, Roberson PK, Manolagas SC. **Giant osteoclast** formation and long-term oral bisphosphonate therapy. N Engl J Med. 2009 Jan 1;360(1):53-62. Long-term alendronate treatment is associated with an increase in the number of osteoclasts, which include distinctive giant, hypernucleated, detached osteoclasts that are undergoing protracted apoptosis.

Wells G, Cranney A, Peterson J, Boucher M, et al. **Alendronate** for the primary & secondary prevention of osteoporotic fractures in postmenopausal women. **Cochrane** Database Syst Rev. **2008** Jan 23;(1):CD001155. At 10 mg per day, both clinically important and statistically significant reductions in vertebral, non-vertebral, hip and wrist fractures were observed for secondary prevention ('gold' level evidence, www.cochranemsk.org). We found no statistically significant results for primary prevention, with the exception of vertebral fractures, for which the reduction was clinically important ('gold' level evidence).

Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. **Etidronate** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. **Cochrane** Database Syst Rev. **2008** Jan 23;(1):CD003376. Etidronate, at 400 mg per day, demonstrated a statistically significant and clinically important benefit in the secondary prevention of vertebral fractures. No statistically significant reductions in vertebral fractures were observed when it was used for primary prevention. In addition, no statistically significant reductions in non-vertebral, hip, or wrist fractures were found, regardless of whether etidronate was used for primary or secondary prevention. The level of evidence for all outcomes is Silver (www.cochranemsk.org.).

Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. **Risedronate** for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. **Cochrane** Database Syst Rev. **2008** Jan 23;(1):CD004523. At 5 mg/day a statistically significant and clinically important benefit in the secondary prevention of vertebral, non-vertebral and hip fractures was observed, but not for wrist. The level of evidence for secondary prevention is Gold (www.cochranemsk.org) for vertebral and non-vertebral and Silver for hip and wrist. There were no statistically significant reductions in the primary prevention of vertebral and non-vertebral fractures. The level of evidence is Silver.

Winzenberg T, Shaw K, Fryer J, Jones G. Effects of **calcium** supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ. 2006 Sep 15; [Epub ahead of print]

Wong R, Wiffen PJ. **Bisphosphonates** for the relief of pain secondary to **bone metastases**. Cochrane Database Syst Rev. 2002;(2):CD002068.

Wysowski DK, Chang JT. **Alendronate and risedronate: reports of severe bone, joint, and muscle pain**. Arch Intern Med. 2005 Feb 14;165(3):346-7.

Wysowski DK. Reports of **esophageal cancer** with oral bisphosphonate use. N Engl J Med. 2009 Jan 1;360(1):89-90.

Zizic TM. Pharmacologic prevention of osteoporotic fractures. Am Fam Physician. 2004 Oct 1;70(7):1293-300.

Bioidentical Hormone:

Progesterone cream no more effective than placebo for relief of menopausal symptoms" was the conclusion in a double-blind placebo-controlled study to evaluate the effect of progesterone cream on postmenopausal women (Menopause International, Volume 15, Issue 2, June 2009, Pages 63-69

Medical Letter. Bioidentical Hormones. May 31, 2010.

Menopause: The Journal of The North American Menopause Society Vol. 17, No. 2, pp. 242/255.

FDA press release: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116832.htm

Pattimakiel L, Thacker HL. Bioidentical hormone therapy: Clarifying the misconceptions. Cleve Clin J Med. 2011 Dec;78(12):829-36.

Links:

NAMS: Position Statements: http://www.menopause.org/aboutmeno/consensus.aspx

The North American Menopause Society www.menopause.org

National Library of Medicine, MedlinePlus www.nlm.nih.gov/medlineplus/menopause.html

TOP

Acknowledgements: Contributors & Reviewers: Tessa Laubscher MD, CCFP (Academic Family Medicine, U of S, Saskatoon), Jill Newstead-Angel MD, FRCPC (Internal Medicine, Obs/Gyne, U of S, Saskatoon), Nora McKee RN, MD, CCFP (Academic Family Medicine, U of S, Saskatoon), Terra Arnason MD, PhD, FRCPC (Adult Endocrinology, Saskatoon, SHR/UofS), Jocelyne Martel MD, FRCPC (Obs/Gyne College of Medicine, U of S, Saskatoon), Shanna Fenton MD, CCFP (Family Medicine, Saskatoon), Jonathan Hey MD (Family Medicine, Saskatoon), Karen Jensen BSP (SDIS, Saskatoon), Carmen Bell BSP (SDIS, Sasktoon) & the RxFiles Advisory Committee. Prepared by: *L.Kosar* BSP,MSc, *L. Regier* BA ,BSP, *B. Jensen* BSP

References: Peri-Pregnancy Drug Treatment Considerations

General References:

Briggs G et al. Drugs in Pregnancy and Lactation, 9th edition. 2011.

LactMed. http://toxnet.nlm.nih.gov/

Other References:

[1] Health Canada. **Prenatal Nutrition Guidelines** for Health Professionals. 2009. http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/pubs/guide-prenatal-eng.pdf (Accessed December 5th, 2011).

Who should take vitamin supplements? Med Lett Drugs Ther. 2011 Dec 12;53(1379-1380):101-3.

Wilson RD et al; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada and The Motherisk Program. **Pre-conceptional vitamin/folic acid supplementation** 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2007 Dec;29(12):1003-26.

American Academy of Pediatrics. Policy Statement - SECTION ON BREASTFEEDING. Breastfeeding and the use of human milk. Pediatrics. 2012 Mar;129(3):e827-41.

Fernandes TF et al. Effect on Infant Illness of Maternal Supplementation With 400 000 IU Vs 200 000 IU of Vitamin A. Pediatrics. 2012 Mar 12.

[2] Health Canada. Food & Nutrition: High Dose **Folic Acid Supplementation** – Questions and Answers for Health Professionals. 2010.

Talaulikar VS, Arulkumaran S. **Folic acid** in obstetric practice: a review. Obstet Gynecol Surv. 2011 Apr;66(4):240-7.

[3] Canadian Pediatric Society. **Vitamin D Supplementation**: Recommendations for Canadian mothers and infants. 2007, Reaffirmed 2010. http://www.cps.ca/english/statements/ii/fnim07-01.htm#RECOMMENDATIONS (Accessed December 5th, 2011).

Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D, 2011.

RxFiles Q&A Summary: Vitamin D – Therapeutic Overview and Evaluation of Evidence for Current Claims, 2010.

De-Regil LM et al. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2012 Feb 15;2:CD008873.

Whitehouse AJ et al. Maternal Serum Vitamin D Levels During Pregnancy and Offspring Neurocognitive Development. Pediatrics. 2012 Feb 13.

Vanstone MB et al. Hypercalcemia in Children Receiving Pharmacologic Doses of Vitamin D. Pediatrics.2012 Mar 12.

[4] Anemia Review Panel. Anemia Guidelines for Family Medicine. 2nd ed. Toronto: MUMS Guideline Clearinghouse; 2008.

[5] **Diabetes Guidelines:**

Canadian Diabetes Association. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: **Diabetes and Pregnancy**. 2008. Pages S168-180.

American Diabetes Association. Standards of Medical Care in Diabetes 2012. Diabetes Care 2012;35:S11-S63.

NICE 2008 Guidelines: Diabetes in pregnancy management of diabetes and its complications from preconception to the postnatal period. http://www.nice.org.uk/nicemedia/live/11946/41320/41320.pdf (Accessed January 30, 2012)

[6] Other Diabetes References:

Pollex E et al. Safety of **insulin glargine** use in pregnancy: a systematic review and meta-analysis. Ann Pharmacother. 2011 Jan;45(1):9-16.

Louie JC et al. A randomized controlled trial investigating the effects of a **low-glycemic index diet** on pregnancy outcomes in gestational diabetes mellitus. Diabetes Care. 2011 Nov;34(11):2341-6.

Bell R et al. Peri-conception hyperglycaemia & nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. Diabetologia. 2012 Feb 8.

Murphy HR et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. Diabetes Care. 2010 Dec;33(12):2514-20.

Simmons D et al. Gestational diabetes mellitus: NICE for the U.S.? A comparison of the American Diabetes Association and the American College of Obstetricians and Gynecologists guidelines with the U.K. National Institute for Health and Clinical Excellence guidelines. Diabetes Care. 2010 Jan;33(1):34-7. Epub 2009 Oct 16.

Lapolla A, Dalfrà MG, Fedele D. Pregnancy complicated by diabetes: what is the best level of HbA1c for conception? Acta Diabetol. 2010 Sep;47(3):187-92. Epub 2010 May 26.

Guerin A et al. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. Diabetes Care. 2007 Jul;30(7):1920-5.

[7] **Metformin & Glyburide Use During Pregnancy:**

Rowan JA et al. MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med.2008 May 8;358(19):2003-15.

Rowan JA et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. Diabetes Care. 2011 Oct;34(10):2279-84.

Dhulkotia JS et al. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010 Nov;203(5):457.e1-9.

Moore LE et al. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2010 Jan;115(1):55-9.

Briggs G et al. Drugs in Pregnancy and Lactation, 9th edition. 2011.

[8] Davenport MH et al. A walking intervention improves capillary glucose control in women with gestational diabetes mellitus: a pilot study. Appl Physiol Nutr Metab. 2008 Jun;33(3):511-7.

TOP

Stafne SN et al. Regular exercise during pregnancy to prevent gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2012 Jan;119(1):29-36.

[9] **Hypertension Guidelines:**

Magee LA et al. Hypertension Guideline Committee; Strategic Training Initiative in Research in the Reproductive Health Sciences (STIRRHS) Scholars. Diagnosis, evaluation, and management of the **hypertensive disorders of pregnancy**. J Obstet Gynaecol Can. 2008 Mar;30(3 Suppl):S1-48.

Royal College of Obstetricians and Gynecologists. **Hypertension in pregnancy**: the management of hypertensive disorders during pregnancy. **2011 NICE Guidelines.**

Other Hypertension References:

Raheem IA et al. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG. 2012 Jan;119(1):78-85.

Fraser A et al. Associations of Pregnancy Complications with Calculated CVD Risk & Cardiovascular Risk Factors in Middle Age: The Avon Longitudinal Study of Parents and Children. Circulation. 2012 Feb 17.

Shennan AH et al. Are most maternal deaths from pre-eclampsia avoidable? Lancet. 2011 Dec 14.

Bukowski R et al. Delivery of a small for gestational age infant and greater maternal risk of ischemic heart disease. PLoS ONE. March 2012.

[10] Conde-Agudelo A et al. Supplementation with **vitamins C and E during pregnancy for the prevention of preeclampsia** and other adverse maternal and perinatal outcomes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2011 Jun;204(6):503.e1-12.

Roberts JM et al. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. **Vitamins C and E** to prevent complications of pregnancy-associated hypertension. NEJM. 2010 Apr 8;362(14):1282-91.

[11] Li DK et al. Maternal exposure to **angiotensin converting enzyme inhibitors** in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ. 2011 Oct 18;343.

[12] **Thyroid Guidelines:** Stagnaro-Green A et al. American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. **Guidelines of the American Thyroid Association** for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011 Oct;21(10):1081-125.

[13] **Other Thyroid References:**

Chen CH et al. Risk of adverse perinatal outcomes with antithyroid treatment during pregnancy: a nationwide population-based study. BJOG. 2011 Oct;118(11):1365-73.

Lazarus JH et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med.2012 Feb 9;366(6):493-501.

Brent GA. The debate over thyroid-function screening in pregnancy. N Engl J Med. 2012 Feb 9;366(6):562-3.

Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012 Jan 20.

Sullivan KM. Iodine supplementation for pregnancy and lactation: United States and Canada: recommendations of the American Thyroid Association. Thyroid. 2007 May;17(5):483-4.

Infectious Disease References:

[14] Anti-infective Review Panel. Anti-infective guidelines for community-acquired infections. Toronto: MUMS Guideline Clearinghouse; 2012.

[15] Capital Health Regional Pharmacy Services. Bugs & Drugs. Edmonton; 2006.

[16] Canadian Guidelines on Sexually Transmitted Infections, 2008 Edition. Ottawa, ON: Public Health Agency of Canada.

[17] CDC 2010 STI Clinical Guidelines. http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf (Accessed January 2012).

[18] American College of Obstetricians & Gynaecologists. Committee Opinion #485. Prevention of Early-Onset Group B Streptococcal Disease in Newborns. April 2011.

Society of Obstetricians & Gynaecologists. Clinical Practice Guidelines: The prevention of early-onset neonatal Group B Streptococcal Disease. September 2004.

[19] Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. September 14, 2011. 1-207. Avalaible at http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf. Accessed February 15, 2012.

Saskatchewan Prevention Institute. HIV/AIDS & Pregnancy: A guide to care. 2011.

[20] Yudin M et al. SOGC Clinical Practice Guidelines: 2008 Screening and management of **bacterial vaginosis** in pregnancy.

[21] **Genital Herpes Simplex:**

Money D, Steben M; Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines: Guidelines for the management of herpes simplex virus in pregnancy. Number 208, June 2008. Int J Gynaecol Obstet. 2009 Feb;104(2):167-71.

Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004946.

Su C, McKay B. Treatment of HSV Infection in late pregnancy. Am Fam Physician. 2012 Feb 15;85(4):390-393.

Kang SH et al. Safety of antiviral medication for the treatment of herpes during pregnancy. Can Fam Physician. 2011 Apr;57(4):427-8.

[22] **Urinary Tract Infections/Asymptomatic Bacteriuria:**

Widmer M et al. Duration of treatment of asymptomatic bacteriuria during pregnancy. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD000491.

Guinto VT et al. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD007855.

Lee M et al. Motherisk Update: Urinary tract infections in pregnancy. Can Fam Physician June 2008 54: 853-854

[23] **Other Infectious Disease References:**

Medical Letter. Vaccines and Pregnancy. Medical Letter 2011; 53(1378):94-96.

CADTH. Rapid Response Report: Treatment of Yeast Infections in Breastfeeding Mothers and Babies – Clinical Evidence and Guidelines. November 2011.

Dauby N et al. Uninfected but not unaffected: chronic maternal infections during pregnancy, fetal immunity, and susceptibility to postnatal infections. Lancet Infect Dis. 2012 Feb 23.

Narducci A, Einarson A, Bozzo P. Human papillomavirus vaccine and pregnancy. Canadian Family Physician 2012;58:268-9.

McCartney M. Streptococcus B in pregnancy: to screen or not to screen? BMJ. 2012 Apr 18;344:e2803.

[24] Bozzo P et al. Motherisk Update: Safety of skin care products during pregnancy. Canadian Family Physician 2011;57:665-667.

TOP

[25] Namazy JA, Schatz M. **Asthma and pregnancy**. J Allergy Clin Immunol. 2011 Dec;128(6):1384-1385.

Depression References:

[26] Yonkers KA et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry. 2009 Sep-Oct;31(5):403-13.

Cohen LS et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006 Feb 1;295(5):499-507.

Canadian Pediatric Society Position Statement. Selective serotonin reuptake inhibitors in pregnancy and infant outcomes. Pedatric Child Health 2011; 16(9):562.

American Psychiatric Association. 2010 Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd edition. http://psychiatryonline.org/data/Books/prac/PG_Depression3rdEd.pdf Accessed February 21st, 2012.

Bonari L et al. Risks of untreated depression during pregnancy. Can Fam Physician. 2004 Jan;50:37-9.

National Institute for Health and Clinical Excellence. NICE Clinical Guideline 45 – Antenatal and postnatal mental health: Clinical management and service guidance. February 2007. http://www.nice.org.uk/nicemedia/live/11004/30433/30433.pdf Accessed February 21st, 2012.

Ryan D, Milis L, Misri N. Depression during pregnancy. Can Fam Physician. 2005 Aug;51:1087-93.

Stewart DE. Clinical practice. Depression during pregnancy. N Engl J Med. 2011 Oct 27;365(17):1605-11.

Davalos DB, Yadon CA, Tregellas HC. Untreated prenatal maternal depression and the potential risks to offspring: a review. Arch Womens Ment Health. 2012 Feb;15(1):1-14.

Rubinchik SM, Kablinger AS, Gardner JS. Medications for panic disorder and generalized anxiety disorder during pregnancy. Prim Care Companion J Clin Psychiatry. 2005;7(3):100-5.

Galbally M, Snellen M, Lewis AJ. A review of the use of psychotropic medication in pregnancy. Curr Opin Obstet Gynecol. 2011 Dec;23(6):408-14.

Einarson A. Motherisk Update: Paroxetine use in pregnancy and increased risk of heart defects. Canadian Family Physician 2010;56:767-8.

Occhiogrosso M, Omran SS, Altemus M. Persistent pulmonary hypertension of the newborn and selective serotonin reuptake inhibitors: lessons from clinical and translational studies. Am J Psychiatry. 2012 Feb 1;169(2):134-40.

Patil AS et al. Antidepressants in pregnancy: a review of commonly prescribed medications. Obstet Gynecol Surv. 2011 Dec;66(12):777-87.

Kalra S, Einarson A, Koren G. Taking antidepressants during late pregnancy. Canadian Family Physician 2005; 51: 1077-8.

Fortinguerra F et al. Psychotropic drug use during breastfeeding: a review of the evidence. Pediatrics 2009;124(4):547-556.

Flynn HA et al. Comparative performance of the Edinburgh Postnatal Depression Scale and the Patient Health Questionnaire-9 in pregnant and postpartum women seeking psychiatric services. Psychiatry Res. 2011 May 15;187(1-2):130-4.

Shah N. Mood disorder in the perinatal period. BMJ. 2012 Mar 1;344:e1209.

Viguera AC et al. Episodes of mood disorders in 2,252 pregnancies and postpartum periods. Am J Psychiatry. 2011 Nov;168(11):1179-85.

Howell EA, et al. Reducing postpartum depressive symptoms among black and latina mothers: a randomized controlled trial. Obstet Gynecol. 2012 May;119(5):942-9.

Koren G, Nordeng H. Antidepressant use during pregnancy: the **benefit-risk ratio**. Am J Obstet Gynecol. 2012 Feb 21.

Mann R, Adamson J, Gilbody SM. Diagnostic accuracy of case-finding questions to **identify perinatal depression**. CMAJ. 2012 Apr 2.

[27] Natural Medicines Comprehensive Database. Natural Medicines Used During Pregnancy & Lactation. http://naturaldatabase.therapeuticresearch.com.ezproxy.shirp.ca/ce/CECourse.aspx?cs=&pm=5&s=nd&pc=11-102&searchid=31811148#keywordanchor (Accessed December 29th, 2011)

Health Canada. Women's Health Information: Pregnancy – Herbal Remedies. http://www.sogc.org/health/pregnancy-herbal_e.asp (Accessed December 29th, 2011)

Mozurkewich EL, Klemens C. Omega-3 fatty acids and pregnancy: current implications for practice. Curr Opin Obstet Gynecol. 2012 Mar;24(2):72-7.

Imhoff-Kunsch B et al. Prenatal docosahexaenoic Acid supplementation and infant morbidity: randomized controlled trial. Pediatrics. 2011 Sep;128(3):e505-12.

[28] Society of Obstetricians and Gynaecologists of Canada. 2002 Clinical Practice Guidelines: The management of **nausea and vomiting** of pregnancy. J Obstet Gynaecol Can 2002;24(10):817-23.

Maitre S, Neher J, Safranek S. Ginger for the treatment of **nausea and vomiting** in pregnancy. American Family Physician 2011;84(10).

[29] Rebordosa C et al. Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. Int J Epidemiol. 2009 Jun;38(3):706-14.

Babb M, Koren G, Einarson A. Treating pain during pregnancy. Can Fam Physician. 2010 Jan;56(1):25, 27.

[30] Cupp M. Analgesics in Pregnancy and Lactation. Pharmacists Letter. February 2012.

O'Mara. New pregnancy warnings: opioids, topiramate, and antipsychotics. Pharmacist's Letter. April 2011.

Nakhai-Pour HR et al. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ. 2011 Oct 18;183(15):1713-20.

Palacioz K. NSAIDs and Miscarriage. Pharmacist's Letter. October 2003.

[31] Nappi RE, Albani F, Sances G, Terreno E, Brambilla E, Polatti F. **Headaches** during pregnancy. Curr Pain Headache Rep. 2011 Aug;15(4):289-94.

Gilmore B, Michael M. Treatment of acute **migraine headache**. Am Fam Physician. 2011 Feb 1;83(3):271-80.

[32] Wiener S. Diagnosis and management of Candida of the nipple and breast. JMidwifery Womens Health. 2006 Mar-Apr;51(2):125-8.

[33] Davies GA et al. Society of Obstetricians and Gynecologists of Canada, SOGC Clinical Practice Obstetrics Committee. **Joint SOGC/CSEP clinical practice guideline: exercise in pregnancy and the postpartum period**. Can J Appl Physiol. 2003 Jun;28(3):330-41.

Szymanski LM, Satin AJ. Exercise during pregnancy: fetal responses to current public health guidelines. Obstet Gynecol. 2012 Mar;119(3):603-10.

Wise et al. A prospective cohort study of physical activity and time to pregnancy. Fertility and Sterility. 2012.

Hui A et al. Lifestyle intervention on diet and exercise reduced excessive gestational weight gain in pregnant women under a randomized controlled trial. BJOG 2012(1);119:70-77.

[34] Health Canada. Mercury in Fish: Question and Answers, January 2011. http://www.hc-sc.gc.ca/fn-an/securit/chem-chim/environ/mercur/merc_fish_qa-poisson_qr-eng.php (Accessed February 9, 2012)

TOP

Health Canada. Eating well with Canada's Food Guide – First Nations, Inuit and Metis, March 2010. http://www.hc-sc.gc.ca/fn-an/pubs/fnim-pnim/index-eng.php#a_7 (Accessed February 9, 2012).
[35] Davies GA et al. Society of Obstetricians and Gynaecologists of Canada. **Obesity in pregnancy**. J Obstet Gynaecol Can. 2010 Feb;32(2):165-73.
Arendas K, Qiu Q, Gruslin A. **Obesity** in pregnancy: pre-conceptional to postpartum consequences. J Obstet Gynaecol Can. 2008 Jun;30(6):477-88.
Baker JL et al. Breastfeeding reduces postpartum weight retention. Am J Clin Nutr. 2008 Dec;88(6):1543-51.
[36] Health Canada. Canadian Gestational Weight Gain Recommendations. http://www.hc-sc.gc.ca/fn-an/nutrition/prenatal/qa-gest-gros-qr-eng.php (Accessed December 1st, 2011)
[37] Society of Obstetricians and Gynaecologists of Canada. 2010 Alcohol use and pregnancy: consensus clinical guidelines. Journal of Obstetrics and Gynaecology Canada 2010; 32(8):supplement 3.
Nice FJ, Luo AC. Medications and breast-feeding: Current concepts. J Am Pharm Assoc (2003). 2012 Jan 1;52(1):86-94.
Dynamed. Medication and drug exposure during pregnancy. Accessed February 22, 2012.
Patra J et al. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. BJOG. 2011 Nov;118(12):1411-21.
[38] Health Canada. Health Canada Reminds Canadians to Manage Caffeine Consumption, March 2010. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_40-eng.php (Accessed December 5th, 2011).
Santos IS, Matijasevich A, Domingues MR. Maternal Caffeine Consumption and Infant Nighttime Waking: Prospective Cohort Study. Pediatrics. 2012 Apr 2.
[39] Koren G. Pharmacokinetics in pregnancy; clinical significance. J Popul Ther Clin Pharmacol. 2011;18(3):e523-7.
CADTH. Rapid Response Update: Second hand smoke and pregnancy women – clinical evidence. February 7th, 2012.
Nice FJ, Luo AC. Medications and breast-feeding: Current concepts. J Am Pharm Assoc (2003). 2012 Jan 1;52(1):86-94.
Filion KB et al. The effect of smoking cessation counselling in pregnant women: a meta-analysis of randomised controlled trials. BJOG. 2011 Nov;118(12):1422-8.
CADTH Rapid Response: Smoking cessation interventions for pregnancy women and mothers of infants – a review of the clinical effectiveness, safety & guidelines. March 2012.
CAN-ADAPTT: Practice-informed and evidence-based smoking cessation guideline [Internet]. Toronto: Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco (CAN-ADAPTT); 2011. http://www.can-adaptt.net/English/Guideline/Introduction.aspx. Accessed March 12, 2012.
Coleman T et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. NEJM 2012; 366(9):808-18.
Oncken C. Commentary - Nicotine replacement for smoking cessation during pregnancy. NEJM 2012; 366(9):846-7.
Milidou I et al. Nicotine replacement therapy during pregnancy and infantile colic in the offspring. Pediatrics 2012;652-8.
Baardman ME et al. Combined adverse effects of maternal smoking and high body mass index on heart development in offspring: evidence for interaction? Heart. 2012 Mar;98(6):474-9.
Mackay DF et al. Impact of Scotland's Smoke-Free Legislation on Pregnancy Complications: Retrospective Cohort Study. PLoS Med. 2012 Mar;9(3):e1001175.
[40] Black A et al. Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines: **Canadian contraception consensus**. J Obstet Gynaecol Can. 2004 Mar;26(3):219-96.
Black A et al. Society of Obstetricians and Gynaecologists of Canada. **Canadian contraception consensus**. J Obstet Gynaecol Can. 2004 Apr;26(4):347-87, 389-436.
Centers for Disease Control and Prevention (CDC). Update to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2010: revised recommendations for the use of contraceptive methods during the postpartum period. MMWR Morb Mortal Wkly Rep. 2011 Jul 8;60(26):878-83.
Truitt ST et al. Combined hormonal versus nonhormonal versus progestin-only contraception in lactation. Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD003988.
[41] Academy Of Breastfeeding Medicine Protocol Committee. ABM Clinical Protocol #9: Use of galactogogues in initiating or augmenting the rate of maternal milk secretion (First Revision January 2011). Breastfeed Med. 2011 Feb;6(1):41-9.
Mannion C, Mansell D. Breastfeeding self-efficacy and the use of prescription medication: a pilot study. Obstet Gynecol Int. 2012;2012:562704. Epub 2011 Dec 15.
Natural Medicines Comprehensive Database. Blessed thistle, caraway, fennel, fenugreek, and Goat's rue Monographs. http://naturaldatabase.therapeuticresearch.com.cyber.usask.ca/home.aspx?cs=&s=ND. (Accessed February 9, 2012).
Health Canada Advisory: Domperidone Maleate Association with Serious Abnormal Heart Rhythms and Sudden Death (Cardiac Arrest) - For Health Professionals. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/domperidone_hpc-cps-eng.php. Accessed March 14th, 2012.
Oladapo OT, Fawole B. Treatments for suppression of lactation. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD005937. DOI: 10.1002/14651858.CD005937.pub2.
[42] Vause TD et al. Society of Obstetricians and Gynecologists of Canada. Ovulation induction in **polycystic ovary syndrome**. J Obstet Gynaecol Can. 2010 May;32(5):495-502.
Wilson JF. In the clinic. The polycystic ovary syndrome. Ann Intern Med. 2011 Feb 1;154(3):ITC2-2-ITC2-15; quiz ITC2-16. Review.
Fauser BC et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012 Jan;97(1):28-38.e25.

Additional References:

Alabdulrazzaq F, Koren G. **Topical corticosteroid** use during pregnancy. Can Fam Physician. 2012 Jun;58(6):643-4.
Amant F et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol. 2012 Mar;13(3):256-64.
Birthplace in England Collaborative Group. Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnancies: the Birthplace in England national prospective cohort study. BMJ. 2011 Nov 23;343:d7400. doi: 10.1136/bmj.d7400.
Bodurtha J, Strauss JF 3rd. Genomics and perinatal care. N Engl J Med. 2012 Jan 5;366(1):64-73. Review.
Boyle EM et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. BMJ. 2012 Mar 1;344:e896.
Bukowski R et al. Delivery of a small for gestational age infant and greater maternal risk of ischemic heart disease. PLoS ONE2012 Mar; 7:e33047.

TOP

Camacho E et al. Multiple adverse pregnancy outcomes before symptom onset are associated with a worse disease outcome in women with recent-onset inflammatory polyarthritis. Ann Rheum Dis. 2012 Apr;71(4):528-33.
Cardonick E. Treatment of maternal cancer and fetal development. Lancet Oncol.2012 Mar;13(3):218-20. Epub 2012 Feb 10.
Catalano PM, McIntyre HD, Cruickshank JK, et al. **HAPO** Study Cooperative Research Group. The **hyperglycemia and adverse pregnancy outcome study**: associations of GDM and obesity with pregnancy outcomes. Diabetes Care. 2012 Apr;35(4):780-6.
Celermajer DS. Manipulating nature: might there be a cardiovascular price to pay for the miracle of **assisted conception**? Circulation. 2012 Apr 17;125(15):1832-4.
Cressman AM, Pupco A, Kim E, et al. **Smoking cessation** therapy during pregnancy. Can Fam Physician. 2012 May;58(5):525-7.
Deshpande NA, James NT, Kucirka LM et al. Pregnancy outcomes of liver transplant recipients: A systematic review and meta-analysis. Liver Transpl. 2012 Jun;18(6):621-9.
Davis EF, Lazdam M, Lewandowski AJ, et al. **Cardiovascular Risk Factors in Children and Young Adults Born to Preeclamptic Pregnancies**: A Systematic Review. Pediatrics. 2012 May 21.
Davies MJ, Moore VM, Willson KJ, et al. **Reproductive Technologies** and the Risk of Birth Defects. N Engl J Med. 2012 May 5.
Daw JR et al. Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). Clin Ther. 2012 Jan;34(1):239-249.e2. Epub 2011 Dec 14.
Goya M, Pratcorona L, Merced C, et al. **Cervical pessary** in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. Lancet. 2012 Apr 2.
Hernández-Díaz S, Smith CR, Shen A, et al; For the North American AED Pregnancy Registry; North American AED(Antiepileptic Drug) Pregnancy Registry; Scientific Advisory Committee; North American AED Pregnancy Registry. Comparative safety of **antiepileptic drugs during pregnancy**. Neurology. 2012 May 22;78(21):1692-1699.
Iams JD, Lynch CD. Stillbirth and lessons for pregnancy care. JAMA. 2011 Dec 14;306(22):2506-7.
Johnson KC, Laprairie JL, Brennan PA, et al. **Prenatal Antipsychotic Exposure and Neuromotor Performance** During Infancy. Arch Gen Psychiatry. 2012 Apr 2.
Kelly D, O'Dowd T, Reulbach U. Use of **folic acid supplements** and risk of cleft lip and palate in infants: a population-based cohort study. Br J Gen Pract 2012; doi:10.3399/ bjgp12X652328.
Kingston D, Heaman M, Fell D, Chalmers B; on behalf of the Maternity Experiences Study Group of the Canadian Perinatal Surveillance System, Public Health Agency of Canada. Comparison of **Adolescent, Young Adult, and Adult Women's Maternity Experiences** and Practices. Pediatrics. 2012 Apr 23.
Lakhi N, Govind A. Unplanned pregnancy in a woman with **Crohn** disease. Can Fam Physician. 2012 May;58(5):531-2.
Lebrun-Vignes B, Le Cleach L, Giraudeau B, Chosidow O. Safety of **topical corticosteroid** use during pregnancy. Arch Dermatol. 2012 Apr;148(4):525-7.
Lecarpentier E, Morel O, Fournier T, Elefant E, Chavatte-Palmer P, Tsatsaris V. **Statins and Pregnancy**: Between Supposed Risks and Theoretical Benefits. Drugs. 2012 Apr 5.
Louzada ML, Campagnolo PD, Rauber F, Vitolo MR. Long-term Effectiveness of **Maternal Dietary Counseling** in a Low-Income Population: A Randomized Field Trial. Pediatrics. 2012 May 7.
Luke B, Brown MB, Wantman E, et al. Cumulative birth rates with linked **assisted reproductive technology** cycles. N Engl J Med. 2012 Jun 28;366(26):2483-91.
MacMahon E. Investigating the pregnant woman exposed to a child with a rash. BMJ. 2012 Mar 26;344:e1790. (chickenpox)
Macdonald-Wallis C, Lawlor DA, Fraser A, et al. **Blood pressure change** in normotensive, gestational hypertensive, preeclamptic, and essential hypertensive pregnancies. Hypertension. 2012 Jun;59(6):1241-8.
Meador KJ, Baker GA, Browning N, et al; For the NEAD Study Group. Effects of **fetal antiepileptic drug exposure**: Outcomes at age 4.5 years. Neurology. 2012 Apr 17;78(16):1207-1214.
Morales-Suarez-Varela MM, Bille C, Christensen K, Olsen J. **Smoking habits, nicotine use**, and congenital malformations. Obstet Gynecol. 2006 Jan;107(1):51-7.
Munk-Olsen T, Laursen TM, Meltzer-Brody S et al. **Psychiatric disorders with postpartum onset**: possible early manifestations of bipolar affective disorders. Arch Gen Psychiatry. 2012 Apr;69(4):428-34.
Murphy KE, Willan AR, Hannah ME, et al. Effect of **Antenatal Corticosteroids** on Fetal Growth and Gestational Age at Birth. Obstet Gynecol. 2012 May;119(5):917-923.
Nielsen-Saines K, Komarow L, Cu-Uvin S et al. Infant Outcomes After Maternal Antiretroviral Exposure in Resource-Limited Settings. Pediatrics. 2012 Jun;129(6):e1525-e1532.
Pasternak B, Svanström H, et al. Vaccination against **pandemic A/H1N1 2009 influenza in pregnancy** and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.
Retnakaran R, Ye C, Hanley AJG, et al. Effect of **maternal weight**, adipokines, glucose intolerance and lipids on infant birth weight among women without gestational diabetes mellitus. CMAJ 2012; May 21 [
Romøren M, Lindbaek M, Nordeng H. Pregnancy outcome after **gestational exposure to erythromycin**-a population-based register study from Norway. Br J Clin Pharmacol. 2012 Mar 30.
Scherrer U, Rimoldi SF, Rexhaj E, et al. Systemic and pulmonary vascular dysfunction in children conceived by **assisted reproductive technologies**. Circulation. 2012 Apr 17;125(15):1890-6.
Seshadri S, Oakeshott P, Nelson-Piercy C, Chappell LC. **Prepregnancy** care. BMJ. 2012 May 31;344:e3467.
Siberry GK, Williams PL, Mendez H, et al. for Pediatric HIVAIDS Cohort Study (PHACS). Safety of **tenofovir** use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. AIDS. 2012 Feb 29.
SIGN: Scottish Intercollegiate Guidelines Network, 2012. Management of **perinatal mood disorders**: a national clinical guideline [online]. Available: http://www.sign.ac.uk/guidelines/fulltext/127/index.html
Stern SJ, Matok I, Kapur B, Koren G. Dosage Requirements for **Periconceptional Folic Acid** Supplementation: Accounting for BMI and Lean Body Weight. J Obstet Gynaecol Can. 2012 Apr;34(4):374-8.
Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. JAMA. 2011 Dec 14;306(22):2469-79.
Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. JAMA. 2011 Dec 14;306(22):2459-68.
Thangaratinam S, Rogozińska E, Jolly K, et al. Effects of **interventions in pregnancy on maternal weight** and obstetric outcomes: meta-analysis of randomised evidence. BMJ 2012;344:e2088.
Vinet E et al. A population-based assessment of live births in women with systemic lupus erythematosus. Ann Rheum Dis. 2012 Apr;71(4):557-9. Epub 2011 Nov 14.

TOP

HERBAL DRUG INTERACTION CHART

Additonal references:

Adawi R, Walsh L. Bradycardia & edema in a patient receiving herbal therapy for fertility. Ann Intern Med. 2005 Nov 15;143(10):763. Although the specific ingredient responsible for the bradycardia and edema was not identified, a literature search identified some possibilities. There is a known association between **Aconitum napellus** and various arrhythmias, including severe bradycardia and left bundle-branch block pattern (1). Licorice contains glycyrrhizic acid, which inhibits renal 11[beta]-hydroxysteroid dehydrogenase and causes a state of mineralocorticoid excess by impeding inactivation of cortisol.

Agha-Hosseini M, Kashani L, et al. **Crocus sativus L. (saffron)** in the treatment of **premenstrual syndrome**: a double-blind, randomised and placebo-controlled trial. BJOG. 2008 Mar;115(4):515-9. Saffron was an effective treatment for PMS in this well-designed but small & short-term study. Consider recommending saffron, if cost is not an obstacle. Larger & longer studies are needed to confirm this result. (LOE = 1b)

Alfalfa: Patients may ask about a widely reported recall of Caldwell Fresh Foods alfalfa sprouts. The company has recalled all of its raw sprouts (marketed under the brands Caldwell Fresh Foods, California Exotics, and Nature's Choice) because they may be contaminated with a strain of **salmonella**. Since March, at least 22 cases of salmonella infections in 10 states have been linked to the sprouts, according to the FDA. California has 11 confirmed cases; the 9 other affected states are Arizona, Colorado, Idaho, Illinois, Missouri, New Mexico, Nevada, Oregon, & Wisconsin. Six people have been hospitalized; no deaths have been reported. FDA news release (Free) Manufacturer press release (Free)

Ali WM, Al Habib KF, Al-Motarreh A, et al. Acute coronary syndrome use and **khat herbal amphetamine use (Catha edulis)**. An observational report.Circulation 2011

Amsterdam JD, Li Y, Soeller I, et al. A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (**chamomile**) extract therapy for generalized anxiety disorder. J Clin Psychopharmacol. 2009 Aug;29(4):378-82. n=61 over 8 weeks. This is the first controlled clinical trial of chamomile extract for GAD. The results suggest that chamomile may have modest anxiolytic activity in patients with mild to moderate GAD

Ang-Lee MK, Moss J, Yuan CS. **Herbal medicines and perioperative care**. JAMA 2001;286:208-16.

Arnold J, Ouwehand WH, Smith GA, Cohen H. A young woman with petechiae.Lancet. 1998 Aug 22;352(9128):618. (**tahini** (pulped sesame seeds))

Aviner S, Berkovitch M, Dalkian H, et al. Use of a homeopathic preparation (**Gali-col Baby**) for "infantile colic" and an apparent life-threatening event. Pediatrics. 2010 Feb;125(2):e318-23.

Azuno Y, Yaga K, Sasayama T, Kimoto K. Thrombocytopenia induced by **Jui**, a traditional Chinese herbal medicine. Lancet. 1999 Jul 24;354(9175):304-5.

Bandolier. **Avocado/soybean** unsaponifiables for OA. April 2004;122-23. Web site: http://www.jr2.ox.ac.uk/bandolier/band122/b122-3.html. The limited data to date support the safety and possible efficacy of ASU for osteoarthritis of the knee. More and longer studies are needed before we can recommend this to our patients without hesitation. (LOE = 1b-)

Barbosa-Cesnik C, Brown MB, Buxton M, et al. **Cranberry juice** fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clin Infect Dis. 2011 Jan;52(1):23-30.

Barnes J. **Pharmacovigilance of herbal medicines** : a UK perspective. *Drug Saf*. 2003. 26(12): 829–51.

Barrett Bruce, Brown Roger, Rakel Dave, et al. **Echinacea** for Treating the Common Cold: A Randomized Trial. Ann Intern Med December 21, 2010 153:769-777.

Barry MJ, Meleth S, Lee JY, et al. Complementary and Alternative Medicine for Urological Symptoms (**CAMUS**) Study Group. Effect of increasing doses of **saw palmetto extract** on lower urinary tract symptoms: a randomized trial. JAMA. 2011 Sep 28;306(12):1344-51.

Bayles Bryan, Usatine Richard. **Evening primrose oil** . Am Fam Physician. 2009;80(12):1405–1408.

Benjamin J, Muir T, Briggs K, Pentland B. A case of cerebral haemorrhage-can **Ginkgo** biloba be implicated? Postgrad Med J. 2001 Feb;77(904):112-3.

Bent S, et al. Saw **palmetto** 160mg bid x1 yr for benign prostatic hyperplasia. N Engl J Med. 2006 Feb 9;354(6):557-66. n=255 (InfoPOEMs: The authors of this rigorously designed trial found that saw palmetto produces no improvement in symptoms for men with moderate to severe benign prostatic hyperplasia (BPH), a finding that differs from the bulk of the previous literature. (LOE = 1b))

Biggee BA, et al. Effects of oral **glucosamine** sulphate on serum **glucose** & insulin during an oral glucose tolerance test of subjects with osteoarthritis. Ann Rheum Dis. 2006 Jul3; [Epub ahead of print] The results suggest that glucosamine ingestion may affect glucose levels and consequent glucose uptake in individuals who have untreated diabetes or glucose intolerance.

Birks J, Grimley EV, Van Dongen M. **Ginkgo bilo**ba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2002;(4):CD003120. CONCLUSIONS: Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and we cannot exclude publication bias. Overall there is promising evidence of improvement in cognition and function associated with Ginkgo. However, the three more modern trials show inconsistent results. Our view is that there is need for a large trial using modern methodology and permitting an intention-to-treat analysis to provide robust estimates of the size and mechanism of any treatment effects.

Birdee GS, Phillips RS, Davis RB, Gardiner P. Factors associated with **pediatric use of complementary and alternative medicine**. Pediatrics. 2010 Feb;125(2):249-56. Epub 2010 Jan 25.

Birks J, Grimley Evans J. **Ginkgo biloba** for cognitive impairment and dementia. Cochrane Database Syst Rev. **2009** Jan 21;(1):CD003120. Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.

Bishop, Felicity L., Prescott, Philip, Chan, Yean Koon, et al. Prevalence of Complementary Medicine Use in **Pediatric Cancer**: A Systematic Review. Pediatrics 2010 125: 768-776.

Black C, Clar C, Henderson R, et al. The clinical effectiveness of **glucosamine and chondroitin** supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. Health Technol Assess. **2009** Nov;13(52):1-148.

Bonakdar RA, Guarneri E. Coenzyme Q10. Am Fam Physician. 2005 Sep 15;72(6):1065-70.

Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese **green tea** (Camellia sinensis). Ann Intern Med. 2006 Jan 3;144(1):68-71. (Gloro R, Hourmand-Ollivier I, et al. Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea. Eur J Gastroenterol Hepatol. 2005 Oct;17(10):1135-7.)

Bookstaver DA, Burkhalter NA, et al. Effect of **Coenzyme Q10 Supplementation (60mg po bid)** on Statin-Induced Myalgias. Am J Cardiol. 2012 May 17. n=76 no more effective than placebo

Borrelli F, Capasso R, Aviello G, Pittler MH, Izzo AA. Effectiveness and safety of **ginger** in the treatment of pregnancy-induced nausea and vomiting. Obstet Gynecol. 2005 Apr;105(4):849-56.

Broussard CS, Louik C, Honein MA, Mitchell AA; National Birth Defects Prevention Study. Herbal use before and during **pregnancy**. Am J Obstet Gynecol. 2009 Dec 23. [Epub ahead of print]

Bruyere O, et al. **Glucosamine** sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies. Menopause. 2004 Mar-Apr;11(2):138-43.

Buettner C, Yeh GY, Phillips RS, Mittleman MA, Kaptchuk TJ. Systematic review of the effects of **ginseng** on cardiovascular risk factors. Ann Pharmacother. 2006 Jan;40(1):83-95. Epub 2005 Dec 6.

Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after **glucosamine** sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage 2008; 16: 254–60.

Carney RM.; et al. **Omega-3 Augmentation of Sertraline** in Treatment of Depression in Patients With Coronary Heart Disease: A Randomized Controlled Trial. JAMA. 2009;302(15):1651-1657.

Chaiyakunapruk N, Kitikannakorn N, Nathisuwan S, et al. The efficacy of **ginger** for the prevention of postoperative nausea and vomiting: a meta-analysis. Am J Obstet Gynecol. 2006 Jan;194(1):95-9.

Chatterjee N, Domoto-Reilly K, Fecci PE, et al. **Licorice-associated reversible cerebral vasoconstriction** with PRES (**encephalopathy**). Neurology. 2010 Nov 23;75(21):1939-41.

Cheong JL. Retinal vein thrombosis associated with a herbal **phytoestrogen** preparation (black cohosh, dong quai, red clover & wold Mexican yam) in a susceptible patient. Postgrad Med J. 2005 Apr;81(954):266-7.

Chen XY, Wu TX, Liu GJ, et al. **Chinese medicinal herbs for influenza**. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD004559. The present evidence is too weak to support or reject the use of Chinese medicinal herbs for preventing and treating influenza.

Chen CH, Dickman KG, Moriya M, et al. **Aristolochic acid-associated urothelial cancer** in Taiwan. Proc Natl Acad Sci U S A. 2012 Apr 9.

Chen HY, Lin YH, Wu JC, Chen et al. Characteristics of Pediatric **Traditional Chinese Medicine** Users in Taiwan: A Nationwide Cohort Study. Pediatrics. 2012 May 14. The use of TCM was correlated with both patient and parental factors, among which children's age and parental TCM use were the most prominent.

Chow T, Browne V, et al. **Ginkgo biloba** & acetazolamide prophylaxis for acute mountain sickness: a randomized, placebo-controlled trial. Arch Intern Med. 2005 Feb 14;165(3):296-301.

Chuchalin AG, Berman B, Lehmacher W. Treatment of acute bronchitis in adults with a pelargonium sidoides preparation (EPS 7630): a randomized, double-blind, placebo-controlled trial. Explore 2005;1:437-45. (InfoPOEMs: The pelargonium sidoides extract (Umckaloabo in Germany) produced a significantly greater reduction in symptoms of acute bronchitis than placebo, & more patients were satisfied with treatment. As with all herbal products, results may be different with pelargonium products other than this extract. (LOE = 1b))

Clegg et al . National Institutes of Health (NIH) Glucosamine/Chondroitin Arthritis Intervention Trial (**GAIT**) Clegg DO, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808. CONCLUSIONS: Glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. Exploratory analyses suggest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain. (The 1,538-pts GAIT trial compared the effectiveness & safety of these supplements taken alone and in combination in patients with painful knee osteoarthritis (WOMAC Pain 125-400 mm) treated at 16 academic medical centers in the U.S. The response rate for all patients was 60.1% in a placebo group, 64% in a glucosamine hydrocholoride arm (500 mg TID); 65.4% in a chondroitin alone arm (400 mg TID); & 66.6% in a glucosamine-plus-chondroitin arm (500 mg/400mg TID) (p=0.09), according to a study results reported at the American College of Rheumatology meeting in San Diego Nov/05). http://nccam.nih.gov/news/19972000/121100/qa.htm (InfoPOEMs: Glucosamine HCl and chondroitin provides modest if any symptomatic benefit for patients with mild osteoarthritis of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (LOE = 1b)) Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham CO 3rd, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE,Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: A report from the glucosamine/chondroitin arthritis intervention trial. (GAIT) Arthritis Rheum. 2008 Sep 29;58(10):3183-3191. [Epub ahead of print] At 2 years, no treatment achieved a predefined threshold of clinically important difference in JSW loss as compared with placebo. However, knees with K/L grade 2 radiographic OA appeared to have the greatest potential for modification by these treatments.

Coghlan ML, Haile J, Houston J, et al. **Deep Sequencing of Plant and Animal DNA** Contained within Traditional Chinese Medicines Reveals Legality Issues and Health Safety Concerns. PLoS Genet. 2012 Apr;8(4):e1002657.

Cohen PA. American roulette--**contaminated dietary supplements**. N Engl J Med. 2009 Oct 15;361(16):1523-5. Epub 2009 Oct 7.

Complementary and alternative medicine-what people ≥50 are using & discussing with their doctor Jan/07 Nearly two-thirds of older people in the U.S. use complimentary or alternative therapies, but less than a third of the users discuss the practice with their physicians, according to a survey commissioned by the NIH and the AARP. The survey was based on interviews last year with about 1600 people aged 50 and older. The leading reason people said they don't discuss alternative therapies -- which include herbal and dietary supplements, massage, and chiropractic manipulation -- is that physicians never ask. Others said, among other reasons, that they did not know they should or they did not have enough time during the office visit. In addition, nearly 75% of respondents report taking one or more prescription medications, and nearly 60% said they take over-the-counter medications. http://assets.aarp.org/rgcenter/health/cam_2007.pdf

Connor KM, Payne V, Davidson JR. **Kava** in generalized anxiety disorder: three placebo-controlled trials. Int Clin Psychopharmacol. 2006 Sep;21(5):249-53. No evidence of hepatotoxicity was found with kava, and all of the treatments were well tolerated. Findings from these three controlled trials do not support the use of kava in DSM-IV generalized anxiety disorder.

Cox MC, et al. Influence of **garlic** (Allium sativum) on the pharmacokinetics of docetaxel. Clin Cancer Res. 2006 Aug 1;12(15):4636-40. This study indicates that garlic does not significantly affect the disposition of docetaxel. However, it cannot be excluded that garlic decreases the clearance of docetaxel in patients carrying a CYP3A5*1A allele.

Cvijovic K, Boon H, Barnes J et at. A **tool for rapid idenfification** of potential herbal medicine –drug interactions. Can Pharm J 2009;142:224-227. (September-October 2009) http://www.cpjournal.ca/archive/1913-701X/142/5/pdf/i1913-701X-142-5-e1.pdf

TOP

Cvijovic K, Boon H, Jaeger W, Vohra S; for the SONAR group. Polypharmacy, multiple **natural health products and hepatotoxicity**. CMAJ. 2011 Oct 4;183(14):E1085-E1089.

Dahmer S, Schiller RM. **Glucosamine**. Am Fam Physician. 2008 Aug 15;78(4):471-6.

Dahmer S, Scott E. Health effects of **hawthorn**. Am Fam Physician. 2010 Feb 15;81(4):465-8.

Dekosky ST, Williamson JD, Fitzpatrick AL, et al.; for the Ginkgo Evaluation of Memory (**GEM**) Study Investigators. **Ginkgo** biloba for Prevention of Dementia: A Randomized Controlled Trial. JAMA. 2008 Nov 19;300(19):2253-2262. (n=3,069 6.1yrs) In this study, G biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.

Denham Bryan E. Dietary Supplements—**Regulatory Issues (DSHEA)** and Implications for Public Health. JAMA. 2011;Published online July 5, 2011. doi:10.1001/jama.2011.982

De Silva V, El-Metwally A, Ernst E, et al. Evidence for the efficacy of complementary and alternative medicines in the management of **osteoarthritis**: a systematic review. Rheumatology (Oxford). 2011 May;50(5):911-20. The available data for most complementary and alternative medicine (CAM) in treating patients with degenerative joint disease is limited. Topical capsaicin and S-adenosyl methionine (SAMe) appear to be effective in treating pain, but even these data are limited and potentially subject to bias in favor of publishing positive results. (LOE = 1a-)

De Smet PA. **Herbal remedies**. N Engl J Med. 2002 Dec 19;347(25):2046-56.

Dhesi Pavittarpaul; Ng Rita; Shehata Michael M.; Shah Prediman K.. Ventricular Tachycardia After Ingestion of **Ayurveda Herbal** Antidiarrheal Medication Containing **Aconitum**. Arch Intern Med. 2010;170(3):303-305.

Dhiman RK, Chawla YK. Herbal medicines for liver diseases. Dig Dis Sci. 2005 Oct;50(10):1807-12. (InfoPOEMs: There is insufficient evidence to recommend most commonly used herbal medicines for the treatment of liver disease. Of the 4 products evaluated in this review -- Phyllanthus, Silybum marianum (milk thistle), **glycyrrhizin** (licorice root extract), and Liv 52 (a mixture of herbs) -- available evidence supports only the use of the **licorice root extract** in the treatment of subacute liver failure and the prevention of hepatocellular carcinoma in patients with chronic hepatitis C. (LOE = 2a))

Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of ginkgo biloba for the prevention of cognitive decline. Neurology. 2008 Feb 27; [Epub ahead of print] n=118 42 month In unadjusted analyses, **ginkgo biloba** extract (GBE) neither altered the risk of progression from normal to Clinical Dementia Rating (CDR) = 0.5, nor protected against a decline in memory function. Secondary analysis taking into account medication adherence showed a protective effect of GBE on the progression to CDR = 0.5 and memory decline.

Draves AH, Walker SE. Analysis of the hypericin and pseudohypericin content of commercially available **St John's Wort** preparations. Can J Clin Pharmacol. 2003 Fall;10(3):114-8.

Draves AH, Walker SE. Parthenolide content of Canadian commercial **feverfew** preparations (Label claims are misleading in most cases). CPJ Dec 2003/Jan 2004, Vol. 136, No. 10, p23-30.

Drieling RL.; Gardner CD.; Ma Jun; et al. No Beneficial Effects of **Pine Bark Extract** 200mg daily on Cardiovascular Disease Risk Factors. Arch Intern Med. 2010;170(17):1541-1547. n=130, 12 wk.

Effect of **Gamma-Linolenic Acid** on the Transcriptional activity of the Her- 2/neu (erbB-2) oncogene. Journal of the National Cancer Institute, Vol. 97, No. 21, November 2, 2005, p. 1611-1615.

Elderberry extract has long been used as a folk remedy for cold and influenza symptoms. A recent randomized trial provides evidence for its efficacy (level 2 [mid-level] evidence). During the spring 2009 influenza season in China, 64 patients with ≥ 3 influenza-like symptoms (fever, headache, myalgias, coughing, nasal mucus discharge, nasal congestion) were randomized within 24 hours of symptom onset to elderberry extract lozenge (175 mg) vs. placebo orally 4 times daily for 2 days. After 48 hours, the rate of complete symptom relief was higher in the elderberry group (28% vs. 0%, no p value reported), with at least some symptom relief (only 0-2 mild symptoms remaining) reported in 88% vs. 16% for placebo (no p value reported). Elderberry extract was associated with significantly improved symptom severity scores for headache, nasal congestion, muscle aches, and fever at 24 hours ($p < 0.001$) and for all symptoms at 48 hours ($p < 0.001$). The elderberry group had higher symptom scores at baseline, however, suggesting that the groups may have been at different stages in their overall illness course despite randomization within 24 hours (Online J Pharmacol Pharmacokin 2009;5:32).

Ernst E. **Cardiovascular adverse effects of herbal medicines**: a systematic review of the recent literature. Can J Cardiol. 2003;19:818-27.

Fava M, Alpert J, et al. A Double-blind, Randomized Trial of **St John's Wort**, Fluoxetine, and Placebo in Major Depressive Disorder. J Clin Psychopharmacol. 2005 Oct;25(5):441-447.

FDA May 2007 FDA chemical analysis revealed that **Energy Max** contains thione analog of sildenafil, a substance with a structure similar to sildenafil, the active ingredient in Viagra, an FDA-approved drug for ED.Substances like this are called analogs because they have a structure similar to another drug and may cause similar side effects and drug interactions. **True Man** contains a thione analog of sildenafil or piperadino vardenafil, an analog of vardenafil, the active ingredient in Levitra, another FDA-approved prescription drug for ED. Neither the thione analog of sildenafil nor piperadino vardenafil are components of approved drug products.

FDA Feb/08 Palo Alto Labs and FDA notified consumers and healthcare professionals of a voluntary nationwide recall of two dietary supplements, **Aspire36** and **Aspire Lite**. The products were recalled because they were found to contain Aildenafil in trace amounts and Dimethyl sildenafil thione, an analog of Sildenafil, a drug used to treat erectile dysfunction.

FDA Mar/08 The U.S. Food and Drug Administration is advising consumers not to purchase or use "**Blue Steel**" or "**Hero**" products, marketed nationally as dietary supplements, because these products contain undeclared ingredients similar to sildenafil.

FDA April/08 **Herbal Science International**, Inc. and FDA informed consumers and healthcare professionals of a nationwide recall of twelve dietary supplements that contain ephedra, aristolochic acid or human placenta because they may present a serious health hazard to consumers. FDA has long regarded dietary supplements containing ephedra, a botanical that contains ephedrine alkaloids, as a potential health hazards because the alkaloid raises blood pressure and otherwise stress the circulatory system.

FDA May/08 is requesting that the manufacturer of **Xiadafil** — an "all natural" dietary supplement sold to treat erectile dysfunction — recall all its stock from natural food stores & discontinue marketing it on the Web since it contains an analog of sildenafil.

FDA May/08 notified consumers and healthcare professionals that supplement products sold under the brand name of **Viril-ity Power** (VIP) Tablets is being recalled because one lot was found to contain a potentially harmful undeclared ingredient, hydroxyhomosildenafil, an analog of sildenafil.

FDA May/08 The US Food and Drug Administration advised consumers not to use the products **Total Body Formula** in Tropical Orange and Peach Nectar flavours, and **Total Body Mega Formula** in Orange/Tangerine flavour, because they contain high doses of selenium and chromium.

FDA July/08 Jack Distribution, LLC issued a voluntary nationwide recall of selected lots of **Rize 2 The Occasion Capsules** and **Rose 4 Her Capsules**, marketed as dietary supplements. The products were recalled because certain lots contained thiomethisosildenafil, an undeclared analog of sildenafil, a FDA-approved drug used for Erectile Dysfunction.

FDA July/08 not to buy or use **Viapro** 375mg Capsules because one lot of the product was found to contain a potentially harmful undeclared ingredient, thio-methisosildenafil, an analog of sildenafil.

FDA Nov/08 Balanced Health Products, Inc. announced a recall of **STARCAPS** due to the presence of an undeclared drug ingredient, Bumetanide. Bumetanide is a diuretic indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease including nephrotic syndrome.

FDA Nov/08 Fashion Sanctuary announced a recall of **Zhen De Shou Fat Loss** Capsules because FDA analysis found the product to contain undeclared sibutramine, an FDA approved drug used as an appetite suppressant for weight loss.

FDA Dec/08 alerted consumers not to purchase or consume more than **25 different products** marketed for weight loss because they contain undeclared, active pharmaceutical ingredients that may put consumers' health at risk. The undeclared active pharmaceutical ingredients in some of these products include sibutramine (a controlled substance), rimonabant (a drug not approved for marketing in the USA), phenytoin (an anti-seizure medication), and phenolphthalein (a solution used in chemical experiments and a suspected cancer causing agent). The weight loss products, some of which are marked as "dietary supplements," are promoted and sold on various web sites and in some retail stores. FDA advises consumers who use the products to stop taking them and consult their healthcare professional immediately as the health risks posed by these products can be serious (for example, high blood pressure, seizures, tachycardia, palpitations, heart attack or stroke). FDA also encourages consumers to seek guidance from healthcare professional before purchasing weight loss products. See the FDA News Release for a listing of the names of the 25 referenced products. Read the MedWatch 2008 safety summary, including links to the News Release and Questions and Answers, at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Weight

FDA Jan/09 notified consumers not to take **Venom HYPERDRIVE 3.0**, a product sold as a dietary supplement but containing sibutramine.

FDA Apr/09: **ABC Beauty Supply** & FDA notified consumers and healthcare professionals of a recall of 34 dietary supplement products. FDA lab analyses identified undeclared **sibutramine**, an FDA- approved drug, used as an appetite suppressant for weight loss. http://www.fda.gov/oc/po/firmrecalls/universalabc04_09.html

FDA Apr/09 Nature & Health Co. and FDA notified healthcare professionals of a recall of a supplement product, **Libimax**. FDA analysis found the product contains tadalafil

FDA May/09 warned consumers to immediately stop using **Hydroxycut** products by Iovate Health Sciences, Inc. Hydroxycut products are associated with a number of serious **liver injuries**. Hydroxycut products are dietary supplements that are marketed for weight-loss, as fat burners, as energy-enhancers, as low carb diet aids, and for water loss under the **Iovate and MuscleTech brand** names. FDA has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, an indicator of potential liver injury, to liver damage requiring liver transplant. One death due to liver failure has been reported to FDA. Other health problems reported include seizures; cardiovascular disorders; and rhabdomyolysis, a type of muscle damage that can lead to other serious health problems such as kidney failure.

FDA June/09 notified consumers and healthcare professionals to discontinue use of three **Zicam Nasal Gel/Nasal Swab** products sold over-the-counter as cold remedies because they are associated with the loss of sense of smell that may be long-lasting or permanent.

FDA July/09 and Haloteco notified healthcare professionals and consumers of a nationwide voluntary recall of Libipower Plus. Lab analysis of **Libipower Plus** samples were found to contain undeclared Tadalalafil.

FDA July/09 notified healthcare professionals that four weight loss dietary supplements sold and marketed by the firm (**Slimbionic, One Weight Loss Pill, SlimDemand Capsules, Botanical Weight Loss**) contain sibutramine.

FDA Aug/09 not to use body-building products marketed as containing steroids or steroid-like substances. The affected products are TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, and TT-40-Xtreme..

FDA Nov/09 notified consumers that **Stiff Nights**, a product sold as a dietary supplement, contains sulfoaildenafil, a chemical similar to sildenafil (Viagra).

FDA Nov/09 & GMP Herbal Products notified consumers and healthcare professionals of a recall of **Pai You Guo**, a weight loss dietary supplement, due to the presence sibutramine & phenolphthalein.

FDA Nov/09 & RockHard Laboratories notified consumers that **RockHard Weekend**, a product sold as a dietary supplement, contains sulfoaildenafil, an analogue of sildenafil.

FDA Nov/09 & IDS Sports notified consumers that five of the IDS's dietary supplement products (**Bromodrol, Dual Action Grow Tabs, Grow Tabs, Mass Tabs, and Ripped**

TOP

Tabs TR) contain the following undeclared substances, which FDA considers to be steroids: "Madol," "Turinabol," "Superdrol," &/or "Androstenedione."

FDA Dec/09 for **S-DROL**: a voluntary recall by the manufacturer of one lot (lot# 810481, expiry date 01/2012) of S-DROL after FDA testing found it to contain undeclared desoxymethyltestosterone.

FDA Dec/09 warned consumers to stop using bodybuilding products manufactured by American Cellular Labs after they were found to contain unauthorized synthetic steroids in **TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, TT-40-Xtreme.**

FDA Dec/09 warned that **Atlas Operations, Inc**. notified consumers of a nationwide recall of the company's dietary supplements for sexual enhancement. These products are sold as dietary supplements throughout the USA. FDA lab analyses found that the products tested from certain batches contain Sulfoaildenafil.

FDA Dec/09 The Texas Department of State Health Services and FDA notified healthcare professionals and consumers, especially pregnant or breastfeeding women, to avoid consuming a product called "**Nzu**", taken as a traditional remedy for morning sickness,because of the potential health risks from high levels of lead and arsenic, noted on laboratory analysis by Texas DSHS. Nzu, which is sold at African specialty stores is also called Calabash clay, Calabar stone, Mabele, Argile and La Craie. It generally resembles balls of clay or mud and is usually sold in small plastic bags with a handwritten label identifying it as "Nzu" or "Salted Nzu."

FDA Jan/10 & **MuscleMaster(dot)com**, Inc. notified consumers and healthcare professionals of the voluntary nationwide recall of all lots and expiration dates of the seventeen dietary supplements listed in the firm press release, sold between June 1, 2009 and November 17, 2009. FDA informed MuscleMaster(dot)com that it believes that the recalled products contain ingredients that are **steroids**.

FDA Jan/10 notified consumers and healthcare professionals about a counterfeit and potentially harmful version of **Alli 60 mg capsules** (120 count refill kit). The **counterfeit** version contained the controlled substance sibutramine and did not contain orlistat, the active ingredient.

FDA Mar/10 & Natural Wellness notified consumers that **MasXtreme**, a product sold as a dietary supplement contains aildenafil close in structure to sildenafil and is expected to possess a similar pharmacological and adverse event profile as well as the drug phentolamine which is an alpha-adrenergic blocker.

FDA Apr/10 & Kanec USA notified healthcare professionals of a nationwide recall of **Stud Capsule For Men** [Lot #060607-01/060108-01, Exp 6-2013], after being informed by FDA that laboratory analysis of a sample found the product to be adulterated with sildenafil, an FDA approved drug.

FDA May/10 notified healthcare professionals, their patients, and consumers not to consume **Vita Breath**, a dietary supplement manufactured by American Herbal Lab and marketed at health fairs and on the Internet, because the product may contain hazardous levels of lead.

FDA June/10 **Magic Power Coffee**: Product marketed as a dietary supplement for sexual enhancement contains the drug ingredient hydroxythiohomosildenafil.

FDA July/10 analysis of **Que She** found that it contains: fenfluramine – a stimulant drug withdrawn from the U.S. market in 1997 after studies demonstrated that it caused serious heart valve damage, propranolol – a prescription beta blocker drug that can pose a risk to people with bronchial asthma and certain heart conditions, sibutramine – a controlled substance and prescription weight loss drug, sibutramine was the subject of a recent study whose preliminary findings showed an association between sibutramine use and increased risk of heart attack and stroke in patients who have a history of heart disease, & ephedrine – a stimulant drug that is legally marketed over-the-counter for temporary relief of asthma but can pose a risk to people with certain cardiovascular conditions.

FDA Aug/10 lab analysis of **Solo Slim** was found to contain the undeclared drug ingredient Didesmethyl Sibutramine.

FDA Aug/10 lab analysis of **Revivexxx Extra Strength** was found to contain undeclared tadalafil.

FDA Aug/10 notified Novacare LLC that certain products appear to contain sulfoaildenafil: **Stiff Nights, Aziffa, Size Matters, Erex, Mojo, Hard Drive, Eyeful, Red Magic, Straight Up, Zotrex, Monster Excyte, WOW, Xaitrex, Verect, Prolatis, Xytamax, Maxyte, Libidinal, OMG, OMG45, and Zilex (with Golden Spear) summers**.

FDA July/10 lab analysis of **Slim-30** Herb Supplement distributed by the company was found to contain undeclared N-Desmethyl Sibutramine and traces of Sibutramine.

FDA July/10 & Good Health, Inc. is conducting a voluntary recall after FDA lab analyses found that the product tested from certain batches of **Vialipro** contain Sulfoaildenafil.

FDA July/10 lab analysis of this herb supplement, **Joyful Slim** Herb Supplement, was found to contain the undeclared drug, desmethyl sibutramine.

FDA July/10 warned consumers not to consume or use **Miracle Mineral Solution**, an oral liquid solution also known as "Miracle Mineral Supplement" or "**MMS**." The product, when used as directed, produces an industrial bleach.

FDA July/10 notified consumers that lab analysis of lots of ejaculoid **XXTREME** and **stimuloid II** found that the products, sold as dietary supplements, contain sulfoaildenafil

FDA Aug/10 had Lab analysis of **Mr. Magic** to contain hydroxythiohomosildenafil and sulfoaildenafil.

FDA Aug/10 analyzed **TimeOut** and determined that it contains hydroxythiohomosildenafil.

FDA Sep/10: Products marketed as dietary supplements contain **aromatase inhibitors**, commonly known as "ATD." Adverse events associated with the use of aromatase inhibitors could include the following: decreased rate of bone maturation and growth, decreased sperm production, infertility, aggressive behavior, adrenal insufficiency, kidney failure, and liver dysfunction. Advanced Muscle Science (Arom-X, Arom-X UTT, Arom-XL, 4-AD, and Decavol), ArimaDex, Clomed, Off Cycle II Hardcore, iForce – Reversitol.

FDA Oct/10 advised consumers to avoid "**chelation**" products that are marketed over-the-counter (OTC) to prevent or treat diseases. There are serious safety issues associated with chelation products. Depending on the condition, when relying on unproven OTC chelation products to treat serious conditions, patients may delay seeking effective medical care. Even when used under medical supervision, these products can cause serious harm, including dehydration, kidney failure, and death.

FDA Nov/10 ISSUE: Lab analysis has found **Duro Extend** Capsules for Men to contain Sulfoaidenafil, an analogue of Sildenafil.

FDA Dec/10 warned consumers not to use **Man Up Now** capsules, marketed as a dietary supplement for sexual enhancement, because FDA analysis determined that the product contains sulfoaildenafil.

FDA Dec/10 notified the public that testing determined that **RockHard Weekend** Lot Numbers 100159 and 100260 sold as blister packs, 3ct bottles and 8ct bottles & **Pandora** Lot Numbers 100378 sold as blister packs & **Passion Coffee** contain an analogue of sildenafil.

FDA Dec/10 has received multiple reports of adverse events associated with the use of **Fruta Planta**, including several cardiac events and one death. FDA laboratory analysis confirmed that Fruta Planta contains sibutramine.

FDA Jan/11 laboratory analysis confirmed that **Celerite Slimming Capsules** contain sibutramine

FDA Mar/11 lab analysis of **Svelte 30** orange & gray capsules determined that the product contains Sibutramine.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analysis confirmed that **Black Ant** contains sildenafil.

FDA Mar/11 **:** USA Far Ocean Group, Inc. issues voluntary nationwide recall of **U-Prosta**, a product marketed as a dietary supplement that contains undeclared terazosin.

FDA Mar/11 ISSUE: Tested samples of **Soladek** contained levels of vitamin A and vitamin D that were many times the recommended daily allowances for these vitamins.

FDA Mar/11 laboratory analyses of **Celerite Slimming Tea**: Recall - were found to contain undeclared Sibutramine.

FDA Mar/11 ISSUE: FDA lab analysis of **X-Hero** found the product contains sulfosildenafil, the analogue of the active ingredient of an FDA-approved drug. In addition, FDA analysis of **Male Enhancer** sample found the product contains tadalafil.

FDA Apr/11 Lab analyses of **Best Enhancer** found that the product contain Sulfoaildenafil.

FDA Apr/11 "**U-Prosta Natural support for prostate health**" is being voluntarily recalled in Canada by Sunnylife International Inc. after the U.S. Food and Drug Administration (FDA) found the product contains undeclared terazosin.

FDA May/11 **Regenerect**: Recall - Undeclared Drug Ingredient of lab confirmed the presence of Sulfoaildenafil.

FDA May/11 laboratory analysis confirmed that "**Slim Xtreme Herbal Slimming Capsule**" contains sibutramine.

FDA June/11 lab analyses found Via **Xtreme Ultimate Sexual Enhancer Dietary** Supplement for Men to contain sulfoaildenafil methanesulfonate.

FDA June/11 Nature Relief and FDA notified the public of a recall of **Nature Relief Instant Wart and Mole Remover**. FDA has advised that the active ingredient, calcium oxide, can cause severe burns of the skin, particularly to areas of thin or sensitive skin, such as the face, area around the eyes, and genitalia.

FDA July/11 is advising consumers not to purchase or use "**Slim Forte Slimming Capsules**," "**Slim Forte Slimming Coffee**," and "**Botanical Slimming Soft Gel**

TOP

& Slim Forte Double Power Slimming Capsules. FDA laboratory analysis confirmed that these products contain sibutramine.

FDA Oct/11 notified the manufacturer that lab analyses found that the product; **Uprizing 2.0** , sold as a testosterone booster, contains superdrol, a synthetic steroid, making it an unapproved new drug.

FDA Nov/11 lab analysis for Lot 10090571 found **Virility Max** to contain sulfoaildenafil.

FDA Dec/11 Eclectic Institute is voluntarily recalling specific lots of its freeze-dried capsules containing **Gotu Kola** (Centella asiatica) and **Bladderwrack** (Fucus vesiculosus) capsules because of potential Salmonella contamination.

FDA Feb/12 Healthy People Co. notified the public of a recall of the company's dietary supplements sold under the brand names Healthy People Co. FDA lab analysis confirmed the presence of Sibutramine and Tadalafil, making these products unapproved new drugs. (Mince Belle Dietary Supplement, PERFECT Men Dietary Supplement , EVERLAX Dietary Supplement, EVER Slim Dietary Supplement, Herbal Drink Acai-man Mangosteen Dietary Supplement, EVER SLIM Shake Mix Dietary Supplement)

FDA Feb/12 Regeneca, Inc. notifed the public of a nationwide recall of **RegenArouse**, Lot Number 130100. FDA lab analysis confirmed the presence of Tadalafil.

FDA Feb/12 is advising consumers not to purchase or use "**Hard Ten Days**," & "**Man King**" a product for sexual enhancement sold on various websites. FDA laboratory analysis confirmed that "Hard Ten Days" contains sildenafil

FDA Feb/12 is advising consumers not to purchase or use "**Japan Weight Loss Blue**," a product for weight loss sold on various websites, laboratory analysis confirmed that "Japan Weight Loss Blue" contains sibutramine, analogs of sibutramine, and ephedrine alkaloids.

FDA Mar/12 notified healthcare professionals and warned consumers not to use skin creams, beauty and antiseptic soaps, or lotions that might contain **mercury**. The products are marketed as **skin lighteners and anti-aging** treatments that remove age spots, freckles, blemishes and wrinkles. Adolescents also may use these products as acne treatments.

FDA Apr/12 laboratory analysis confirmed that "**Japan Rapid Weight Loss Diet Pills Yellow**" contains sibutramine and phenolphthalein.

FDA Apr/12 laboratory analysis confirmed that "**France T253**" contains sildenafil.

FDA Apr/12 is advising consumers not to purchase or use "**X-Rock**," a product for sexual enhancement manufactured by CRM Laboratories and sold on various websites, including www.xrockme.com. FDA laboratory analysis confirmed that "X-Rock" contains sildenafil and hydroxythiohomosildenafil.

FDA Apr/12 laboratory analysis confirmed that "**Instant Hard Rod**" contains aminotadalafil. FDA laboratory analysis confirmed that "**ZenMaxx**" contains aminotadalafil. FDA laboratory analysis confirmed that "**RigiRx Plus**" contains aminotadalafil.

FDA May/12 is advising consumers not to purchase or use "**VMaxx Rx**," a product for sexual enhancement sold on various websites, including www.vmaxxrx.com. FDA laboratory analysis confirmed that "VMaxx Rx" contains the undeclared ingredient sulfoaildenafil. FDA is also advising consumers not to purchase or use "**Boost — Ultra Sexual Enhancement Formula**." This product is promoted and sold on various websites, including www.boostultra.biz. FDA laboratory analysis confirmed that "Boost—Ultra Sexual Enhancement Formula" contains sildenafil. FDA is also advising consumers not to purchase or use "**Firminite**," a product for sexual enhancement sold on various websites, including **www.firminite.com.** FDA laboratory analysis confirmed that "Firminite" contains tadalafil.

FDA May/12 West Coast Nutritionals, Ltd. is conducting a recall of all lots of their dietary supplements **Firminite, Extra Strength Instant Hot Rod, and Libidron** to the consumer level. An FDA lab analysis of Firminite was found to contain undeclared Tadalafil.

FDA May/12 is advising consumers not to purchase or use "**EreXite**," a product for sexual enhancement sold on various websites, including www.amazon.com. FDA laboratory analysis confirmed that "EreXite" contains tadalafil.

FDA June/12 cautioned late last week against using **Reumofan Plus**, a dietary supplement marketed as a "natural" pain reliever for arthritis, osteoporosis, and other conditions. The drug, which is made in Mexico but available online, contains unlabeled and potentially harmful pharmaceutical ingredients: diclofenac, methocarbamol & sometimes dexamethasone.

Fish Oil Testing: Independent test for contaminants Nutrasource Diagnostics at the University of Guelp www.nutrasource.ca/ifos_new

Fleshner N, Harvey M, et al. Evidence for contamination of herbal **erectile dysfunction** products with phosphodiesterase type 5 inhibitors. J Urology 2005; 174:636-41.(InfoPOEMs: At least some natural products marketed for the treatment of erectile dysfunction are adulterated with phosphodiesterase type 5 inhibitors. Many of these products claim to be free of adverse effects but in truth may be potentially fatal to patients concomitantly using nitrates. (LOE = 4)) Two of 7 products (Super-X and Stamina-RX) contained significant amounts of **sildenafil** (Viagra, 30 mg) and tadalafil (Cialis, 20 mg), respectively.

Freeman MP, Mischoulon D, Tedeschini E, et al. **Complementary and alternative medicine for major depressive** disorder: a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. J Clin Psychiatry. 2010 Jun;71(6):682-8. Participants in CAM trials were more likely to be female and to have a lower placebo-response rate compared to those in standard antidepressant trials for MDD. Trials of standard antidepressants and CAM therapies were composed of patients with similar depression severity.

Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effect of **chondroitin sulfate 4&6** in hand osteoarthritis the finger osteoarthritis chondroitin treatment study (FACTS). Arthritis Rheum. 2011 Sep 6.

Gagnier JJ, van Tulder MW, Berman B, Bombardier C. Herbal medicine for low back pain: a Cochrane review. Spine. 2007 Jan 1;32(1):82-92. Harpagophytum procumbens, Salix alba, and Capsicum frutescens seem to reduce pain more than placebo. Additional trials testing these herbal medicines against standard treatments will clarify their equivalence in terms of efficacy. The quality of reporting in these trials was generally poor; thus, trialists should refer to the CONSORT statement in reporting clinical trials of herbal medicines. (InfoPOEMs: If these authors have included all the relevant studies, it appears that there is modest evidence that herbal remedies (oral Harpagophytum procumbens [devil's claw] and Salix alba [white willow bark], as well as topical Capsicum frutescens [cayenne]) alleviate acute episodes of chronic nonspecific low back pain in adults. In general, the reporting of the trials included in this systematic review was poor. Finally, this body of literature is prone to bias in favor of publishing positive results. (LOE = 1a-)) See also Cochrane Database Syst Rev. 2006 Apr 19;(2):CD004504.

Gardiner P, Phillips R et al. Herbal and Dietary Supplement- **Drug Interactions in Patients with Chronic Illnesses**. Am Fam Physician. 2008;77 (1):73-78.

Gardiner P, et al. Factors associated with dietary **supplement use** among prescription medication users. Arch Intern Med. 2006 Oct 9;166(18):1968-74. One in 4 prescription medication users took an NVDS in the prior 12 months, yet the majority did not share this with a conventional medical professional.

Gardner CD, Lawson LD, Block E, et al. Effect of raw garlic versus commercial **garlic** supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia. Arch Int Med 2007; 167:346-353. None of the forms of garlic used in this study, including raw garlic, when given at an approximate dose of a 4-g clove per day, 6 d/wk for 6 months, had statistically or clinically significant effects on LDL-C or other plasma lipid concentrations in adults with moderate hypercholesterolemia.

Gastpar M, et al. Comparative Efficacy and Safety of a Once-Daily Dosage of **Hypericum** Extract STW3-VI and Citalopram in Patients with Moderate Depression: A Double-Blind, Randomised, Multicentre, Placebo-Controlled Study.Pharmacopsychiatry. 2006 Mar;39(2):66-75.

Geller SE, Shulman LP, van Breemen RB, et al. Safety and efficacy of **black cohosh** and red clover for the management of vasomotor symptoms: a randomized controlled trial. Menopause 2009;16:1156–66.

Genazzani AR et al. Effect of 1-year, low-dose **DHEA** therapy (10mg daily) on climacteric symptoms and female sexuality. Climacteric. 2011 Dec;14(6):661-8.

Geng J, Dong J, Ni H, et al. Ginseng for cognition. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD007769. DOI: 10.1002/14651858.CD007769.pub2. Currently, there is a lack of convincing evidence to show a cognitive enhancing effect of Panax ginseng in healthy participants and no high quality evidence about its efficacy in patients with dementia. Randomized, double-blind, placebo-controlled, parallel group trials with large sample sizes are needed to further investigate the effect of ginseng on cognition in different populations, including dementia patients.

Genistein: Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2007 Aug;92(8):3068-75. Epub 2007 May 22. These results suggest that 54mg genistein plus calcium, vitamin D(3), and a healthy diet was associated with favorable effects on both glycemic control and some cardiovascular risk markers in a cohort of osteopenic, postmenopausal women. D'Anna R, Cannata ML, Atteritano M, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause. 2007 Jul-Aug;14(4):648-55. The phytoestrogen genistein has been shown to be effective on vasomotor symptoms without an adverse effect on endometrium. Marini H, Minutoli L, Polito F, et al. Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):839-47. Summary for patients in: Ann Intern Med. 2007 Jun 19;146(12):I34. Twenty-four months of tx with genistein has positive effects on BMD in osteopenic postmenopausal women.

Gertsch JH, Basnyat B, et al. Randomised, double blind, placebo controlled comparison of **ginkgo biloba** and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). BMJ. 2004 Apr 3;328(7443):797. Epub 2004 Mar 11.

Goldbach-Mansky R., et al. Comparison of **Tripterygium wilfordii** Hook F Versus Sulfasalazine in the Treatment of Rheumatoid Arthritis: A Randomized Trial. Ann Intern Med 2009; 229-240.

Gordon RY.; Cooperman T; Obermeyer W; et al. Marked Variability of Monacolin Levels in Commercial **Red Yeast Rice** Products: Buyer Beware! Arch Intern Med. 2010;170(19):1722-1727.

Grant SJ, Bensoussan A, Chang D, Kiat H, Klupp NL, Liu JP, Li X. Chinese herbal medicines for people with **impaired glucose tolerance or impaired fasting blood glucose**. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006690. The positive evidence in favour of Chinese herbal medicines for the treatment of IGT or IFG is constrained by the following factors: lack of trials that tested the same herbal medicine, lack of details on co-interventions, unclear methods of randomisation, poor reporting and other risks of bias.

Greco A et al. Acute hepatitis caused by a **natural lipid-lowering** product: when "alternative" medicine is no "alternative" at all. J Hepatology 2009; 50:1273.

Grossman E, et al. **Melatonin** reduces night blood pressure in patients with nocturnal hypertension. Am J Med. 2006 Oct;119(10):898-902. n=38 4weeks

Guo R, Canter PH, Ernst E. A systematic review of randomised clinical trials of individualised herbal medicine in any indication. Postgrad Med J. 2007 Oct;83(984):633-7. There is a sparsity of

evidence regarding the effectiveness of individualised herbal medicine & **no convincing evidence to support the use of individualised herbal medicine in any indication**.

Gunton JE, Cheung NW, et al. **Chromium** Supplementation Does Not Improve Glucose Tolerance, Insulin Sensitivity, or Lipid Profile: A randomized, placebo-controlled, double-blind trial of supplementation in subjects with impaired glucose tolerance. Diabetes Care. 2005 Mar;28(3):712-3.

Hadley S, Petry JJ. **Valerian**. Am Fam Physician. 2003 Apr 15;67(8):1755-8.

Health Canada is warning consumers: Jan/06 African herbal products **M2 Formula** & **Energy 2000** pose potential health risks http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_01_e.html

Health Canada is warning Aril/06 consumers not to not to use advises consumers not to use unauthorized products containing **anabolic steroids** (Five products containing illegal anabolic steroids, as they can potentially cause serious health issues such as liver disorders and heart problems. The five products are: Anabolic Xtreme Superdrol, Methyl-1-P, Ergomax LMG, Prostanozoland, and FiniGenX Magnum Liquid.)

Health Canada is warning consumers not to not to use **Kaizen Ephedrine HCL tablets for weight loss Dec/05** http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_138_e.html

Health Canada is warning consumers not to ingest the herb **chaparral** in the form of loose leaves, teas, capsules or bulk herbal products because of the risk of liver and kidney problems. Dec/05 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_135_e.html

Health Canada is warning consumers not to use certain **Ayurvedic medicinal** products because they contain high levels of heavy metals such as lead, mercury and/or arsenic. July/05 http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_80.html

Health Canada Jan/06 Natural health product **Libidfit** may pose health risks (promoted for sexual enhancement and erectile dysfunction, but contains an undeclared amount of a pharmaceutical ingredient similar to sildenafil) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_02_e.html

Health Canada is warning consumers Feb/06: Not to use the Chinese medicinal product White Peony Scar-repairing pills, manufactured in Hong Kong by White Peony Pharmaceuticals Limited, due to high levels of lead. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_05_e.html

Health Canada is warning consumers Feb/06 not to use 13 Chinese herbal products manufactured by the Hong Kong Chi Chun Tang Herbal Factory due to bacterial contamination that could lead to serious health risks. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_08_e.html

Health Canada advises consumers April/06 not to use Super Fat Burning and LiDa Daidaihua Slimming Capsules for weight loss because they have been found to contain sibutramine http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_15_e.html

Health Canada is advising consumers Apr/06 not to use unapproved products containing **yohimbine or yohimbe bark**, including Strauss Energy SIX capsules. Yohimbine is a prescription substance that can pose serious health risks for people with underlying risk factors. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_16_e.html

Health Canada is advising consumers Apr/06 not to use unapproved Miracle Bion products as it could be contaminated with bacteria such as *E. coli*. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_23_e.html

Health Canada May/06 is warning consumers not to use the product **Nasutra** because it has been found to contain the sildenafil (chemical name for Viagra) that could lead to serious health risks, especially for patients with existing medical conditions such as heart problems, those who may be taking heart medications, or those who may be at risk for strokes.

Health Canada May/06 is advising consumers not to use Ocean Plasma **Isotonic Living Water and Ocean Plasma Hypertonic Living Water** because they are unapproved products that contain unacceptable amounts of aerobic bacteria.

Health Canada June/06 is advising consumers not to use four unapproved **Ayurvedic medicinal products** from India because they contain high levels of lead and/or mercury. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_46_e.html

Health Canada July/06 is advising Fat Rapid Loss Capsules (Xin Yan Zi Pai Mei Zi Jiao Nang) because may contain sibutramine http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_55_e.html

Health Canada July/06 is advising consumers not to use 4 foreign health products due to concerns about possible side-effects: **Zhuifeng Tougu Wan** & **Fufang LuHui Jiaonang**, two traditional Chinese medicines that contain toxic levels of mercury; **Safi**, a herbal product manufactured in India and Pakistan that contains toxic levels of arsenic; and **Baike Wan**, a herbal product from Malaysia that contains the prescription drugs piroxicam and frusemide, and the over-the- counter drug chlorpheniramine.

Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well Dietary Supplement** because a sample has been found to contain **estazolam.**

Health Canada Warns Consumers August 04, 2006 Not To Use **Neophase** Formula For Men Due To Potential Health Risks which has been found to contain an undeclared ingredient similar to the active pharmaceutical ingredient found in Viagra. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_67_e.html

Health Canada Aug/06 is reminding consumers not to use Miracle II Miracle Neutralizer or any other products exported or sold by Tedco, Inc. of Louisiana because they could contain harmful bacteria. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_68_e.html

Health Canada Aug/06 is advising consumers about a possible link between health products containing the herbal medicine **black cohosh and liver damage**. There have been a number of international case reports of liver damage suspected to be associated with the use of black cohosh, including three case reports in Canada and one published case of death in the United States. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html

Health Canada Aug/06 is advising consumers not to use four foreign health products due to concerns about possible side-effects: **Reduce Weight**, a proprietary Chinese Medicine marketed as a weight-loss product. Contains the prescription drug sibutramine (the generic name for Meridia) **Yixinjiaonang**, a proprietary Chinese medicine marketed as a sexual enhancement & erectile dysfunction product, contains the prescription drug tadalafil (the generic name for Cialis) **Meng Rong**, a proprietary Chinese medicine marketed as a sexual enhancement and erectile dysfunction product, contains the prescription drug sildenafil (the generic name for Viagra) **VG**, a proprietary Chinese medicine marketed as a sexual enhancement and erectile dysfunction product, contains the prescription drug sildenafil (the generic name for Viagra) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/index_e.html

Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well** Dietary Supplement because a sample analyzed by Health Canada has been found to contain the undeclared drug Estazolam. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_82_e.html

Health Canada Aug/06 is advising consumers not to use two foreign health products due to concerns about possible side-effects: **Chao Nongsu Qingzhi Jiaonang** (OPC Care) is promoted as a weight-loss product. The product is adulterated with sibutramine and mazindol, two prescription medications used to suppress appetite. **Conting Qianweisu Slimming Herbs** Capsule is marketed as a weight-loss product. The product is adulterated with sibutramine, a prescription medication used to suppress appetite. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/2006/2006_84_e.html http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/2006/2006_83_e.html

Health Canada Sept/06 advises against use of the **Ayurvedic medicinal product Jambrulin** due to lead content http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_89_e.html

Health Canada Sept/06 is warning consumers not to use the natural health product **Libidus** because it contains an undeclared pharmaceutical ingredient, a modified form of vardenafil.

Health Canada Oct/06 is advising consumers not to use the unauthorized natural health products **Emperor's Tea Pill (Tian Huang Bu Xin Wan)** and **Hepatico Extract (Shu Gan Wan)** because certain lots of these products contain high levels of lead and mercury. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_98_e.html

Heath Canada Nov/ 06 is warning Canadians not to use the unauthorized product **Embrun de mer** promoted for the treatment of skin irritation in newborns and adults because it contains unacceptable amounts of harmful bacteria.

Health Canada Dec/06 is advising consumers not to use a product called **Eden Herbal Formulations Sleep Ease Dietary Supplement**, because it was found to contain an undeclared drug estazolam http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_127_e.html

Health Canada Dec/06 is advising consumers not to use two foreign health products due to concerns about possible side-effects: **Slim & Detox Peptide**, which are weight-loss products. Containing the prescription drug sibutramine (the generic name for Meridia) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/index_e.html

Health Canada Jan/07 is advising consumers not to use **Kang Da** and **four unlabelled products** are marketed as herbal sexual enhancements and treatments for erectile dysfunction. The products are adulterated with a prescription medication used in the treatment of sexual dysfunction. **Qing Zhi** and one unlabelled product are marketed as herbal weight-loss products. The products are adulterated with sibutramine, a prescription medication used to suppress appetite.

Health Canada Feb/07 is advising consumers not to use a product called **Sleepees**, because it was found to contain an undeclared drug **estazolam**, which can be habit-forming when used for as little as a few months. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_16_e.html

Health Canada Feb/07 is updating Canadians about adverse reaction reports it has received concerning the use of **EMPowerplus**, a vitamin mineral supplement, for serious medical conditions. Health Canada has received nine case reports of serious adverse reactions associated with the use of EMPowerplus. Most of the adverse reactions relate to worsening of psychiatric symptoms in those patients with serious underlying mental health problems, such as bipolar disorder and depression.

Health Canada Feb/07 is advising consumers not to use the following product listed in the table below due to concerns about possible side-effects. More info **Power 58; Platinum Power 58; Ehanix; Jolex; Onyo; Deguozonghengtianxia** because they contained acetildenafil. Acetildenafil is an analogue of sildenafil, a prescription medication indicated for treatment of erectile dysfunction.

Health Canada Mar/07 is Health Canada is advising consumers not to use **MIAOZI Slimming Capsules** because they have been found to contain sibutramine, a prescription medication that should only be taken under medical supervision.

Health Canada Mar/07 is warning consumers not to use the unauthorized natural health product **XOX For Men**, because it contains an undeclared pharmaceutical ingredient, tadalafil, an ingredient found in the prescription drug Cialis. The use of XOX For Men could pose serious health risks, especially for patients with existing medical conditions such as heart problems, those taking heart medication, or those at risk of stroke.

Health Canada Mar/07 is warning consumers not to use the unauthorized product **Vigorect** Oral Gel Shooter, because it contains an undeclared drug substance tadalafil.

Health Canada Apr/07 is warning consumers about **Bitter orange** & cardiovascular reactions in the Canadian Adverse Reactions April 2007 Newsletter.

Health Canada Apr/07 is warning consumers from The Hong Kong Department of Health found **Lanmei Keili Ji to be adulterated with gliclazide**, a hypoglycaemic agent (lowers blood sugar). The Hong Kong Department of Health found **Lexscl Fat Rapid Loss capsules to be adulterated with sibutramine** and thyroid hormones. The United States Food and Drug Administration found **V.MAX and Rhino Max (Rhino V Max) to contain undeclared amounts of aminotadalafil**, an analogue of tadalafil, used to treat erectile dysfunction.

Health Canada April/07is advising consumers not to use a product called **Eden Herbal Formulations Serenity Pills II** because it contains the undeclared drug **estazolam**.

TOP

Health Canada April/07is advising consumers not to use a product **FiberChoice plus Multivitamins** is marketed as a fibre supplement. The product is contaminated with **fish gelatin**, a known allergen that could cause life-threatening reactions in some sensitive individuals.

Health Canada May/07 is warning consumers **Urat Madu** capsules are marketed for the treatment of erectile dysfunction. The product is adulterated with **sildenafil**, a prescription drug that has been associated with serious side effects including sudden vision loss, penile tissue damage and urinary tract infection.

Health Canada May/07 is advising consumers not to use **Xiaokeshuping Jiangtangning Jiaonang** capsules in Hong Kong to contain the undeclared pharmaceutical drugs phenformin, rosiglitazone, and glibenclamide, which may be used in diabetes to lower blood sugar.

Health Canada May/07 is advising consumers that **HS Joy of Love** product is marketed as a dietary supplement and was found to contain piperadino **vardenafil**.

Health Canada May/07 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: **Power 58 Extra, Platinum Power 58 Extra, Enhanix New Extra Men's Formula, Valentino, King Power Oral Solution, and Stretch Up** Capsules are marketed as treatments for erectile dysfunction. The products contain analogues of sildenafil and vardenafil, which are prescription drugs used for the treatment of erectile dysfunction.

Health Canada June/07 is advising consumers not to use **Optimum Health Care SleePlus TCM** or **BYL SleePlus**, because the products contain the undeclared drug **clonazepam.**

Health Canada June/07 is warning consumers not to use the product **Encore Tabs for Men**, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.

Health Canada July/07 is warning Canadians not to use the dietary supplement **MdMt**, or any other supplements containing the synthetic steroids methyl-1-testosterone or methyldienolone that are obtained without a prescription, due to potentially serious health risks including reduced fertility and liver disorders.

Health Canada July/07 is warning consumers not to use **Zencore** Tabs, a product advertised as a dietary supplement for sexual enhancement, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.

Health Canada July/07 & the US Food and Drug Administration (FDA) found ***Liviro3*** to contain tadalafil, a prescription drug that should only be taken under the guidance of a health professional.

Health Canada July/07 is advising consumers not to use the sleep supplement product **Optimum Health Care Sleep Easy**, because it contains the undeclared drug clonazepam.

Health Canada July/07 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: **Jie Jie Pills** and **Chuan Xiong Cha Tiao Wan** are proprietary Chinese medicines that have been found to contain aristolochic acid, a natural toxin known to cause kidney failure and cancer in humans. Medsafe, the New Zealand health regulatory authority, advised the public not to use the products **Darling Capsules**, **Dali Capsules**, **Spanish Fly Capsules**, and an unnamed product, because they were found to contain sildenafil. Medsafe also advised the public not to use the product **Dai Dai Hua Jiao Nang** because it was found to contain sibutramine. The Hong Kong Department of Health [HKDH] found batch #WA00030 of the product K**ui Hua Chut Lee San Bird's Nest & Pearl** to exceed the acceptable limit for microbiological contaminants set out by the HKDH. Further investigation revealed that this product also exceeded the limit for bacterial contamination in Natural Health Products in Canada.

Health Canada Aug/07 Consumers who use **Excite for women or Ultimates for men** may be at risk of serious side effects similar to those associated with sildenafil.

Health Canada Aug/07 is advising Canadians of a recall in the United States of one lot of **Metaboslim Apple Cider Vinegar**, which is marketed as a dietary supplement, because it has been found to contain **sibutramine**, a prescription medication that should only be taken under medical supervision.

Health Canada Sept/07 is advising consumers not to use 13 foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang, J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada. **Satis 60 Hours Ever Lasting Formula** is used for the treatment of erectile dysfunction/sexual enhancement. It was found to contain piperidenafil an analogue of vardenafil, a drug that should only be used under the supervision of a health professional. **Qiangli Zhuanggutongbiling** has reportedly been used for joint pain and stiffness. It was found to contain the undeclared prescription drugs prednisolone acetate, cortisone acetate, piroxicam, and diclofenac. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional. **Endopile Capsules** is used for the treatment of hemorrhoids and piles, and related symptoms and was found to contain potentially toxic levels of lead and mercury. **BuXie PaiDu XiaoDou Su** is used as an acne treatment and was found to contain the prescription drug rifampicin (rifampin). **True Man** and **Energy Max** are used as sexual enhancement/ erectile dysfunction products and were found to contain an analogue of sildenafil or vardenafil which are prescription medications.

Health Canada Sept/07 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: **Top Gun for Men Herbal Extracts** has been found to contain a substance similar to tadalafil. **Oyster Plus** has been found to contain tadalafil. **Deguozhanjiang** contains sildenafil and tadalafil, prescription drugs used for the treatment of erectile dysfunction. **Chongcaoliubian Jiaonang** and **Santi Scalper Penis Erection** Capsule contain sildenafil.

Health Canada Sept/07: **Khun-Phra** is a health product promoted for pain relief that has been found to contain the undeclared drugs dexamethasone, prednisolone, phenylbutazone, diazepam, cyproheptadine and mebhydrolin.. **Asam Urat Flu Tulang, PJ Dewandaru** is a health product promoted to treat joint pain, rheumatism and arthritis. It has been found to contain the undeclared drugs dexamethasone, diclofenac and acetaminophen.

Health Canada Oct/07 Foreign Product Alerts: ***Zhen Feng Da Brand Xi Tong Wan*** is promoted as a pain reliever. Lot #060908 has been found to contain undeclared indomethacin, a prescription anti-inflammatory drug that should only be taken under the guidance of a health professional. ***Wellring Brand Yin Qiao Jie Du*** is a health product promoted to treat cold and flu symptoms. Lot#51005 has been found to contain undeclared acetaminophen. ***Gu Ci Dan*** and ***Xu Log Bou*** are promoted as pain relievers and have been found to contain undeclared indomethacin. Indomethacin is a prescription anti-inflammatory drug that should only be taken under the guidance of a health professional.

Health Canada Oct/07 is advising, especially pregnant & breastfeeding women, not to use **Calabash chalk** because of the potential health risk due to high levels of lead.

Health Canada Oct/07: Foreign Product Alerts: **Red Yeast Rice, Red Yeast Rice/Policosonal Complex and Cholestrix, and Xie Gan Wan**. Red Yeast Rice, Red Yeast Rice/Policosonal Complex and Cholestrix are promoted as dietary supplements for the treatment of high cholesterol. These products may contain **lovastatin**, a prescription medication for the treatment of high cholesterol that should only be taken under the guidance of a health professional. Xie Gan Wan is a Proprietary Chinese Medicine with unknown indication for use. Xie Gan Wan, was found to contain **Aristolochia** plant species.

Health Canada Oct/07: **Royal Medic No.1 Chinese Caterpillar Fungus** is a proprietary Chinese medicine promoted as a general health tonic, but Health Canada advises Canadians not to use this product due to microbial contamination. **Steripaste Medicated Paste Bandages** may not be sterile therefore there is a possibility the bandage may cause a wound infection.

Health Canada Nov/07 is advising consumers not to use **Axcil** and **Desirin**, are promoted as natural sexual enhancement/ erectile dysfunction products. Consumers are warned not to use Axcil and Desirin because both products were found to contain the prescription drug **sildenafil**.

Health Canada Dec/07 is advising Canadians not to use unauthorized products manufactured by **Wild Vineyard** because of the potential health risk to consumers. Wild Vineyard is not authorized to manufacture, package, label or import natural health products in Canada.

Health Canada Jan/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **Baby's Bliss Gripe Water** (apple flavour), code 26952V, a natural health product given to infants to ease stomach discomfort and gas, was found to contain the parasite cryptosporidium. Cryptosporidium may cause severe, chronic or even fatal effects, especially in infants. **Zhong Ti Xiao Er Jian Pi San** is a natural health product. Batch number JPS0704 has been recalled due to microbial contamination.

Health Canada Jan/08 is warning Canadians not to use the unauthorized product **Yeniujyn** because the product contains heavy metal contaminants and may pose a serious health risk. Yeniujyn is advertised as a natural health product, for adults and children, to be used "to cure involuntary passage of urine diseases." The product was found to contain high levels of **lead and arsenic**.

Health Canada Jan/08 is warning Canadians not to use the unauthorized product 1- ZhenZhu HouFengSan Penji; Vyling Cornu Saigae Tataricae Cooling Tea; Natorny Kwek's Herb 106; Chinese Herbal Heritage Herbal Slimming Tea; Vyling Urticaria Itch-Killer A; Vyling Water- Melon Pearls Powder; Phoenix Brand Tea For Sore Throat And Fever; Qing Yin Bai Hua Tea; and Yinqiao Flu & Fever Tea. **Nine specific batches** of Chinese medicines and teas manufactured in Singapore that have been recalled due to microbial (bacterial) and/or yeast and mould **contamination**.

Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules (batch number 28012007 / expiration date: Jan 2009). This product is promoted for weight loss and has been found to contain a derivative of the prescription drug **sibutramine**.

RGC-RMC Rheumax Capsule (batch number REM1-SI93016N). This batch of RGC-RMC Rheumax Capsule has been found to contain **progesterone**, a steroid hormone that can have adverse effects on the brain, breast and skin and should only be taken if prescribed by a health professional.

Health Canada Feb/08 warning Canadians not to use Foreign Products: 1) **Jingzhi Kesou Tanchuan; Guanxin Suhe capsules**; **Qing Re An Cang Wan**; & **Guan Xin Su He** 2) **Xiao Qin Long Capsules** 3) **Xiao Qin Long Wan**; **Chuan Xiong Cha Tiao Wan Tablets**; **Bai Tou Weng Wan** 4) **Wannianqing Pai Danggui Niantong Tang** (batch number 050401) These products have been found to contain aristolochic acid, a toxin associated with serious and potentially fatal health effects.

Health Canada Feb/08 warning Canadians not to **use VPX 'No Shotgun' and BSN 'Cell Mass' Body Building Powders** These products have been found to contain coumarin.

Health Canada Feb/08 warning Canadians not to use 1) Ding Lu Brand Guipi Wan (batch number 060401); Ding Lu Brand Bushen Yijing Wan (batch number 060401); Ding Lu Brand Shiquan Dabu Wan (batch number 060401); **Ding Lu Brand Xiangsha Liujun Wan** (batch number 060401); Ding Lu Brand Xiaoyao Wan (batch

TOP

number 060401); Medco Brand Vitality Essence Extract Of Deer Fetus (batch number 61007); Plasmin (batch number 20060102) 2) **Yogaraja Gulgulu Pills** (batch number GK039) and Pilsol Capsule 3) **Conforer Global Yang Tonic-2** (batch number 060117) 4) **Liang Gel San Concentrated Powder** (batch number G3238913) and **Qing Xin Lian Zi Yin Concentrated** Powder (batch number G3239274) These products were found to contain excessive amounts of heavy metals.

Health Canada Mar/08 is warning consumers not to use **Libidus**, an unauthorized product promoted on the web site of the manufacturer for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the undeclared prescription drug sildenafil.

Health Canada April/08 is warning consumers not to use Foreign Product Alert: **Tetrasil, Genisil, Aviralex, OXi-MED, Beta-mannan Micronutrient, Qina** and **SlicPlus**. They are marketed for the prevention or treatment of a variety of sexually transmitted diseases.

Health Canada April//08 is advising consumers not to use 2 foreign products, **Aspire 36** & **Aspire Lite**, because they were found to contain undeclared sildenafil analogues.

Health Canada April/08 is warning consumers not to use **Vigoureux**, an unauthorized product promoted for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the prescription drug sildenafil

Health Canada April/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **Tian Li** was found to contain tadalafil and hydroxyhomosildenafil, and should only be taken under the guidance of a healthcare professional. **Xian Zhi Wei II** was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.

Health Canada April/08 is advising consumers not to use The Hong Kong Department of Health advised the public not to use the product **Tian Sheng Yi Bao** because it was found to contain two pharmaceutical products, glibenclamide and phenformin

Health Canada April/08 is advising consumers about The Health Sciences Authority (HSA) of Singapore recalled **Qili Brand Tongbianling Jiaonang, Sincere Brand ChuanXinLian Jiaonang, Xiangyao Brand Xiangyao Weian Jiaonang, Biflora Brand Fufang Danshen Pian (film-coated), Biflora Brand 306 Xiaoyan Jiedu capsules, and Xiang Sha Liu Jun Wan** as they were found to contain high levels of arsenic and/or mercury that exceeded the permissible limits outlined by the HSA standards of safety and quality.

Health Canada May/08 is advising consumers not to use **vpxl No1** Dietary Supplement for Men was found to contain tadalafil

Health Canada May/08 is reminding consumers who choose to use unapproved Ayurvedic medicinal products that some of these products may contain high levels of heavy metals. Consumption of excessive amounts of heavy metals, such as lead, mercury, and arsenic, pose serious health risks.

Health Canada May/08 is warning consumers not to use **Trophic Kelp & Glutamic Acid HCl** due to the health risk posed by exposure to high levels of iodine.

Health Canada May/08 is warning consumers not to use **Desire**, an unauthorized product promoted to enhance male sexual performance as this product may pose serious health risks in certain patients. Lot 0070263 of the product was found to contain the prescription drug phentolamine.

Health Canada June/08 is advising that **Desire** contains Phentolamine, which should only be used under the supervision of a health care professional.

Health Canada June/08 **6-OXO**, which contains the compound 4-androstene-3,6,17-trione, is an unauthorized natural health product in Canada. **1-AD** contains 1-androstenediol, an anabolic steroid that is regulated as a controlled substance in Canada

Health Canada July/08 Foreign Product Alerts: **Super Shangai,Strong Testis, Shangai Ultra, Shangai Ultra X, Lady Shangai, Shangai Regular (also known as Shangai Chaojimengnan), Actra-Sx, An unknown product containing the plant Lycium barbarum L., Adam Free, NaturalUp, Erextra, Yilishen, Blue Steel, Hero, & Naturalë Super Plus.** These products have been found to contain sildenafil or an unapproved substance similar to sildenafil.

Health Canada July/08 is advising consumers not to use 4 foreign health products due to concerns about possible side-effects: Wodibo. **Wodibo** is promoted as an all-natural Chinese potency-enhancing product for the treatment of erectile dysfunction. The Danish Medicines Agency has warned against the use of Wodibo because it was found to contain sildenafil and tadalafil, prescription drugs authorized for treatment of erectile dysfunction. Both of these medications should only be used under the supervision of a health care professional. **Viril-Ity-Power** (VIP) Tabs. The U.S. Food and Drug Administration has warned consumers not to use Viril-Ity-Power (VIP) Tabs because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil. The product has been recalled by the manufacturer in the U.S. **Therma Power** (red and blue varieties) and **Grenade Fat Burner**. The U.K. Medicines and Healthcare products Regulatory Agency (MHRA) warned consumers not to use the ephedrine-containing products Therma Power (red variety) and Grenade Fat Burner after the products were associated with serious adverse reactions. The MHRA also warned consumers to not use the ephedrine-free Therma Power (blue variety) because it contains synephrine and caffeine, a combination that has been associated with cardiovascular adverse reactions.

Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Dan Bai Shou Shen Su** was found to contain undeclared thyroid hormones and sibutramine. **Karntien and Karntien Easy to Slim** were adulterated with sibutramine and a compound that is similar in structure to sibutramine (N-desmethylsibutramine). **Armstrong Natural Herbal Supplement, Enhanix New Extra Men's Formula, Power 58 Extra, and Platinum Power 58 Extra** were adulterated with tadalafil or unapproved substances with structures similar to tadalafil and vardenafil. **More Slim** was found to contain the undeclared pharmaceutical ingredient sibutramine. **Soloslim** was found to contain an undeclared substance similar in structure to the prescription drug sibutramine. It also contains the prescription drug L-carnitine, as well as synephrine, which is not authorized for sale in weight loss products in Canada.

Health Canada Aug/08 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of Natural (Xin Yi Dai) and Lasmi because Natural (Xin Yi Dai) was found to contain sibutramine and phenolphthalein, and Lasmi was found to contain sibutramine and spironolactone. The Hong Kong Department of Health warned against the use of AA Qu Feng Shu Jin Wan because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. Apisate contained fenfluramine and Energy ll contained sibutramine. Obat Asam Urat and Asam Urat both contained dexamethasone, phenylbutazone and piroxicam. The Hong Kong Department of Health warned against the use of Slim 3in1 (Xiao Nan zhi Bao) because it was found to contain the undeclared pharmaceutical ingredients sibutramine and phenolphthalein.

Health Canada Sept/08 is advising consumers not to use any unauthorized health products sold under the brand names **Life Choice, Healthy Choice, Doctor's Choice and Your Choice** as well as other products without a brand name. All of these unauthorized health products have the same identifying image on their label.

Health Canada Sep/08 is advising consumers not to use 3 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lover Liquid Nutriment Herbal Supplement and Onyo** because they were found to contain undeclared pharmaceutical ingredients. **Lover Liquid Nutriment Herbal Supplement** was found to contain sildenafil while Onyo was found to contain sildenafil, as well as unapproved substances with structures similar to sildenafil and vardenafil. The U.S. Food and Drug Administration warned consumers not to use the product **Rose 4 Her** because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil.

Health Canada Sep/08 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Dr. Life** or **Chong Cao Ju Wang** because they were found to contain undeclared pharmaceutical ingredients. Dr. Life contains an unauthorised substance similar in structure to tadalafil while Chong Cao Ju Wang contains sildenafil. The Hong Kong Department of Health warned against the use of **Hanguo shoushen yihao** (meiti xing) because it was found to contain the undeclared pharmaceutical ingredient sibutramine. The U.S. Food and Drug Administration alerted consumers to a voluntary recall of 32-ounce plastic bottles of **Liquimax Complete Nutrition Multivitamin Formula** (UPC codes 7497052290, 7497023607 or 7497023696) because the product may contain undeclared fish (not shellfish), tree nuts (almonds, pecans, and/or walnuts), and wheat. People with sensitivities to fish, tree nuts and/or wheat may risk serious or life-threatening allergic reactions if they consume these products. The Hong Kong Department of Health warned against the use of **ARMA - Sin Gang San** and **New ARMA - Sin Gang San** because they were found to contain the undeclared pharmaceutical ingredients sibutramine and fenfluramine.

Health Canada Oct/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: Swissmedic warned consumers not to buy or use the product **Powertabs** because it contains an unauthorised substance similar in structure to sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Sweet Energizer Vitality** Candy because it was found to contain an unauthorised substance similar in structure to tadalafil.

Health Canada Nov/08 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lu Quan** because it contains undeclared glibenclamide and sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine, and **Zhuang Yao Gu Shen** Capsule because it contains sildenafil.

TOP

Health Canada Nov/08 is advising consumers not to use 13 foreign health products due to concerns about possible side-effects: The U.S. FDA warned consumers not to buy or use **Viapro** because it contains an unauthorised substance similar in structure to sildenafil. Sildenafil is a prescription drug used in the treatment of erectile dysfunction and should only be used under the supervision of a health care practitioner.
The U.S. Food and Drug Administration informed consumers of a voluntary manufacturer recall of these 12 products because they contain human **placenta, aristolochic acid and/or ephedra**, and may pose serious health risks. All 12 products are manufactured by **Jen-On Herbal Science** International Inc. (also known as **Herbal Science International Inc**.). Consumers who had purchased these products were advised to discontinue their use immediately and return them to the place of purchase for a full refund.

Health Canada Nov/08 is warning consumers not to use **Firm Dose** and **Granite Rooster**, two products promoted to enhance male sexual performance, as these products may pose serious health risks. Firm Dose was found to contain similar to sildenafil, while Granite Rooster was found to contain similar to tadalafil.

Health Canada Nov/08 is advising consumers not to use the unauthorized product, Kwan Loong Medicated Oil, as it contains chloroform. Foreign Product Alerts: Seng Jong Tzu Tong Tan,Tou Tong San (Headache Formula),Du Huo Ji Sheng ,Tang (Du Huo Joint Relief), Wu Yao Shun Qi San, Qing Bi Tang (Nasal Cleanser), Zhong Fong Huo Luo Wan (Stroke Revito Formula), Xiao Qing Long Tang (Little Green Dragon), Ding Chuan Tang (Breathe Smooth), Xiao Xu Ming Tang, Feng Shi Zhi Tong Wan (Joint Relief),,Guo Min Bi Yan Wan, Fang Feng Tong Sheng San.

Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains sibutramine.

Health Canada Mar/09 Foreign Product Alerts: **68 Weight Loss Products**; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien; Relacore -plus Lami, Linglongquxian, Menergy M-Essence, Nyal Day & Night Cold & Flu Fighter (AUST L 146264), Nyal Cold & Flu Fighter (AUST L 146263), 999 Radix Notoginseng, Batch no. 0807021, Slim Pure, Carbohydrate, Kalomee, K Carbohydrate, K Tighten Slim, & K Slimming Pills. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php

Health Canada June/09 Foreign Product Alerts: **Fangocur Mineral Drink** (undeclared arsenic); **Jia Yi Jian** (undeclared sibutramine & tadalafil);**Fortodol**, which is also sold under the names (undeclared nimesulide with liver concern) of Donsbach Miradin, Lepicol Miradin, Leppin Miradin, & Miradin; **Shan Dian Qiang Xiao Shou** (undeclared sibutramine & phenolphthalein); **Zencore Plus** (undeclared benzamidenafil) & **Zhong Guo Shen Fang** (undeclared med like sildenafil).

Health Canada June/09 is warning consumers not to use the unauthorized product **Slim Magic Herbal**, which is promoted as a weight-loss product, as it was found to contain an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning consumers not to use the unauthorized product **Nutural Slim**, which is promoted as a weight-loss product, as it was found to contain the undeclared pharmaceutical ingredient sibutramine and also an undeclared pharmaceutical ingredient similar to sibutramine.

Health Canada June/09 warns of foreign Product Alerts: **Herbal Xenicol** because it contains undeclared cetilistat. **BioEmagrecim**, which the FDA had previously warned contained sibutramine, was also found to contain fluoxetine, furosemide and fenproporex. Products: **Slimbionic, Xsvelten, 999 Fitness Essence, 24" ince, Light Some, Paiyouji, Pearl White Slimming, & Reducing Weight Easily** contain undeclared pharmaceutical ingredients (sibutramine and/or phenolphthalein) and/or excessive levels of lead, and may cause serious health effects..

Health Canada July/09 is warning consumers not to use the unauthorized health product labelled as **Specific-Formula Arthro-Ace** as it was found to contain undeclared dexamethasone and may cause serious health effects.

Health Canada July/09 is warning that the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **Air Ikan Haruan** after it was found to contain undeclared dexamethasone. The Hong Kong Department of Health warned consumers not to buy or use the product **Neovidan** after it was found to contain undeclared prednisolone and mefenamic acid. Plus the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **XP Tongkat Ali Supreme** after it was found to contain undeclared tadalafil.

Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) warned that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine, while **Cao Gen Bai Lin Wan** contains undeclared dexamethasone and chlorpheniramine.

Health Canada Oct/09: **Bao Ling**- The Singapore Health Sciences Authority advised consumers not to buy or use since contained undeclared betamethasone, hydrochlorothiazide & chlorpheniramine. **Dynasty Worldwide Jinglida So Young Formula**- The Singapore Health Sciences Authority (HSA) warned consumers to not buy or use since contained undeclared aminotadalafil. **STEAM** lot#80214, 90260 -The U.S. FDA informed consumers of a voluntary manufacturer recall of two lots of STEAM after FDA testing found these lots to contain undeclared sulfoaildenafil (lot# 80214) & undeclared tadalafil (lot# 90260). **Syntrax Fyre (contained Yohimbine)**, **Texiao Fengshi Gutong Ling (contained indomethacin)**, **Kam Yuen Brand Wan Ying Yang Gan Wan (contained sildenafil)** - The Hong Kong Department of Health warned consumers not to buy or use these three products after they were found to contain undeclared pharmaceutical substances.

Health Canada Nov/09 is advising Canadians not to consume Chaotic Beverages sold under the brand names Mind Strike, Fearocity, Elixir of Tenacity and Power Pulse because they are unauthorized products marketed to a vulnerable population (children) with ingredients that may pose a health risk. **Mind Strike:** Contains an unknown amount of caffeine despite advertising that it is not an energy drink and contains several herbs which are not included in Health Canada's list of botanicals with a history of safe use in children. **Fearocity:** Contains an unknown amount of caffeine, several herbs not included in Health Canada's list of botanicals with a history of safe use in children, taurine at an unacceptable level for children, and niacin at a level three times higher than that recommended for children aged 1 to 13 years. **Elixir of Tenacity:** Contains green tea extract, which is not included in Health Canada's list of botanicals with a history of safe use in children, and vitamin A at a level unacceptable for children aged 1 to 8 years. **Power Pulse:** Contains chromium picolinate at levels of possible concern in a product taken by children.

Health Canada Nov/09 is warning consumers not to use Herblex "**Once More**"since it was found to contain sildenafil.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products advertised for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is warning consumers not to use "**RevolutionDS Weight Loss**", an unauthorized health product promoted for weight loss, because it contains benzylpiperazine (BZP), and may pose serious health risks.

Health Canada Dec/09 is advising consumers not to use the following foreign health products: 1. **Power-Plus P**: The Singapore Health Sciences Authority issued a recall notice for Power-Plus P (expiry date 03/03/2011) after it was found to contain undeclared tadalafil. 2. **Show Party**: The Hong Kong Department of Health warned consumers not to buy or consume Show Party [shou-shen pai] after it was found to contain undeclared sibutramine and phenolphthalein. 3. **Zeng Da Yan Shi Wan**: The Hong Kong Department of Health warned consumers not to buy or use after it was found to contain undeclared sildenafil.

Health Canada Jan/10 informs that Finish Food Safety Authority: **Full Contact Max Potency** contains thio-sildenafil and thio-homosildenafil; Singapore Health Sciences Authority: **M-Action** contains desmethylacetildenafil and acetilacid. U.S. FDA: **RockHard Weekend** contains sulfoaildenafil; & **Pai You Guo** contains sibutramine and phenolphthalein. Hong Kong Department of Health: **Ku Xiu Ba Xiang Jian Fei Wan** contains sibutramine and an unauthorized substance similar to sibutramine; **Super Slim (Yani)** contains sibutramine and phenolphthalein; **SHoufsy** contains sibutramine & **MIGAC (sic) FAT BURMING (sic) FACTOR** contains sibutramine.

Health Canada Jan/10 is advising consumers not to use the unauthorized product "**Stiff Nights**" after the U.S Food and Drug Administration (FDA) found that this product contains an undeclared substance similar to the prescription drug sildenafil.

Health Canada Jan/10 is warning consumers not to use the unauthorized product "**The Slimming Coffee**," which was previously sold as "**Lose Weight Coffee**," because it was found to contain sibutramine.

Health Canada Jan/10 is advising consumers not to use any unauthorized health products sold under the brand names **Natural Choice Vitamin B-17**, **Natural Choice Kava Kava** and **Natural Choice Lithium Orotate**. The unauthorized Natural Choice Vitamin B-17, according to what is listed on the product label, contains amygdalin which is a compound derived from bitter apricot kernels that has the potential to release cyanide when ingested by humans. The unauthorized Natural Choice Kava Kava, according to what is listed on the product label, contains kava lactones & agencies have received reports associating the use of kava with serious liver dysfunction.

TOP

Health Canada Jan/10 is advising Canadians that natural health products containing the ingredient **glucomannan** in tablet, capsule or powder form, which are currently on the Canadian market, have a potential for harm if taken without at least 8 ounces of water or other fluid.

Health Canada Feb/10 is advising consumers that the unauthorized product "**Complete 7-Day Cleanse**" is being recalled because it contains a number of active ingredients with a combined effect that may pose serious health risks. "Complete 7-Day Cleanse" is a multi-ingredient natural health product promoted for "cleansing" or removing toxins from the body. According to package labelling, the product contains over 30 active ingredients, some having a diuretic (water pill) or laxative (stimulant, and bulk-forming) effect.

Health Canada Feb/10: **2H & 2D**- Hong Kong Department of Health (HKDH) warned consumers not to buy or use 2H & 2Dafter it was found to contain undeclared tadalafil. Products distributed by **Atlas Operations Inc**. The FDA informed consumers of a voluntary recall by Atlas Operations Inc. of certain lots of some products that were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil. Products distributed by **Bodybuilding.com** The FDA informed consumers of a voluntary recall of 65 bodybuilding products as these products may contain the following anabolic steroids: "Superdrol," "Madol," "Tren," "Androstenedione," and/or "Turinabol." **STRO Emperor** Capsules The Irish Medicines Board warned consumers not to buy or use STRO Emperor Capsules after it was found to contain undeclared tadalafil. **Tian Yang Xu Huo Oral Ulcer** Capsule Singapore Health Sciences Authority issued a recall notice for one batch (batch number 0812003, expiry date 11.2011) of Tian Yang Xu Huo Oral Ulcer Capsuleafter it was found to contain undeclared aristolochic acid.

Health Canada Mar/10 is warning Canadians that an unapproved health product, **POWER-MAX** that contains sildenafil.

Health Canada Mar/10 is warning Canadians that an unauthorized health product, "**Herbal Diet Natural**" has been found on the Canadian market and contains an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning Canadians that an unauthorized health product, "**West Pharm Therma Lean Fat Burner Energizer**" was found on the Canadian market. West Pharm Therma Lean Fat Burner Energizer contains Ephedrine and caffeine, which combined together, may cause serious and possibly fatal adverse effects.

Health Canada Apr/10 is warning Canadians that an unauthorized health product, "**Slim-30**" distributed in Ontario and Quebec by Duxx Enterprises Inc., contains an undeclared pharmaceutical ingredient similar to the prescription drug, sibutramine.

Health Canada May/10 consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Ba Bao Xiao Ke Dan** The Hong Kong Department of Health warned consumers not to buy or use Ba Bao Xiao Ke Dan after it was found to contain undeclared glibenclamide. 2. **Bao Shu Tang Wu Zi Yan Zong Wan** The Hong Kong Department of Health warned consumers not to buy or use Bao Shu Tang Wu Zi Yan Zong Wan after it was found to contain excessive levels of lead, a heavy metal. 3. **Lin Yan Yin Chiao** The Singapore Health Sciences Authority issued a recall notice for one batch (batch# JI0324, expiry date 03/2011) of Lin Yan Yin Chiao after it was found to contain undeclared chlorpheniramine and paracetamol (acetaminophen). 4. **Man Power** The Hong Kong Department of Health warned consumers not to buy or use Man Power product after it was found to contain undeclared tadalafil. 5. 17 products sold through **MuscleMaster.com** (see Foreign Product Alert for a complete product list) The FDA informed consumers of a voluntary recall of the 17 bodybuilding products as they may contain the following anabolic steroids: "Superdrol," "Madol," "Tren," "Androstenedione," and/or "Turinabol." 6. **Seven Slim 7 Seshou** (Qingchun Shaonüxing, Jieshixing, Guifurenxing, Songchixing), Shoushen Jiaoguan-Tinei Yundong Wan (Jian Xiabanshen, Jian Quanshen Feipang) The Hong Kong Department of Health warned consumers not to buy or use the six products listed above after they were found to contain undeclared sibutramine and phenolphthalein.

Health Canada May/10 is advising consumers not to use 1. **Botanical Slimming 100% Natural Soft Gel, also sold as Meizitang** The Australian Therapeutic Goods Administration warned consumers not to buy or use this product after it was found to contain undeclared sibutramine. 2. **Marsha Slim Plus** The Hong Kong Department of Health warned consumers not to buy or use Marsha Slim Plus after it was found to contain undeclared sibutramine, an unauthorized substance similar to sibutramine and phenolphthalein. 3. **S&S Super Slender** The Hong Kong Department of Health warned consumers not to buy or use S&S Super Slender after two samples were found to contain agent similar to sibutramine. One of the tested samples also contained undeclared sibutramine and phenolphthalein.

Health Canada June/10 is warning Canadians that the unauthorized health products "**Vigofit**" and "**Once More**," which are promoted to enhance male sexual performance, have been seized by Health Canada inspectors from retail stores in Abbotsford and Surrey, British Columbia. These two products contain sildenafil.

Health Canada June/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **COMECOO, ZHONGCAOYAO-JIANKANGJIANFEI** The Hong Kong Department of Health warned consumers not to buy or consume these two products after they were found to contain undeclared phenolphthalein, sibutramine and two unauthorized substances similar to sibutramine. 2. **Qingzhi Santian Shou** The Hong Kong Department of Health warned consumers not to buy or consume Qingzhi Santian Shou after it was found to contain undeclared sibutramine and an unauthorized substance similar to sibutramine. 3. **Vita Breath** The U.S. FDA warned consumers not to buy or consume Vita Breath because it may contain hazardous levels of lead, which is a heavy metal.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) due to concerns about possible adverse reactions: 1. **Stud Capsule For Men** The U.S. FDA informed consumers of a voluntary recall of one lot (Lot #060607-01/060108-01 Exp 6-2013) after it was found to contain undeclared Sildenafil. 2. **Po Chai Pills** (capsule form) The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain undeclared sibutramine and phenolphthalein. Sibutramine is a prescription drug and should only be used under the supervision of a health care practitioner while phenolphthalein is no longer authorized for sale in Canada because it may cause cancer. Po Chai Pills (capsule form) has been recalled by the manufacturer. 3. **LiPO-8 Cap and Glucomi 600 Cap** The Hong Kong Department of Health warned consumers not to buy or use these products because they contain undeclared sibutramine.

Health Canada July/10 is advising Canadians about "**UP Ultimate Performance for Men**", an unauthorized health product containing undeclared sildenafil.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume *1 Body Beautiful* after it was found to contain undeclared phenolphthalein and sibutramine. 2. **USA Yaku Cell Slimming Capsules, Dong Gua Pai You Su, Qing Gua Pai You Su, and Mu Gua Pai You Su** The Hong Kong Department of Health warned consumers not to buy or consume these four products after they were found to contain undeclared phenolphthalein, sibutramine and an unauthorized substance similar to sibutramine. 3. **Atlas Operations Inc. expands its U.S. recall of over 30 sexual enhancement supplements** The U.S. FDA informed consumers of an expanded recall of certain lots of products after some were found to contain undeclared sulfoaildenafil. The products are being voluntarily recalled nationwide in the U.S. by the company Atlas Operations Inc. 4. **Stallion, SZM Formula for Men, Tomcat Ali and Volcanic** New Zealand's Medsafe warned consumers not to buy or use these four products after they were found to contain undeclared tadalafil. 5. **Vitalex for men and Vitalex for women** The U.S. FDA informed consumers that the *Vitalex*products were found to contain acetildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada Aug/10 says **Fulda Unitang Herbs Sleep Plus**, an unauthorized product promoted as an herbal sleep aid, has been found to contain high levels of estazolam.

Health Canada July/10 Unauthorized Health Products Sold by **Marigold Natural Pharmacy Ltd**. May Pose Health Risks. These products (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_126bk-eng.php) were made available to Canadians via the company's pharmacy in Courtenay, British Columbia and via their website (http://www.marigoldnaturalpharmacy.com).

Health Canada July/10 is advising consumers not to use the following foreign health product(s): **Huo Luo Jing Dan** The Singapore Health Sciences Authority warned consumers not to buy or consume Huo Luo Jing Dan after it was found to contain undeclared indomethacin, dexamethasone and prednisolone. Kam Chik San The Hong Kong Department of Health (HKDH) cautioned against the use of **Kam Chik San** after samples were found to contain mercury at a level much higher than permitted by the HKDH. **Magic Power Coffee** The U.S. FDA warned consumers not to buy or use Magic Power Coffee after it was found to contain undeclared hydroxythiohomosildenafil, which is an unauthorized substance similar to sildenafil. **Que She** The U.S. FDA warned consumers not to buy or use Que She after it was found to contain undeclared fenfluramine, propranolol, sibutramine and ephedrine. **Sheng Yuan Fang** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use Sheng Yuan Fang after it was found to contain undeclared phenolphthalein and sibutramine.

Health Canada July/10 is informing Canadians that **Marché Euromix**, a retail store in Pierrefonds (Montréal), was found to be selling a health product that was not authorized for sale by Health Canada and that closely resembled in appearance an authorized drug, Viagra.

Health Canada Aug/10: "**SeXXX DRIVE**", promoted as a herbal supplement to enhance male sexual performance, & Health Canada found hydroxyhomosildenafil.

Health Canada Aug/10 has seized the unauthorized sexual enhancement supplements "**Male Enhancement ExtenZe**" and "**Women ExtenZe**" imported and sold by the Happy Paradise Adult Store in

TOP

Burnaby, British Columbia. The labels of each of these unauthorized products list the prescription ingredient pregnenolone and the controlled drug, DHEA (dehydroepiandrosterone). The labels of the unauthorized "Male Enhancement ExtenZe Nutritional Supplements" list the ingredient yohimbe extract (bark).

Health Canada Sep/10 **E.O.D. Erection on Demand**" being promoted as a herbal to enhance male sexual performance, the product was tested by Health Canada and found to contain tadalafil.

Health Canada Sep/10: "**Arth-Forth**", an unauthorized product promoted as an herbal supplement and distributed by Ka Wing Hong Ltd., was tested by Health Canada and found to contain a steroid prescription drug, dexamethasone.

Health Canada Sep/10 is advising consumers not to use : 1. **Golden aryuru, Baisheng wei ge, Zhonghua niubian, Ten ka dai 1 bou, Kuai gan bei zeng chao yue zi wo (Happy felling doubly increase [sic]), Ling tou lang, SkyFruit, Chu bi ho ken, Jinbolang, Suika Koso, Lov, I ka ou (2009 nen sin hoso) and/or I ka ou (saisinsui shutsu hoso)** The Japanese Ministry of Health, Labour and Welfare warned consumers not to buy or use the 12 products listed above because they were found to contain undeclared sildenafil and/or other unauthorized substances similar to sildenafil that may pose similar health risks (norhongdenafil, acetil acid, and tioqinapiperifil). 2. **Joyful Slim Herb** Supplement The U.S. FDA informed consumers of a recall of one lot (#101408) of Joyful Slim Herb Supplement after FDA tests found it to contain undeclared desmethyl sibutramine. The lot is being voluntarily recalled nationwide in the U.S. by the company J & H Besta Corp. 3. **Vialipro** The U.S. FDA informed consumers of a recall of certain lots of Vialipro after FDA tests found product samples to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada Sep/10 **Exemption number**: This will help with the backlog of applications for a licence. Exemptions will be given to natural products that have passed an initial assessment of safety, quality, and efficacy. These products will be given an exemption number (EN)...instead of a Natural Product Number (NPN) or Drug Identification Number-Homeopathic Medicine (DIN-HM)...until they are fully reviewed by Health Canada.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil. Arrow Brand Medicated Oil & Embrocation: The U.S. FDA warned consumers not to buy or use **Arrow Brand Medicated Oil & Embrocation** because it contains ingredients that are potentially poisonous, particularly in children. **Beijing 101 Hair Consultants: Hair Growth Formula D-2653-Band Hair Growth Tonic E-0583-D**: The Singapore Health Sciences Authority advised consumers to stop using one batch of these products (Beijing 101 Hair Consultants Hair Growth Formula D-2653-B batch# 20091201, and Hair Growth Tonic E-0583-D batch# 20091201) after testing of these batches revealed the presence of undeclared minoxidil. **101 Zhangguang: Gold 101 Super Effective Hair Growth Agentand Fabao 101D Doctor Zhao's Chinese Traditional Herbal Hair Care Formula**: The Hong Kong Department of Health warned consumers not to buy or use these two products after they were found to contain undeclared minoxidil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Goya–Bitter Melon - Miyura Fit'x Capsules** contained undeclared phenolphthalein and sibutramine **2. MasXtreme** contains undeclared aminotadalafil while the other (#911035) contains undeclared aildenafil and phentolamine **3. Mr. Magic Male Enhancer from Don Wands** contained hydroxythiohomosildenafil and sulfoaildenafil **4. So Hard for Men - Pulse8 for Women - The Rock – Tonic 66** contained the undeclared pharmaceutical substances tadalafil, sildenafil, and/or hydroxyhomosildenafil **5. Solo Slim Extra Strength - Revivexxx Extra Strength** contained undeclared didesmethyl sibutramine **6. TimeOut** contained undeclared hydroxythiohomosildenafil.

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 "**Durazest**" and "**Once More**": Certain lots of two male sex enhancement products recalled as they may pose serious health risks. Certain lots (listed below) of two health products promoted for male sexual enhancement, "Durazest for Men" and "Once More," have been voluntarily recalled by Natural Performance Products Ltd. Health Canada laboratory tests identified the presence of a chemical similar to tadalafil (nortadalafil) in one lot of each product.

Health Canada Dec/10 is informing Canadians that NorthRegentRx has begun to voluntarily recall its product, **ResurreXX** from the Canadian market. NorthRegentRx is requesting that wholesalers, distributors and retailers stop sale of this product since contained an undeclared substance "hydroxyhomosildenafil".

Health Canada Dec/10 has been advised "**Flat Stomach Concept Extra**" is being voluntarily recalled by Les Produits Naturels Leblanc Inc due to missing label statements related to duration of use, risks and contraindications. Information missing from the label of Flat Stomach, a product contained within the Flat Stomach Concept Extra kit, may result in potential chronic use of aloe, which can lead to bowel dependence, and electrolyte imbalance.

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Slimming Beauty Bitter Orange Slimming Capsule** (Slimming Beauty) The U.S. Food and Drug Administration warned consumers not to buy or use Slimming Beauty after FDA lab tests revealed that this product contains undeclared sibutramine. 2. **Shaguar, Signature Signergy, VIGRX (green capsule), VIGRX (white capsule), VigRx, VigRX Plus** New Zealand's MedSafe warned consumers to not buy or use these products after they were found to contain undeclared sildenafil, hydroxyhomosildenafil, thiosildenafil, and/or tadalafil. 3. **ArimaDex**, **Clomed** The U.S. Food and Drug Administration informed consumers that ArimaDex and Clomed are being recalled in the U.S. because they may contain an aromatase inhibitor. ArimaDex and Clomed are being voluntarily recalled by G.E.T. and KiloSports Inc., respectively.

Health Canada Dec/10 Three Probiotic Natural Health Products May Pose Serious Health Risks to Canadians with Milk or Soy Allergies. Consumers with milk or soy allergies are advised that three probiotic natural health products are being voluntarily recalled from the market because they are labelled as not containing dairy(milk) and/or soy but may contain trace amounts of milk or soy protein from ingredients used in the production process. **Saccharomyces Boulardii** (NPN 80013551) Advanced Orthomolecular Research Inc. (AOR); **Herbasaurs Bifidophilus for Kids** (NPN 80015508) & **Acidophilus Bifidobacterium** (NPN 80015336) by Nature's Sunshine Products of Canada Ltd & **Cultures de Yogourt 2 Milliards** (NPN 80013273 Bio-Dis Inc.

Health Canada Jan/11 The product **Synerate**, manufactured for Strive and distributed by Upper 49th, is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. Synerate, a product used for weight loss or body building, contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Jan/11 **Nutrex Research Lipo 6X** is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. It contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Feb/11 is advising consumers not to use the following foreign health products promoted for sexual enhancement due to the presence of unauthorized substances (PDE5 derivatives eg. sildenafil): **1. Aziffa, Erex, Eyeful, Hard Drive, Libidinal, Maxyte, Mojo, Monster Excyte, OMG, OMG45, Prolatis, Red Magic, Size Matters, Stiff Nights, Straight Up, Verect, WOW, Xaitrex, Xytamax, Zilex (with Golden Spear), Zotrex 2. Prolatis' Duro Extend Capsules For Men 3. Tiger King 4. Vigor-25, Man Up Now**

Health Canada Feb/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Fruta Planta, Reduce Weight Fruta Planta** The U.S. FDA warned consumers not to buy or use Fruta Planta and Reduce Weight Fruta Planta after FDA lab tests revealed that this product contains undeclared sibutramine. **2. RockHard Weekend (lots 100159 and 100260 sold as blister packs, 3-count bottles and 8-count bottles)** The U.S. FDA informed consumers of a nationwide voluntary recall of certain lots (see above) of RockHard Weekend and Pandora after lab tests confirmed the products contain an unauthorized substance similar to sildenafil that may pose similar heath risks. **3. Slimming Factor** The Australian TGA warned consumers not to buy or use Slimming Factor after TGA lab tests confirmed the presence of the undeclared substances sibutramine, fenfluramine and phenolphthalein. According to the TGA release, the product is sold over the Internet.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Celerite Slimming Capsules:** The U.S. FDA informed consumers of a company recall of Celerite™ Slimming Capsules after it was found to contain undeclared sibutramine. **2. Herbal Flos Lonicerae (Herbal Xenicol) Natural Weight Loss Formula:** The product was found to contain undeclared sibutramine at more than twice the dose that was normally prescribed before sibutramine was removed from the UK market in 2010. **3. Magicream:** The Irish Medicines Board warned consumers not to buy or use Magicream after it was found to contain undeclared clobetasol propionate and ketoconazole. **4. Nite Rider Maximum Sexual Enhancer for Men - STUD Capsule for Men:** The U.S. FDA informed consumers of a company recall of these products after they were found to contain undeclared sildenafil.

Health Canada April/11 Consumers with milk or soy allergies are advised that four probiotic natural health products {**Saccharomyces Boulardii (NPN 80013551), Herbasaurs Bifidophilus for Kids (NPN 80015508), Acidophilus Bifidobacterium (NPN 80015336), Cultures de Yogourt 2 Milliards (NPN 80013273)**} are being voluntarily recalled from the market because they are labelled as not containing dairy (milk) and/or soy but may contain trace amounts of milk or soy protein from ingredients used in the production process.

Health Canada Apr/11 has identified the presence of microbial contamination in "**Mary Ginseng House 100% Pure High Calibre Pow Sum Ontario Ginseng**", that may pose a health risk to immune-compromised individuals.

Health Canada May/11 "**Omega Alpha Kidney Flush**" Being Recalled from the Canadian Market: May Cause Serious Adverse Reactions in Pregnant Women and Kidney Disease Patients.

Health Canada May/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Dr. Health Series CM Factor** The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain an unauthorized substance similar to sibutramine that may pose similar health risks. **2. Gold Seagull Long Zhi Wan, Venergy** The Hong Kong Department of Health advised consumers not to buy or use these products after Gold Seagull Long Zhi Wan was found to contain undeclared glibenclamide, while Venergy was found to contain undeclared sildenafil. **3. JianBu HuQian Wan** The HSA warned consumers not to buy or use JianBu HuQian Wan after it was found to contain undeclared dexamethasone and chlorpheniramine. **4. Rock Hard Extreme, Passion Coffee** The U.S. FDA advised consumers not to buy or use these products after they were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada July/11 "**Man Up Now**" Removed From Sale at Delta and Surrey Stores: May Pose Serious Health Risks to Canadians, was removed from sale at "O! Behave" retail stores in Delta and Surrey, B.C. after Health Canada's testing identified undeclared sildenafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products. These products were also removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. {**Sildenafil: in BAOLONG Switzerland Rolex 168 Prolong Time, BAOLONG Yilishen, Black Gold, Herbal Viagra, "Jin Chong Chao - Golden Cordyceps", Lubiangaowansu, MAGNA-RX, MAXMAN II capsules, Shenrong dabuwan, Traditional Chinese Medicine Viagra, V100, VIGER, VigRX for Men, VINIX capsules, Wolf, "XiongBaTian", Zang Gong Mi Lian Nan Bao} & Zeng Bei Jiu Zhan-Tadalafil.**

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Beline Capsules** The U.K. Medicine and Healthcare products Regulatory Agency (MHRA) advised consumers not to use *Beline Capsules* after it was found to contain undeclared chlorpheniramine, an over-the-counter antihistamine drug

TOP

2. Black Ant The U.S. Food and Drug Administration warned consumers to immediately stop using *Black Ant* after it was found to contain undeclared sildenafil at an amount three times the starting dosage for the approved prescription drug product. **3. [Hua Tuo Brand] Youzhi Baoying Dan, [Lee Sze] Texiao Houtong Wan and Prolonged Man Power Essence** The Hong Kong Department of Health (HKDH) warned consumers to not use these products after they were found to contain excessive levels of mercury, lead, or arsenic, which are heavy metals. **4. Natural Vigra VIAGRA Tablets and Satibo Capsules** The Australian Therapeutic Goods Administration (TGA) advised consumers to stop using *Natural Vigra VIAGRA Tablets* after it was found to contain undeclared sildenafil, and *Satibo Capsules* after it was found to contain undeclared tadalafil and hydroxyhomosildenafil. **5. Slim Xtreme Herbal Slimming Capsules** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *Slim Xtreme Herbal Slimming Capsules* was found to contain undeclared sibutramine. **6. X-Hero and Male Enhancer** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *X-Hero* was found to contain undeclared sulfosildenafil while *Male Enhancer* was found to contain undeclared tadalafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products to include a new product, **Tibet Babao**, which was found to contain undeclared sildenafil, a prescription erectile dysfunction drug. This product and several others have been removed from sale at the **Happy Paradise Adult Store in Burnaby, B.C**.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Celerite Slimming Tea** The U.S. FDA informed consumers of a company recall of Celerite Slimming Tea after it was found to contain undeclared sibutramine. **2. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet. **3. Fifteen products promoted for weight loss** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use these 15 products after they were found to contain at least one of the following undeclared substances: phenolphthalein, sibutramine, and/or an unauthorized substance similar to sibutramine.

Health Canada Sep/11 **Bi Yan Pian** Recalled Due to Excessive Amount of Mercury. Wing Quon Enterprises Ltd has initiated a stop sale and is voluntarily recalling a natural health product, Bi Yan Pian (NPN# 80023876) from the Canadian market after the product was found to contain an excessive amount of mercury.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **Slim Forte Slimming Capsules**, **Slim Forte Double Power Slimming Capsules**, **Slim Forte Slimming Coffee** and **Meizitang Botanical Slimming Soft Gel**-The U.S. Food and Drug Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **OxyELITE Pro capsules and Pure Fat Three Days Reduce Weight capsules**- The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine), or a prescription drug (yohimbine). **SXL Sexcellence sachets**- The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains an unauthorized drug (sulfosildenafil). [W.S] **Gan Mao Ling and Chaisentomg Baby's Kam Chik San Powder** - The Hong Kong Department of Health warned that these Chinese health products contain excessive levels of heavy metals (lead or arsenic). **Huo Li Bao and Ren Sem Tu Chon Chin Kuo Pill** - The Singapore Health Sciences Authority warned that these Chinese pain-relief products contain prescription and/or over-the-counter drugs (furosemide, piroxicam, chlorpheniramine, and/or dexamethasone).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Zhui Feng Bao Wei San** The Singapore Health Sciences Authority warned that this health product contains excessive levels of microbial contamination. **2. Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones). **3. Majun Dua Istimewa, Raja Maajun-Jerat Dan Seret Angin, and Horkut Chooi Foong Hor Lok Tan** The Singapore Health Sciences Authority warned that these traditional medicines contain undeclared prescription and over-the-counter drugs (dexamethasone, indomethacin, chlorpheniramine, dextromethorphan and acetaminophen). **4. Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al, and Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine). **5. Slimming Kapsul** The Hong Kong Department of Health warned that this weight-loss product contains an unauthorized drug (sibutramine) and a prescription drug (spironolactone). **6. Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a prescription drug (glyburide). **7. Maxidus capsules, Chao Jimengnan SuperPowerful Man tablets, Fu Yuan Chun capsules, and Qing Tian Zhu tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain prescription drugs (sildenafil, tadalafil) and/or unauthorized drugs (sulfohydroxyhomosildenafil, sulfosildenafil).

Health Canada Nov/11: An unauthorized health product, "**Stiff One Hard 169**" is being voluntarily recalled from the Canadian market after Health Canada's testing identified an undeclared prescription medication in the product (thiodimethylsildenafil, an undeclared substance similar to the prescription medication sildenafil).

Health Canada Dec/11 is advising "**Yanshiwang**", "**Jin Kong Fu**" and "**Chong Cao She Bian Zhuang Yang Dan**". These products were removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. These contained sildenafil.

Health Canada Jan/12 advises: 1)**17 weight loss products (see Alert for a complete list)** A-Slim 100% Natural Slimming Capsule, Acai Berry Soft Gel ABC, Advanced Slim 5 > DaiDaiHuaJiaoNang, Dream Body Slimming Capsule, Fruit Plant Lossing Fat Capsule, Health Slimming Coffee, Ja Dera 100% Natural Weight Loss Supplement, Leisure 18 Slimming Coffee, Lishou, Magic Slim Tea, Magic Slim Weight Reduction Capsule, P57 Hoodia, Pai You Guo Slim Tea, PhentraBurn Slimming Capsules, Slender Slim 11 Tengda. The U.S. Food and Drug Administration warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Uprizing 2.0** The U.S. Food and Drug Administration warned that this body building product contains a controlled prescription drug (superdrol). **3. Get Stiff, Maxi Mize** New Zealand's Medsafe warned that these sexual enhancement products contain prescription drugs (tadalafil, vardenafil, yohimbine) and/or unauthorized drugs (hydroxyhomosildenafil, hydroxythiohomosildenafil). **4. Ying Da Wang tablets** The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains a prescription drug (sildenafil). **5. Slimina weightloss capsules, S-shape slim capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain prescription drugs (propranolol, nifedipine) and/or unauthorized drugs (sibutramine, fenfluramine, phenolphthalein). **6. Athri-Eze, Sear Heang Tienchi Tu Chung Wan, Wiku Jahe Kencur (Akur Mujarab), Cap Wijaya Kusuma (An Ki It)** The Singapore Health Sciences Authority warned that these Traditional Chinese or Traditional Malay Jamu products contain prescription and/or over-the-counter drugs (dexamethasone, prednisolone, furosemide, allopurinol, acetaminophen, chlorpheniramine), and/or an unauthorized drug (phenylbutazone). **7. Cardiotium, Paidusu, SlimEasy Herbs Capsule, Tianran Zuanshi Xianweisu** The Hong Kong Department of Health warned that these health products contain prescription drugs (losartan, atorvastatin, thyroxine) and/or unauthorized drugs (sibutramine, phenolphthalein). Consult a health care practitioner immediately if you have taken "Cardiotium" while pregnant. The use of losartan during pregnancy can cause injury and even death to the fetus. **8. [LuShenPai] Specific Hou Ton Qing, [AA] Pe Min Kan Wan** The Hong Kong Department of Health warned that these traditional Chinese health products contain excessive levels of heavy metals (arsenic or mercury).

Health Canada Feb/12 is advising Canadians that using "MMS", also known as **Miracle Mineral Solution or Miracle Mineral Supplement** may cause serious health problems. The product information lists sodium chlorite as an ingredient and is promoted as a substance that can cleanse toxins from the human body.

Health Canada Feb/12 seized a variety of **Stiff4Ever** and **PurePillz** products from The Love Shop retail outlets located in Ontario. These products are unauthorized drugs and are considered potentially dangerous to the health and safety of Canadians. Health Canada tested the Stiff4Ever products, advertised as male sexual stimulants, and identified sildenafil. The labels of the PurePillz products (see below) state that they contain BZP and TFMPP. Benzylpiperazine (BZP) is a synthetic substance with stimulant-like effects, while 3-trifluoromethylphenylpiperazine (TFMPP) is a synthetic substance with hallucinogen-like effects.

Health Canada Mar/12 **Power-X**" has been removed from a Canadian retail location after Health Canada's testing identified undeclared thiodimethylsildenafil which is similar to the prescription medication sildenafil.

Health Canada May/12: Unauthorized health products, **"X-Rock", "Kaboom" and "One For Her"** have been removed from sale from various retail outlets in British Columbia and Saskatchewan. Health Canada's testing identified undeclared prescription drugs sildenafil and tadalafil, and an undeclared substance, hydroxythiohomosildenafil, which is similar to sildenafil.

Health Canada May/12 **1. CanSui; Lexscl Fat Rapid Loss Capsule; The Extreme-thin Fat Burning Bomb; Xiu Zhi Su L-Carnitine Slimming Capsule** The Hong Kong Department of Health warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Jin Yu Tang Tai Han Kang Pai Pu Ling Jiao Nang; TangBaoKouFuYiDaoSuJiaoNang; Tangren 365 Kangxunpai sangge huoyisu jiaonang; Tong Ren Xiu Fu Kou Fu Yi Dao Su** The Hong Kong Department of Health warned these products, promoted to control high blood sugar, contain a combination of prescription drugs (metformin, glibenclamide [also known as glyburide], rosiglitazone, glimepiride, hydrochlorothiazide) and unauthorized drugs (phenolphthalein, phenformin). **3. [Chung Lien Kulin Brand] Anshen Bunai Pian** The Hong Kong Department of Health warned that this traditional Chinese health product, used for insomnia, contains excessive levels of the heavy metal mercury. **4. Lipro Diet Pills; Xiyouji Qingzhi weight loss capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **5. AdvanceMen capsules; Miraculous Evil Root tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain either a prescription drug (sildenafil) or an unauthorized drug (sulfoaildenafil).

Health Canada June/12 **1. African Black Ant; France T253; Hard Ten Days; Man King; Stree Overlord** : The U.S. Food and Drug Administration warned that these sexual enhancement products contain prescription drugs (sildenafil. One product also contains tadalafil). **2. RegenArouse; RegenErect:** The U.S. Food and Drug Administration informed of a recall because these sexual enhancement products contain a prescription drug (tadalafil). **3. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil). **4. Japan Weight Loss Blue, Japan Rapid Weight Loss Diet Pills Green; Japan Rapid Weight Loss Diet Pills Yellow:** The U.S. Food and Drug Administration warned that these weight loss products contain prescription drugs (sibutramine, ephedrine alkaloids) and unauthorized drugs (phenolphthalein, and substances similar to sibutramine). **5. Koff & Kold; Kold Sore:** The U.S. Food and Drug Administration informed of a recall because these cough and cold products were found to be non-sterile. **6. Ling Zhi She Xiang Tong Mai Dan:** The Hong Kong Department of Health warned this health product contains a prescription drug (dexamethasone). **7. Q & N Omega Tree:** The Singapore Health Sciences Authority informed of a recall after this product was found to contain controlled drug substances (cannabinol and tetrahydrocannabinol (THC)).

Henley DV, Lipson N, Korach KS, Bloch CA. Prepubertal gynecomastia linked to lavender and tea tree oils. N Engl J Med. 2007 Feb 1;356(5):479-85.

Herbal medicines for osteoarthritis. DTB 2012;50:8-12 doi:10.1136/dtb.2011.02.0081.

Herrero-Beaumont G et al. Effects of glucosamine sulfate on a 6-month control of knee osteoarthritis symptoms vs placebo & acetaminophen: Results from the Glucose Unum in Die Efficacy (**GUIDE**) Trial. ACR Meeting Nov 2005.

Herrero-Beaumont G, Ivorra JA, Del Carmen Trabado M, et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: A randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum. 2007 Jan 30;56(2):555-567 [Epub ahead of print] (n=318 over 6 months)

Holbrook AM, Pereira JA, Labiris R, McDonald H, et al. Systematic overview of **warfarin and its drug and food interactions**. Arch Intern Med. 2005 May 23;165(10):1095-106.

Hrastinger A, Dietz B, Bauer R, Sagraves R, Mahady G. Is there clinical evidence supporting the use of botanical dietary supplements in **children**?J Pediatr. 2005 Mar;146(3):311-7.

Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, Duan W, Koh HL, Zhou S. **Herb-drug interactions: a literature review**. Drugs. **2005**;65(9):1239-82.

Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (**St John's wort**) in major depressive disorder: a randomized controlled trial. **JAMA. 2002** Apr 10;287(14):1807-14.

Idan Amanda, Griffiths Kaye A., Harwood D. Tim, et al. Long-Term Effects of **Dihydrotestosterone** Treatment on Prostate Growth in Healthy, Middle-Aged Men Without Prostate Disease: A Randomized, Placebo-Controlled Trial. Ann Intern Med November 16, 2010 153:621-632.

Jagdis A, Sussman G. Anaphylaxis from **bee pollen** supplement. CMAJ 2012.

Jakkula M, Boucher TA, Beyendorff U, et al. A randomized trial of **Chinese herbal medicines** for the treatment of symptomatic hepatitis C. Arch Intern Med. 2004 Jun 28;164(12):1341-6.

Kahan A, Uebelhart D, De Vathaire F, Delmas PD, et al. Long-term effects of **chondroitins 4 and 6 sulfate** on knee osteoarthritis: The study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2009 Jan 29;60(2):524-533. [Epub ahead of print] We performed an international, randomized, double-blind, placebo-controlled trial in which 622 patients with knee OA were randomly assigned to receive either 800 mg CS (n = 309 patients) or placebo (n = 313 patients) once daily for 2 years. The long-term combined structure-modifying and symptom-modifying effects of CS suggest that it could be a disease-modifying agent in patients with knee OA.

Kassab S, Cummings M, Berkovitz S, van Haselen R, Fisher P. Homeopathic medicines for adverse effects of cancer treatments. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004845. This review found preliminary data in support of the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy & Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. These trials need replicating. There is no convincing evidence for the efficacy of homeopathic medicines for other adverse effects of cancer treatments.

Kellermann AJ, C Kloft. Is there a risk of bleeding associated with standardized **ginkgo biloba** extract therapy? A systematic review and meta-analysis. Pharmacotherapy 2011 May;31(5):490–502.

Kemper KJ, Vohra S, Walls R; Task Force on Complementary and Alternative Medicine; Provisional Section on Complementary, Holistic, and Integrative Medicine. American Academy of Pediatrics. The use of **complementary and alternative medicine in pediatrics**. Pediatrics. 2008 Dec;122(6):1374-86.

Kenny AM, Boxer RS, Kleppinger A, et al. **Dehydroepiandrosterone (DHEA)** combined with exercise improves muscle strength and physical function in frail older women. J Am Geriatr Soc. 2010 Sep;58(9):1707-14.

Kleefstra N, et al. **Chromium** tx has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. Diabetes Care. 2006 Mar;29(3):521-5.

Kobak KA, Taylor LV, Warner G, Futterer R. **St. John's Wort** Versus Placebo in Social Phobia: Results From a Placebo-Controlled Pilot Study. J Clin Psychopharmacol. 2005 Feb;25(1):51-8.

Kobak KA, Taylor LV, et al. **St John's wort** versus placebo in obsessive-compulsive disorder: results from a double-blind study. Int Clin Psychopharmacol. 2005;20(6):299-304.

Krisanaprakornkit T, Krisanaprakornkit W, Piyavhatkul N, et al. **Meditation therapy** for anxiety disorders. Cochrane Database Syst Rev 2007; 3:CD004998.

Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for **menopausal symptoms**: a review of randomized, controlled trials. Ann Intern Med. 2002 Nov 19;137(10):805-13.

Kuriyama S, et al. **Green tea** consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA. 2006 Sep 13;296(10):1255-65. Green tea consumption is associated with reduced mortality due to all causes and due to cardiovascular disease but not with reduced mortality due to cancer. (InfoPOEMs: Green tea consumption is associated with reduced cardiovascular and all-cause mortality, but not cancer mortality. Women appear to benefit more than men: Men's mortality was significantly reduced only in those consuming more than 5 cups per day. Furthermore, there appears to be no benefit of green tea consumption in smokers. (LOE = 2b-))

Laing C, et al. **Chinese herbal** (**Longdan Xierganwan**) uropathy and nephropathy. Lancet. 2006 Jul 22;368(9532):338.

Larsson SC, Wolk A. **Tea Consumption and Ovarian Cancer** Risk in a Population-Based Cohort. Arch Intern Med. 2005 Dec 12;165(22):2683-2686.

Lee IT, Chan YC, Lin CW, Lee WJ, Sheu WH. Effect of **cranberry extracts** on lipid profiles in subjects with Type 2 diabetes. Diabet Med. 2008 Dec;25(12):1473-7. Cranberry supplements are effective in reducing atherosclerotic cholesterol profiles, including LDL cholesterol and total cholesterol levels, as well as total : HDL cholesterol ratio, and have a neutral effect on glycaemic control in Type 2 diabetic subjects taking oral glucose-lowering agents.

León H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of **fish oil** on arrhythmias and mortality: systematic review. BMJ. 2008 Dec 23;337

Leyer GJ, Li S, Mubasher ME, Reifer C, et al. **Probiotic** effects on cold and influenza-like symptom incidence and duration in children. Pediatrics. 2009 Aug;124(2):e172-9. Epub 2009 Jul 27.

Liatsos GD, Moulakakis A, Ketikoglou I, Klonari S. Possible **green tea-induced thrombotic thrombocytopenic purpura**. Am J Health Syst Pharm. 2010 Apr 1;67(7):531-4.

Lim WS, Gammack JK, Van Niekerk J, Dangour AD. **Omega 3 fatty acid** for the prevention of dementia. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005379.

Lim Alissa, Cranswick Noel, South Michael. Adverse events associated with the use of complementary and **alternative medicine in children**. Arch Dis Child archdischild183152 Online First: 22 December 2010 doi:10.1136/adc.2010.183152. (Including 4 deaths when failure to use conventional medicine in favor of CAM therapies.)

Liu J, Manheimer E, Yang M. Herbal medicines for treating **HIV infection** and AIDS. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003937.

Liu ZL, Liu ZJ, Liu JP, Yang M, Kwong J. Herbal medicines for **viral myocarditis**. Cochrane Database Syst Rev. 2010 Jul 7;7:CD003711. Some herbal medicines may lead to improvement of symptoms, ventricular premature beat, electrocardiogram, level of myocardial enzymes, and cardiac function in viral myocarditis.

Liu ZL, Liu JP, Zhang AL, et al. **Chinese herbal medicines for hypercholesterolemia**. Cochrane Database Syst Rev. 2011 Jul 6;7:CD008305. Some herbal medicines may have cholesterol-lowering effects. Our findings have to be interpreted with caution due to high or unclear risk of bias of the included trials. {22 RCTs, n=2130, range of 1-6 months with mean duration 2.3 +/- 1.3 months, high or unclear risk of ibias, no outcome data (too short & too small), no SAEs; Xuezhikang most commonly used; possible TC lowering (-0.90mmol/L vs inositol nicotinate)}.

Linde K, Mulrow CD, Berner M, **St John's** wort for depression. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD000448. CONCLUSIONS: Current evidence (37 trials) regarding hypericum extracts is inconsistent and confusing. In patients who meet criteria for major depression, several recent placebo-controlled trials suggest that the tested hypericum extracts have minimal beneficial effects while other trials suggest that hypericum and standard antidepressants have similar beneficial effects. As the preparations available on the market might vary considerably in their pharmaceutical quality, the results of this review apply only to the products tested in the included studies.

Linde K, Berner MM, Kriston L. **St John`s wort** for major depression. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD000448. The available evidence suggests that the hypericum extracts tested in the included trials a) are superior to placebo in patients with major depression; b) are similarly effective as standard antidepressants; c) and have fewer side effects than standard antidepressants. The association of country of origin and precision with effects sizes complicates the interpretation.

Macdonald R, Tacklind JW, Rutks I, Wilt TJ. **Serenoa repens** (Saw palmetto) monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review. BJU Int. 2012 May 2. Serenoa repens Adverse events were generally mild and comparable to placebo. Therapy does not improve LUTS or Q(max) compared with placebo in men with BPH, even at double and triple the usual dose.

MacFarquhar Jennifer K.; Broussard Danielle L.; Melstrom Paul; et al. Acute **Selenium** Toxicity Associated With a Dietary Supplement. Arch Intern Med. 2010;170(3):256-261.

Madisch A, et al. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. Aliment Pharmacol Ther. 2004;19:271-9.

Marcocci C, Kahaly GJ, Krassas GE., et al. for the European Group on Graves' Orbitopathy. **Selenium and the Course of Mild Graves' Orbitopathy**. N Engl J Med 2011; 364:1920-1931.

Marples, Brian November 1, 2007 -- Patients with prostate cancer should be warned against using over-the-counter prostate-related health supplements because these items could make normal prostate cells more sensitive than usual to the effects of radiation, researchers reported here at the 49th annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO). Researchers at William Beaumont Hospitals, Royal Oak, Michigan, United States, led by Brian Marples, PhD, Biology Radiologist, Department of Radiation Oncology, William Beaumont Hospitals, Royal Oak, Michigan, United States, tested three prostate-specific dietary supplements: Trinovin (red clover, biochanin A, formononetin, daidzein, genistein [phytoestrogen]), Provelex (lycopene, soy, saw palmetto, quercetin [phytoestrogen], selenium) and **ProstateRx (saw palmetto).** Their findings indicated that ProstateRx and other similar health store items were problematic in patients undergoing radiotherapy.

Mazza M, Capuano A, Bria P, Mazza S. **Ginkgo biloba and donepezil**: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. Eur J Neurol. 2006 Sep;13(9):981-5.

McDonnell WM, Bhattacharya R, Halldorson JB. Fulminant Hepatic Failure After Use of the Herbal Weight-Loss Supplement **Exilis**. Ann Intern Med. 2009 Nov 3;151(9):673-674.

Medical Letter. Dehydroepiandrosterone (**DHEA**). Vol 47 (Issue 1208) May 9, 2005 p.37-38.

Medicines and Healthcare products Regulatory Agency (MHRA) Dec/07 said: **Xiao Qin Long Wan**, a cold and flu medicine; pain reliever **Chuan Xiong Cha Tiao Wan**; **Bai Tou Weng Wan**, sold for stomach problems, and **Xie Gan Wan**, used to treat stress may contain Aristolochicia, which in unlicensed medicines was banned in UK in 1999

Melchart D, Linde K, Fischer P, **Echinacea** for preventing and treating the **common cold**. Cochrane Database Syst Rev. 2000;(2):CD000530. CONCLUSIONS: The majority of the available studies report positive results. However there is not enough evidence to recommend a specific Echinacea product, or Echinacea preparations for the treatment or prevention of common colds.

MHRA Aug 2011 issues warning over traditional Chinese medicines containing **Lei Gong Teng** (**tripterygium wilfordii**)

MHRA Dec/11Health Sciences Authority in Singapore has issued a press release warning the public of four adulterated health products. **ATHRI-Eze** - is marketed as a traditional Chinese medicine and packaged in a bottle of 20 white capsules. **SEAR HEANG TIENCHI TU CHUNG WAN** - claims to treat rheumatic pain and backache and is sold in a bottle of 40 black pills with a red label. **CAP WIJAYA KUSUMA (AN KI IT)** and **WIKU JAHE KENCUR (AKUR MUJARAB)** - are promoted as Malay Jamu (postnatal) medicines, which are packed in foil sachets of brown powder and are labelled to treat rheumatoid and arthritic conditions.These four products have been found to contain undeclared pharmaceutical medicines. Ingredients found include: dexamethasone, furosemide, paracetamol, chlorpheniramine (also known as chlorphenamine), phenylbutazone, allopurinol & prednisolone.

MHRA Dec/11 In response to an urgent notice issued by MHRA, Bee Health Ltd has agreed to stop marketing FSC Black Cohosh 1000 mg due to concerns about the high dosage of black cohosh in the product. The MHRA advises consumers not to take the FSC Black Cohosh product as it equates to 50 times the dose approved for traditional herbal medicinal products used to relieve menopausal symptoms. It is not known what the risks or effects on the body could be associated with such a high level of Black Cohosh.

MHRA Jan/12 Consumers are advised not to take unlicensed **Butterbur (Petasites hybridus)** herbal remedies. Butterbur contains pyrrolizidine alkaloids (PAs) which studies have shown can result in serious liver damage and organ failure. PAs have also been shown to lead to cancer in animals. Butterbur is most commonly used to treat migraine and hayfever. Butterbur products have been associated with cases of liver toxicity; 40 cases have been reported in the literature. Of these cases, nine were of acute hepatitis and two of the nine cases resulted in liver failure requiring transplantation. The cases of liver toxicity appear to have occurred with extracts of Butterbur where the PAs had been removed and only small amounts remained. There is some evidence that other constituents found in Butterbur such as the sesquiterpene constituents for example petasin may be implicated in the liver toxicity.

MHRA Feb/12 Herbal sliming products found to contain potentially dangerous undeclared pharmaceuticals: **Expelling Grease Slimming Abdomen, V12 Fruit Slimming, 100% Natural Weight Loss**

Coffee, Leisure 18 Slimming Orange Juice, Fashion Slimming Milk Shake, Langli, Ya Buk & Fruit and vegetables lose weight. MHRA has received advice from the Danish Medicines Agency that these unlicensed products have been tested and found to contain the Prescription Only Medicine Sibutramine.

MHRA Feb/12 has received advice from AGES PharmMed in Austria and the Danish Medicines Agency, warning that these unlicensed products have been tested and found to contain Tadalafil and/or Sildenafil: **AH Free/Reflexit, Stree Overlord, Man King, VigRX, Maxman, Maxman III, Viriya, & Imbiza for Men.**

MHRA Feb/12 Following a safety alert issued in October 2010 about slimming products containing Paiyouji the Agency has received a further complaint about a product called **'Paiyouji Plus - Fast Acting Slimming Tea'**. This product has been tested by the Agency and, as in the case of other Paiyouji products, found to contain sibutramine.

MHRA Mar/12 Traditional Chinese Medicine (TCM) **Anshen Bunao Pian** (Chung Lien Kulin Brand) has been found by the Department of Health in Hong Kong to contain 55 times the level of mercury permitted in China. Acute mercury poisoning can damage the neurological system and kidneys. The product is manufactured in mainland China and imported by Fung Wah (HK) Company.

Michel BA, Stucki G, Frey D, et al. **Chondroitins** 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. Arthritis Rheum 2005; 52:779-86. (InfoPOEMs: After 2 years of treatment, chondroitin sulfate had no effect on comfort in patients with severe degenerative arthritis of the knee. Compared with placebo, however, it appears that chondroitin may have a small protective effect on the joint. The clinical relevance of this effect not known. (LOE = 1b))

Mills E, Singh R, Ross C, Ernst E. Sale of **kava** extract in some health food stores. CMAJ. 2003 Nov 25;169(11):1158-9. (January 2002, Health Canada issued an advisory, followed by a ban in August 2002, on the sale of herbal kava. One month after the advisory, 22 (67%) of 33 health food stores approached were selling kava. Two months after the ban, 17 (57%) of 30 stores continued to sell kava. These findings demonstrate that health food stores may need to be better informed about the sale of restricted natural health products.

Miyasaka LS, Atallah AN, Soares BG. **Valerian** for anxiety disorders. Cochrane Database Syst Rev 2006; 4:CD004515. This paper and [17**]

Miyasaka LS, Atallah AN, Soares BG. **Passiflora** for anxiety disorder. Cochrane Database Syst Rev 2007; 1:CD004518.

Mischoulon D. Update and critique of **natural remedies as antidepressant treatments**. Psychiatr Clin North Am 2007; 30:51-68.

Nahas R, Moher M. **Complementary and alternative medicine** for the treatment of type 2 diabetes. Can Fam Physician. 2009 Jun;55(6):591-6. Chromium, and possibly gymnema, appears to improve glycemic control. Fibre, green tea, and fenugreek have other benefits but there is little evidence that they substantially improve glycemic control. Further research on bitter melon and cinnamon is warranted. There is no complementary and alternative medicine research addressing microvascular or macrovascular clinical outcomes.

Nahas Richard, Sheikh Osmaan. **Complementary and alternative medicine** for the treatment of **major depressive disorder** Can Fam Physician June 2011 57: 659-663. (**St John's wort & exercise**)

Nahin RL, Pecha M, Welmerink DB, et al. Ginkgo Evaluation of Memory Study Investigators. Concomitant use of **prescription drugs and dietary supplements** in ambulatory elderly people. J Am Geriatr Soc. 2009 Jul;57(7):1197-205.

Nair KS, et al. **DHEA** in elderly **women** and **DHEA or testosterone** in elderly men. N Engl J Med. 2006 Oct 19;355(16):1647-59. (see also Pharmacist's Letter: Anti-aging Effects of DHEA. Dec/06) (n= 2yr 87 males, 57 women) Men who received testosterone had a slight increase in fat-free mass, and men in both treatment groups had an increase in BMD at the femoral neck. Women who received DHEA had an increase in BMD at the ultradistal radius. Neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life. (InfoPOEMs: There is no evidence that supplementation with dehydroepiandrosterone (DHEA) or testosterone has any meaningful clinical benefit for older patients with low serum levels of those hormones. (LOE = 1b))

Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms ofmenopausewith **black cohosh**, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med 2006;145:869–79.

Nieminen TH, Hagelberg NM, Saari TI, Neuvonen M, Laine K, Neuvonen PJ, Olkkola KT. **St John's wort greatly reduces the concentrations of oral oxycodone**. Eur J Pain. 2010 Jan 25.

Ngo MQ, Nguyen NN, Shah SA. Oral **aloe vera** for treatment of diabetes mellitus and dyslipidemia. Am J Health Syst Pharm. 2010 Nov 1;67(21):1804, 1806, 1808.

Ondrizek RR, Chan PJ, Patton WC, King A. Inhibition of human **sperm** motility by specific herbs used in alternative medicine (eg. St. John's Wort). J Assist Reprod Genet. 1999 Feb;16(2):87-91.

Ooi CP, Yassin Z, Hamid TA. **Momordica charantia** for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010 Feb 17;2:CD007845.

Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: double-blind, randomized clinical trial. Am J Psychiatry. 2010 Aug;167(8):942-8. These preliminary results suggest that SAMe can be an effective, well-tolerated, and safe adjunctive treatment strategy for SRI nonresponders with major depressive disorder and warrant replication.

Parasrampuria J, Schwartz K, Petesch R. Quality control of **dehydroepiandrosterone** dietary supplement products. JAMA. 1998 Nov 11;280(18):1565.

Peng CC, Glassman PA, Trilli LE, et al. Incidence and severity of **potential drug-dietary supplement interactions** in primary care patients: an exploratory study of 2 outpatient practices. Arch Intern Med. 2004 Mar 22;164(6):630-6.

Perri D, Dugoua JJ, Mills E, Koren G. Safety & efficacy of echinacea (E. angustafolia, purpurea & pallida) during pregnancy & lactation. Can J Clin Pharmacol.2006 Fall;13(3):e262-7.Epub 2006Nov3.

Perry, Rachel, Hunt, Katherine, Ernst, Edzard. Nutritional Supplements and Other Complementary Medicines for **Infantile Colic**: A Systematic Review. Pediatrics 2011 127: 720-733

Pharmacist's Letter: Health Benefits of Drinking **Green Tea.** Nov 2006.

Pharmacist's Letter. Is **Chondroitin** effective for Osteoarthritis. June 2007. (Best evidence is with glucosamine sulfate called DONA by Rotta Pharmaceuticals)

Pharmacist's Letter. **New Health Canada Rules Allow More Health Claims for Natural Products**. April 2008.

Pharmacist's Letter. **Hawthorn for Heart Failure**. April 2008.

Pharmacist's Letter. **Flaxseed**: Is It As Beneficial As Fish Oil? July 2009.

Pharmacist's Letter. **Supplements for Prevention and Treatment of Colds and Influenza**. Nov 2009.

Pittler MH, Ernst E. **Horse chestnut** seed extract for chronic venous insufficiency. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003230. The evidence presented implies that HCSE is an efficacious & safe short-term treatment for CVI. However, several caveats exist and more rigorous RCTs are required to confirm the efficacy of this treatment option.

Pittler MH, Ernst E. **Kava** extract for treating anxiety. Cochrane Database Syst Rev. 2003;(1):CD003383. CONCLUSIONS: Compared with placebo, kava extract appears to be an effective symptomatic treatment option for anxiety. The data available from the reviewed studies suggest that kava is relatively safe for short-term treatment (1 to 24 weeks), although more information is required. Further rigorous investigations, particularly into the long-term safety profile of kava are warranted.

Pittler MH, Ernst E. **Feverfew** for preventing migraine. Cochrane Database Syst Rev. 2004;(1):CD002286. CONCLUSIONS: There is insufficient evidence from randomised, double-blind trials to suggest an effect of feverfew over & above placebo for preventing migraine. It appears from the data reviewed that feverfew presents no major safety problems.

Pittler MH, Guo R, Ernst E. **Hawthorn extract** for treating chronic heart failure. Cochrane Database Syst Rev 2008; DOI: 10.1002/14651858.CD005312.pub2. (Not included in the review was the survival and Prognosis: Investigation of Crataegus Extract WS1442 in CHF (**SPICE**) trial, which was ongoing as Pittler et al were screening relevant trials. As reported by heartwire when the study was later presented at the American College of Cardiology 2007 Scientific Sessions, adding the herbal to ACE inhibitors, beta blockers, and other components of contemporary therapy failed to alter a composite primary end point that included sudden cardiac death, death due to progressive heart failure, fatal or nonfatal MI, and HF hospitalization at 24 months. The trial did support hawthorn extract's good safety record, however.)

Portnoi G, Chng LA, et al. Prospective comparative study of the safety & effectiveness of **ginger** for the treatment of nausea and vomiting in pregnancy. Am J Obstet Gynecol. 2003 Nov;189(5):1374-7.

Predy GN, Goel V, Lovlin R, et al. Efficacy of an extract of North American **ginseng (Cold-fx)** containing poly-furanosyl-pyranosyl-saccharides for preventing upper respiratory tract infections: a randomized controlled trial. CMAJ. 2005 Oct 25;173(9):1043-8. INTERPRETATION: Ingestion of a poly-furanosyl-pyranosyl-saccharide-rich extract of the roots of North American ginseng in a moderate dose **400mg (2 capsules) over 4 months** reduced the mean number of colds per person (0.99 vs 0.71), the proportion of subjects who experienced 2 or more colds (24.8 vs 10%), the severity of symptoms and the number of days cold symptoms were reported (from 11.1 days to only 8.7 days). The number of people with 1 cold was 64.4 vs 56.1% with Cold-fX in **healthy** 18-65yrs old (mean 43yrs), n=323 with a history of at least 2 colds in the previous year. Limitations: not virologically proven influenza or more typical common cold illnesses studied will be important in the future, only most severe illnesses were evaluated, mechanism of action & true active constituents are not known.

Qato DM, Alexander GC, et al. Use of **prescription & over-the-counter medications and dietary supplements** among older adults in the United States. JAMA. 2008 Dec 24;300(24):2867-78.

Qiu GX, Weng XS, Zhang K, et al. [A multi-central, randomized, controlled clinical trial of **glucosamine** hydrochloride/sulfate in the treatment of knee osteoarthritis.] Zhonghua Yi Xue Za Zhi. 2005 Nov;85(43):3067-70.

Quinn JF.; Raman R,Thomas RG.; et al. **Docosahexaenoic Acid (DHA) Supplementation** and Cognitive Decline in Alzheimer Disease: A Randomized Trial. *JAMA*. 2010;304(17):1903-1911.

Rambaldi A, Jacobs BP, Iaquinto G. **Milk thistle** for alcoholic and/or hepatitis B or C virus liver diseases. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD003620. CONCLUSIONS: Our results question the beneficial effects of milk thistle for patients with alcoholic and/or hepatitis B or C virus liver diseases and highlight the lack of high-quality evidence to support this intervention. Adequately conducted and reported randomised clinical trials on milk thistle versus placebo are needed.

Ravindran AV, Lam RW, Filteau MJ, et al. Canadian Network for Mood and Anxiety Treatments (**CANMAT**) clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. J Affect Disord. 2009 Aug 8. [Epub ahead of print]

Red yeast: Most clinical studies have used a specific brand product (Cholestin). However, most other red yeast brands contain similar amount of red yeast, 600 mg. For hypercholesterolemia, a typical dose of red yeast is 1200 mg two times daily with food (2624). A total daily dose of 2400 mg red yeast contains approximately 9.6 mg total statins, of which 7.2 mg is lovastatin (2624). For dyslipidemia related to HIV infection, 1200 mg twice daily has been used (9475). www.naturaldatabase.com

Reeds Dominic N., Patterson Bruce W., Okunade Adewole, et al. **Ginseng and Ginsenoside** Re Do Not Improve β-Cell Function or Insulin Sensitivity in Overweight and Obese Subjects With Impaired Glucose Tolerance or Diabetes. Diabetes Care May 2011 34:1071-1076; published ahead of print March 16, 2011, doi:10.2337/dc10-2299

Reginster JY, Deroisy R, Rovati LC, et al. Long-term eff ects of **glucosamine** sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001; 357: 251–56.

Reichenbach S, et al. **Meta-analysis: chondroitin** for osteoarthritis of the knee or hip. Ann Intern Med. 2007 Apr 17;146(8):580-90. Large-scale, methodologically sound trials indicate that the symptomatic benefit of chondroitin is minimal or nonexistent.

Reinhart KM, Coleman CI, Teevan C, et al. Effects of **garlic on blood pressure** in patients with and without systolic hypertension: a meta-analysis. Ann Pharmacother. 2008 Dec;42(12):1766-71. Epub 2008 Nov 18. This meta-analysis suggests that garlic is associated with blood pressure reductions in patients with an elevated SBP although not in those without elevated SBP.

Richy F, et al. Structural and symptomatic efficacy of **glucosamine and chondroitin** in knee osteoarthritis: a comprehensive meta-analysis. Arch Intern Med. 2003 Jul 14;163(13):1514-22.

Ringdahl E, Pandit S. Treatment of **Knee Osteoarthritis**. Am Fam Physician. 2011;83(11):1287-1292.

TOP

Rockwell S, Liu Y, Higgins SA. Alteration of the effects of cancer therapy agents on breast cancer cells bythe herbal medicine **black cohosh**.Breast Cancer Res Treat. 2005 Apr;90(3):233-9.

Roselle H et al. Symptomatic hepatitis associated with the use of herbal **red yeast rice**. Ann Intern Med 2008; 149:516.

Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of **Ginkgo** biloba extract. N Engl J Med. 1997 Apr 10;336(15):1108.

Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic **Ginkgo** biloba ingestion. Neurology. 1996 Jun;46(6):1775-6.

Rozendaal RM, et al. Effect of **glucosamine sulfate on hip osteoarthritis**: a randomized trial. Ann Intern Med. 2008 Feb 19;148(4):268-77. Glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip osteoarthritis.

Saeed SA, et al. **Herbal and Dietary Supplements** for Treatment of **Anxiety** Disorders. American Family Physician 2007;76:549-56. Kava potential for mild to moderate anxiety. Inositol modest effects with panic or OCD disorder. Not encourage St. John's wort, valerian, Sympathyl or passionflower.

Saito YA, Rey E, Almazar-Elder AE, et al. A randomized, double-blind, placebo-controlled trial of **St John's wort** for treating irritable bowel syndrome. Am J Gastroenterol. 2010 Jan;105(1):170-7. Epub 2009 Oct 6. SJW was a less effective treatment for IBS than placebo.

Samuels N, Finkelstein Y, Singer SR, Oberbaum M. **Herbal medicine and epilepsy**: proconvulsive effects and interactions with antiepileptic drugs. Epilepsia 2008;49:373-80.

Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Phillips RS. Heavy metal content of **ayurvedic** herbal medicine products. JAMA. 2004 Dec 15;292(23):2868-73.

Saper RB, Phillips RS, Sehgal A, et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA. 2008 Aug 27;300(8):915-23. Erratum in: JAMA. 2008 Oct 8;300(14):1652. **One-fifth** of both US-manufactured and Indian-manufactured Ayurvedic medicines purchased via the Internet contain **detectable lead, mercury, or arsenic**.

Sawitzke AD, Shi H, Finco MF, Dunlop DD, et al.. Clinical efficacy and safety of **glucosamine, chondroitin sulphate, their combination, celecoxib or placebo** taken to treat osteoarthritis of the knee: 2-year results from **GAIT**. Ann Rheum Dis. 2010 Jun 4.

Schabath MB, Hernandez LM, Wu X, Pillow PC, Spitz MR. Dietary **phytoestrogens** and lung cancer risk. JAMA. 2005 Sep 28;294(12):1493-504.

Schoonees A, Visser J, Musekiwa A, Volmink J. **Pycnogenol**® for the treatment of chronic disorders. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD008294. DOI: 10.1002/14651858.CD008294.pub3. Oxidative stress has been implicated in the development of a number of conditions including cancer, arthritic disorders and cardiovascular disease. Pycnogenol®, a herbal dietary supplement derived from French maritime pine bark extract, is standardised to contain 70% procyanidin which is a powerful antioxidant. Pycnogenol® is marketed as a supplement for preventing or treating a wide range of chronic conditions.Current evidence is insufficient to support Pycnogenol® use for the treatment of any chronic disorder. Well-designed, adequately powered trials are needed to establish the value of this treatment.

Scroggie DA, Albright A. The effect of **glucosamine-chondroitin** supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized clinical trial. Arch Intern Med. 2003 Jul 14;163(13):1587-90.

Segal R, Pilote L. **Warfarin interaction with Matricaria chamomilla**. CMAJ. 2006 Apr 25;174(9):1281-2.

Sengupta G et al. Comparison of **Murraya koenigii- and Tribulus terrestris-Based** Oral Formulation Versus Tamsulosin in the Treatment of Benign Prostatic Hyperplasia in Men Aged >50 Years: A Double-Blind, Double-Dummy, Randomized Controlled Trial. Clin Ther. 2011 Dec; 33(12):1943-52.

Shah SA, Sander S, White CM, et al. Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. Lancet Infect Dis. 2007 Jul;7(7):473-80. Erratum in: Lancet Infect Dis. 2007 Sep;7(9):580. Published evidence **supports echinacea's** benefit in decreasing the incidence and duration of the common cold.

Shang A, Huwiler-Müntener K, et al. Are the clinical effects of **homoeopathy** placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. The Lancet - Vol. 366, Issue 9487, 27 August 2005, Pages 726-732. (InfoPOEMs: High-quality studies demonstrate that homeopathy are no more effective than placebo. (LOE = 1a-))

Shelton RC, Keller MB, et al. Effectiveness of **St John's wort** in major depression: a randomized controlled trial. **JAMA. 2001** Apr 18;285(15):1978-86.

Skalli S, Zaid A, Soulaymani R. **Drug interactions with herbal medicines**. *Ther Drug Monit*. 2007. 29(6): 679–86.

Smith C, Crowther C, Willson K, Hotham N, McMillian V. A randomized controlled trial of **ginger** to treat nausea and vomiting in pregnancy. Obstet Gynecol. 2004 Apr;103(4):639-45.

Snitz Beth E.; O'Meara Ellen S.; Carlson Michelle C.; et al. for the **Ginkgo** Evaluation of Memory (**GEM**) Study Investigators. Ginkgo biloba for Preventing Cognitive Decline in Older Adults: A Randomized Trial. JAMA. 2009;302(24):2663-2670. Compared with placebo, the use of G biloba, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment.

Storch A, Jost WH, Vieregge P, et al. Randomized, Double-blind, Placebo-Controlled Trial on Symptomatic Effects of **Coenzyme Q10** 100mg tid in Parkinson Disease. Arch Neurol. 2007 May 14; [Epub ahead of print] N=131 3months. Nanoparticular CoQ(10) at a dosage of 300 mg/d is safe and well tolerated and leads to plasma levels similar to 1200 mg/d of standard formulations. Add-on CoQ(10) does not display symptomatic effects in midstage Parkinson disease.

Stranges S, Marshall JR, Natarajan R, et al. Effects of Long-Term Selenium Supplementation on the Incidence of Type 2 Diabetes: A Randomized Trial. Ann Intern Med. 2007 Jul 9; [Epub ahead of print] Selenium supplementation does not seem to prevent type 2 diabetes, and it may increase risk for the disease.

Striano P, Zara F, Minetti C, Striano S. **Chitosan** may decrease serum valproate and increase the risk of seizure reappearance. BMJ. 2009 Sep 24;339:b3751. doi: 10.1136/bmj.b3751.

Suzuki E, Yorifuji T, Takao S, et al. **Green tea** consumption and mortality among Japanese elderly people: the prospective Shizuoka elderly cohort. Ann Epidemiol. 2009 Oct;19(10):732-9.

Szegedi A, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (**St John's wort**): randomised controlled double blind non-inferiority trial versus paroxetine. **BMJ. 2005** Feb 11; [Epub ahead of print] (InfoPOEMs: In patients with moderate to severe depression, St John's wort was at least as effective as paroxetine after 6 weeks of therapy. It was also better tolerated than paroxetine. More than half the patients receiving St John's wort required 600 mg 3 times a day of a product with less of the purported active ingredients than is commonly used in other studies. Patients in clinical practice may experience a benefit at a dose of 300 mg 3 times daily using commercial products that contain more of the active ingredients. (LOE = 1b))

Takwale A, Tan E, Agarwal S, et al. Efficacy and tolerability of **borage oil** in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial BMJ 2003;327:1385, doi:10.1136/bmj.327.7428.1385

Taylor MA, Reilly D, Llewellyn-Jones RH, McSharry C, Aitchison TC. Randomised controlled trials of **homoeopathy versus placebo** in perennial allergic rhinitis with overview of four trial series. BMJ 2000;321:471-6.

Taylor James A.,et al. Efficacy and Safety of **Echinacea** in Treating Upper Respiratory Tract Infections in Children. A Randomized Controlled Trial. JAMA. 2003;290:2824-2830. CONCLUSIONS: Echinacea purpurea, as dosed in this study, was not effective in treating URI symptoms in patients 2 to 11 years old, and its use was associated with an increased risk of rash.

Teschke Rolf; Schulze Johannes. Risk of **Kava Hepatotoxicity** and the FDA Consumer Advisory. *JAMA*. 2010;304(19):2174-2175.

Teschke R, Sarris J, Schweitzer I. Kava hepatotoxicity in traditional and modern use: the presumed Pacific kava paradox hypothesis revisited. Br J Clin Pharmacol. 2012 Feb;73(2):170-4.

Towheed TE, Maxwell L, Anastassiades TP, et al. **Glucosamine** therapy for treating osteoarthritis. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD002946. CONCLUSIONS: This update includes 20 studies with 2570 patients. Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function while those studies evaluating the Rotta preparation show that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. WOMAC outcomes of pain, stiffness and function did not show a superiority of glucosamine over placebo for both Rotta and non-Rotta preparations of glucosamine. Glucosamine was as safe as placebo.

Trebaticka J, et al. Treatment of ADHD with French maritime **pine bark extract, Pycnogenol**((R)). Eur Child Adolesc Psychiatry. 2006 May 13; [Epub ahead of print] (n=61 4weeks)

Trinh K, Cui X, Wang YJ. Chinese herbal medicine for chronic neck pain due to cervical degenerative disc disease. Spine (Phila Pa 1976). 2010 Nov 15;35(24):2121-7. There is low quality evidence that an oral herbal medication, Compound Qishe Tablet, reduced pain more than placebo or Jingfukang and a topical herbal medicine, Compound Extractum Nucis Vomicae, reduced pain more than Diclofenac Diethylamine Emulgel.

Tsitsikas DA, Emery M, Pomfret S, et al. Anaemia and unexplained abdominal pain: looking for a lead. BMJ. 2012 May 2;344:e2996. (**lead from ayuverdic remedies**)

Turner RB, Bauer R, Woelkart K et al. An Evaluation of **Echinacea angustifolia** in Experimental Rhinovirus Infections NEJM 2005;353:341-348. CONCLUSIONS: The results of this study indicate that extracts of E. angustifolia root, either alone or in combination, do not have clinically significant effects on infection with a rhinovirus or on the clinical illness that results from it.

Uebelhack R, et al. **Black cohosh and St. John's wort** for climacteric complaints: a randomized trial. (n=301 16weeks) Obstet Gynecol. 2006 Feb;107(2 Pt 1):247-55.

Vadillo-Ortega F, Perichart-Perera O, Espino S, Avila-Vergara MA, Ibarra I, Ahued R, et al. Effect of supplementation during pregnancy with **L-arginine** and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. BMJ 2011;342:d2901.

van Gurp G, Meterissian GB, Haiek LN, McCusker J, Bellavance F. **St John's wort** or sertraline? Randomized controlled trial in primary care. Can Fam Physician. 2002 May;48:905-12.

Vanherweghem JL, et al. Rapidly progressive **interstitial renal fibrosis** in young women: association with **slimming regimen** including **Chinese herbs**. Lancet. 1993 Feb 13;341(8842):387-91.

Viswanathan L, Vigersky RA. The effect of herbal medications on **thyroid hormone economy and estrogen-sensitive hepatic proteins** in a patient with prostate cancer. Arch Intern Med. 2012 Jan 9;172(1):58-60. (PC-SPES etc.)

Vogel JH, Bolling SF, et al. American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine). Integrating **complementary medicine into cardiovascular medicine**. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus. J Am Coll Cardiol. 2005 Jul 5;46(1):184-221.

von Arnim U, Peitz U, Vinson B, Gundermann KJ, Malfertheiner P. **STW 5**, a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. Am J Gastroenterol. 2007 Jun;102(6):1268-75. This placebo-controlled study with an 8-wk treatment period documents the efficacy of STW 5 in FD.

Wandel S, Jüni P, Tendal B, Effects of **glucosamine, chondroitin**, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 341:doi:10.1136/bmj.c4675 (Pub 16 Sept 2010)

Wang C, Cao B, Liu QQ, et al. **Oseltamivir Compared With the Chinese Traditional Therapy Maxingshigan-Yinqiaosan** in the Treatment of H1N1 Influenza: A Randomized Trial. Ann Intern Med. 2011 Aug 16;155(4):217-225.

Wargo KA, Allman E, Ibrahim F. A possible case of **saw palmetto-induced pancreatitis**. South Med J. 2010 Jul;103(7):683-5.

White B. **Ginger**: an overview. Am Fam Physician. 2007 Jun 1;75(11):1689-91.

Wildi LM, Raynauld JP, Martel-Pelletier J, et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. Ann Rheum Dis. 2011 Mar 1. (n=69)

Wilkens Philip; Scheel Inger B.; Grundnes Oliver; et al. Effect of **Glucosamine** on Pain-Related Disability in Patients With Chronic Low **Back Pain** and Degenerative Lumbar Osteoarthritis: A Randomized Controlled Trial. JAMA. 2010;304(1):45-52.

TOP

Williamson E. **Drug interactions between herbal and prescription medicines**. *Drug Saf*. 2003. 26(15): 1075–92.
Wooltorton E. Herbal **kava**: reports of liver toxicity. CMAJ. 2002 Mar 19;166(6):777.
Wyman M, Lenoard M, Morledge T. **Coenzyme Q10**: A therapy for hypertension and statin-induced myalgia? Cleveland Clinic Journal of Medicine 2010; 77(7):435-442
Yale SH., Liu K., **Echinacea** purpurea therapy for the treatment of the common cold. Arch Intern Med. 2004;164:1237-41.
Yang YC, Lu FH, Wu JS, Wu CH, Chang CJ. The protective effect of habitual **tea** consumption on hypertension. Arch Intern Med. 2004 Jul 26;164(14):1534-40.
Yang X, Zeng X, Wu T. **Chuanxiong** preparations for preventing stroke. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006765.
Ye P, Lu ZL, Du BM, et al; for the CCSPS Investigators. Effect of **xuezhikang** on cardiovascular events and mortality in elderly patients with a history of myocardial infarction: a subgroup analysis of elderly subjects from the china coronary secondary prevention study. J Am Geriatr Soc. 2007 Jul;55(7):1015-22. n=1445
Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q(10) 200mg/d supplementation on simvastatin-induced myalgia. Am J Cardiol. 2007 Nov 1;100(9):1400-3. Epub 2007 Aug 16. n=44 12weeks In conclusion, **coenzyme Q(10) supplementation did not improve statin tolerance or myalgia**, although further studies are warranted.
Yuan CS, Wei G, Dey L, et al. Brief communication: **American ginseng** reduces warfarin's effect in healthy patients: a randomized, controlled Trial. Ann Intern Med. 2004 Jul 6;141(1):23-7.
White B. **Ginger**: an overview. Am Fam Physician. 2007 Jun 1;75(11):1689-91.
Wildi LM, Raynauld JP, Martel-Pelletier J, et al. **Chondroitin sulphate** reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. Ann Rheum Dis. 2011 Mar 1.
Wu T, Chen X, Duan X, Juan N, Liu G, Qiao J, Wang Q, Wei J, Zhen J, Zhou L. **Chinese medicinal herbs** for acute bronchitis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004560.
Wu T, et al. **Tongxinluo** (**Tong xin luo or Tong-xin-luo**) capsule for unstable angina pectoris. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004474. Due to the methodological limitations of the studies, the evidence is insufficient to make any conclusive recommendations about the use of this treatment for patients presenting with unstable angina. Large high quality randomised controlled trials are warranted.
Wen MC, et al. Efficacy and tolerability of anti-asthma herbal medicine intervention in adult patients with moderate-severe allergic asthma. J Allergy Clin Immunol. 2005 Sep;116(3):517-24. CONCLUSION: Anti-asthma herbal medicine intervention appears to be a safe and effective alternative medicine for treating asthma. In contrast with prednisone, **ASHMI** had no adverse effect on adrenal function and had a beneficial effect on T(H)1 and T(H)2 balance.
Zeng X, Liu M, Yang Y, Li Y, Asplund K, Zeng X. **Ginkgo biloba** for acute ischaemic stroke. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003691.
Zhu X, ProctorM, Bensoussan A,Wu E, Smith CA. **Chinese herbalmedicine for primary dysmenorrhoea**. CochraneDatabase of Systematic Reviews 2008, Issue 2. Art. No.: CD005288. DOI: 10.1002/14651858.CD005288.pub3. The review found promising evidence supporting the use of Chinese herbal medicine for primary dysmenorrhoea; however, results are limited by the poor methodological quality of the included trials.
Zick SM, Gillespie B, Aaronson KD. The effect of Crataegus oxycantha special extract WS 1442 (**hawthorn**) on clinical progression in patients with mild to moderate symptoms of **heart failure**. Eur J Heart Fail. 2008 Jun;10(6):587-93. Epub 2008 May 19. CSE does not reduce heart failure progression in patients who have HF. CSE appears to increase the early risk of HF progression.

Case Reports

Ang-Lee MK, Moss J, Yuan CS. **Herbal medicines and perioperative care**. JAMA 2001;286:208-16.
Bardia A, Nisly NL, Zimmerman MB, et al. Use of herbs among adults based on evidence-based indications: findings from the National Health Interview Survey. Mayo Clin Proc 2007;82:561-6
Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Adv Data 2004;(343):1-19.
Bebbington A, Kulkarni R, Roberts P. Ginkgo biloba: Persistent bleeding after total hip arthroplasty caused by herbal self-medication. J Arthroplasty 2005;20:125-6.
Benjamin J, Muir T, Briggs K, Pentland B. A case of cerebral haemorrhage-can Ginkgo biloba be implicated? Postgrad Med J 2001;77:112-3.
Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with Ginkgo biloba. A case report and systematic review of the literature. J Gen Intern Med 2005;20;657-61.
Chatterjee N, Domoto-Reilly K, Fecci PE, et al. **Licorice-associated reversible cerebral vasoconstriction** with PRES (encephalopathy). Neurology. 2010 Nov 23;75(21):1939-41.
Cheema P, El-Mefty O, Jazieh AR. Intraoperative haemorrhage associated with the use of extract of Saw Palmetto herb: a case report and review of literature. J Intern Med 2001;250:167-9.
Dhesi Pavittarpaul; Ng Rita; Shehata MM.; et al. Ventricular Tachycardia After Ingestion of **Ayurveda Herbal** Antidiarrheal Medication Containing Aconitum. Arch Intern Med. 2010;170(3):303-305.
Destro MW, Speranzini MB, Cavalheiro Filho C, et al. Bilateral haematoma after rhytidoplasty and blepharoplasty following chronic use of Ginkgo biloba. Br J Plast Surg 2005;58:100-1.
Doyle H, Kargin M. Herbal stimulant containing ephedrine has also caused psychosis. BMJ 1996;313:756.
Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. JAMA 1998;280:1569-75.
Fessenden JM, Wittenborn W, Clarke L. Gingko biloba: a case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy. Am Surg 2001;67:33-5.
Firenzuoli F, Gori L, Galapai C. Adverse reaction to an adrenergic herbal extract (Citrus aurantium). Phytomedicine 2005;12:247-8.
Fong KC, Kinnear PE. Retrobulbar haemorrhage associated with chronic Ginkgo biloba ingestion. Postgrad Med J 2003;79:531-2.
Gange CA, Madias C, Felix-Getzik EM, et al. Variant angina associated with bitter orange in a dietary supplement. Mayo Clin Proc 2006;81:545-8.
Greco A et al. Acute hepatitis caused by a **natural lipid-lowering** product: when "alternative" medicine is no "alternative" at all. J Hepatology 2009; 50:1273.
Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000;343:1833-8.
Hauser D, Gayowski T, Singh N. Bleeding complications precipitated by unrecognized Gingko biloba use after liver transplantation. Transpl Int 2002;15:377-9.
Irefin S, Sprung J. A possible cause of cardiovascular collapse during anesthesia: long-term use of St. John's Wort. J Clin Anesth 2000;12:498-9.
Jacobs KM, Hirsch KA. Psychiatric complications of Ma-huang. Psychosomatics 2000;41:58-62.
Jordan S, Murty M, Pilon K. Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions. Canadian Adverse Reaction Newsletter 2004;14:3-4.
Kennedy J. Herb and supplement use in the US adult population. Clin Ther 2005;27:1847-58.
Keogh AM, Baron DW. Sympathomimetic abuse and coronary artery spasm. Br Med J 1985;291:940.
Liatsos GD, Moulakakis A, Ketikoglou I, Klonari S. Possible **green tea-induced thrombotic thrombocytopenic purpura**. Am J Health Syst Pharm. 2010 Apr 1;67(7):531-4.
MacFarquhar Jennifer K.; Broussard Danielle L.; Melstrom Paul; et al. Acute **Selenium** Toxicity Associated With a Dietary Supplement. Arch Intern Med. 2010;170(3):256-261.
McDonnell WM, Bhattacharya R, Halldorson JB. Fulminant Hepatic Failure After Use of the Herbal Weight-Loss Supplement Exilis. Ann Intern Med. 2009 Nov 3;151(9):673-674.
Meisel C, Johne A, Roots I. Fatal intracerebral mass bleeding associated with Ginkgo biloba and ibuprofen. Atherosclerosis 2003;167:367.
Miller LG, Freeman B. Possible subdural hematoma associated with Ginkgo biloba. J Herb Pharmacotherapy 2002;2:57-63.
Morgenstern LB, Viscoli CM, Kernan WN, et al. Use of Ephedra-containing products and risk for hemorrhagic stroke. Neurology 2003;60:132-5.
Nasir JM, Durning SJ, Ferguson M, et al. Exercise-induced syncope associated with QT prolongation and ephedra-free Xenadrine. Mayo Clin Proc 2004;79:1059-62.
Nykamp DL, Fackih MN, Compton AL. Possible association of acute lateral-wall myocardial infarction and bitter orange supplement. Ann Pharmacother 2004;38:812-6.
Penzak SR, Jann MW, Cold JA, et al. Seville (sour) orange juice: synephrine content and cardiovascular effects in normotensive adults. J Clin Pharmacol 2001;41:1059-63.
Roselle H et al. Symptomatic hepatitis associated with the use of herbal red yeast rice. Ann Intern Med 2008; 149:516.
Rosenblatt M, Mindel T. Spontaneous hyphema associated with ingestion of Gingko biloba extract. N Engl J Med 1997;336:1108.
Rowin J, Lewis SL. Spontaneous bilateral subdural hemotomas with chronic Gingko biloba ingestion. Neurology 1996;46:1775-6.
Vale S. Subarachnoid haemorrhage associated with Ginkgo biloba. Lancet 1998;352:36.
Verhelst X, Burvenich P, Van Sassenbroeck D, et al. Acute hepatitis after treatment for hair loss with oral **green tea** extracts (Camellia Sinensis). Acta Gastroenterol Belg. 2009 Apr-Jun;72(2):262-4.
Walton R, Manos GH. Psychosis related to ephedra-containing herbal supplement use. South Med J 2003;96:718-20.
Wargo KA, Allman E, Ibrahim F. A possible case of **saw palmetto-induced pancreatitis**. South Med J. 2010 Jul;103(7):683-5.
Wyman M, Lenoard M, Morledge T. **Coenzyme Q10**: A therapy for hypertension and statin-induced myalgia? Cleveland Clinic Journal of Medicine 2010; 77(7):435-442; doi:10.3949/ccjm.77a.09078
Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. Am J Cardiol 2006;98:673-80.
Yeu E, Grostern R. Saw palmetto and intraoperative floppy-iris syndrome. J Cataract Refract Surg. 2007 May;33(5):927-8.
Zhang, Yuanting, Fein, Elizabeth B., Fein, Sara B. Feeding of **Dietary Botanical Supplements and Teas to Infants** in the United States. Pediatrics 2011 0: peds.2010-2294

Top Herbal Products (Jan 2008): http://www.medscape.com/viewprogram/8494_pnt

Health Canada: Natural Health Products Directorate[Jan/04]: 1-888-774-5555; 86 monographs;>3000NPN's
http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/nhpd-dpsn/index_e.html

TOP

RxFiles OTC Products Chart - Additional references:

8. Black RA, Hill DA. Over-the-counter medications in **pregnancy**. Am Fam Physician. 2003 Jun 15;67(12):2517-24.
9. Demoly P, Piette V, Daures JP. Treatment of allergic rhinitis during **pregnancy**. Drugs. 2003;63(17):1813-20.
10. Blaiss MS; US FDA; ACAAI-ACOG(American College of Allergy, Asthma, & Immunology and American College of Obstetricians & Gynecologists.). Management of rhinitis and asthma in **pregnancy**. Ann Allergy Asthma Immunol. 2003 Jun;90(6 Suppl 3):16-22.
11. Richter JE. Gastroesophageal reflux disease during **pregnancy**. Gastroenterol Clin North Am. 2003 Mar;32(1):235-61.
12. Schroeder K, Fahey T. Systematic review of randomised controlled trials of over the counter **cough** medicines for acute cough in adults. BMJ. 2002 Feb 9;324(7333):329-31. (Smith J, Owen E, Earis J, Woodcock A. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006 Apr;117(4):831-5. Epub 2006 Feb 7.)
13. Morice AH, Kastelik JA. Cough. 1: Chronic **cough** in adults. Thorax. 2003 Oct;58(10):901-7.
    Irwin RS, et al. American College of Chest Physicians (ACCP). Diagnosis and management of **cough executive summary: ACCP** evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):1S-23S. http://www.chestjournal.org/cgi/content/full/129/1_suppl/1S
    Pharmacist's Letter Oct/006. Pharmacologic Treatment of Cough: Evidence-based guidelines.
    Yoder KE, et al. Child assessment of dextromethorphan, diphenhydramine, and placebo for nocturnal cough due to upper respiratory infection. Clin Pediatr (Phila). 2006 Sep;45(7):633-40.
    Morice AH, Fontana GA, Belvisi MG, et al. European Respiratory Society (ERS). ERS guidelines on the assessment of cough. Eur Respir J. 2007 Jun;29(6):1256-76.
    Morice AH, McGarvey L, Pavord I; British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. Thorax. 2006 Sep;61 Suppl 1:i1-24.
    Woodhead M, Blasi F, Ewig S, et al. European Respiratory Society; European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J. 2005 Dec;26(6):1138-80.
    Tan T, Little P, Stokes T; Guideline Development Group. Antibiotic prescribing for self limiting respiratory tract infections in primary care: summary of NICE guidance. BMJ. 2008 Jul 23;337:a437. doi: 10.1136/bmj.a437.
14. Smucny JJ, Flynn CA, Becker LA, Glazier RH. Are beta2-agonists effective treatment for acute bronchitis or acute cough in patients without underlying pulmonary disease? A systematic review. J Fam Pract. 2001 Nov;50(11):945-51.
15. Smucny J, Flynn C, Becker L, Glazier R. Beta2-agonists for acute bronchitis. Cochrane Database Syst Rev. 2004;(1):CD001726. (Tomerak A, Vyas H, Lakenpaul M, et al. Inhaled beta2-agonists for treating non-specific chronic cough in children. Cochrane Database Syst Rev. **2005** Jul 20;(3):CD005373.) Smucny J, Becker L, Glazier R. Beta2-agonists for acute bronchitis. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD001726.
16. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy. 2000 Feb;55(2):116-34.
17. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma (**ARIA**). J Allergy Clin Immunol. **2001** Nov;108(5 Suppl):S147-334. http://www.whiar.com
18. Lee EE, Maibach HI. Treatment of urticaria. An evidence-based evaluation of antihistamines. Am J Clin Dermatol. 2001;2(1):27-32.
19. Casale TB, Blaiss MS, et al. Antihistamine Impairment Roundtable. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. J Allergy Clin Immunol. 2003 May;111(5):S835-42.
20. Berger WE. Overview of allergic rhinitis. Ann Allergy Asthma Immunol. 2003 Jun;90(6 Suppl 3):7-12.
21. Bender BG, Berning S, Dudden R, Milgrom H, Tran ZV. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. J Allergy Clin Immunol. 2003:111:770-776.
    Medscape CME Sept 23,2003 by Dr. Bender & Milgrom availablet at http://www.medscape.com/viewprogram/2673_pnt accessed Nov14,2003.
22. Murdoch D, Goa K, Keam S. Desloratadine: An Update of its Efficacy in the Management of Allergic Disorders. Drugs. 2003;63(19):2051-2077.
23. Simons FE, J Semus M, Goritz SS, Simons KJ. H1-antihistaminic activity of cetirizine and fexofenadine in allergic children. Pediatr Allergy Immunol. 2003 Jun;14(3):207-11.
24. Stevenson J, et al. ETAC Study Gp. Long-term evaluation of the impact of the h1-receptor antagonist **cetirizine** on behavioral, cognitive & psychomotor development of very young children **1-2yr** with **atopic dermatitis**. Pediatr Res. 2002 Aug;52(2):251-7.
25 Schenkel E, Corren J, Murray JJ. Efficacy of once-daily desloratadine/pseudoephedrine for relief of nasal congestion. Allergy Asthma Proc. 2002 Sep-Oct;23(5):325-30. (Raphael GD, Angello JT, Wu MM, Druce HM. Efficacy of **diphenhydramine** vs desloratadine & placebo in patients with moderate-to-severe seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2006 Apr;96(4):606-14.)
26. Horak F, Stubner P, Zieglmayer R, et al. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. Int Arch Allergy Immunol. 2001 May;125(1):73-9.
27. Van Adelsberg J, Philip G, Pedinoff AJ, Meltzer EO, et al.. For the Montelukast Fall Rhinitis Study Group. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. Allergy. 2003 Dec;58(12):1268-76.
28. Montelukast (singulair) for allergic rhinitis. Med Lett Drugs Ther. 2003 Mar 17;45(1152):21-2.
29. Nathan RA. Pharmacotherapy for allergic rhinitis: a critical review of leukotriene receptor antagonists compared with other treatments. Ann Allergy Asthma Immunol. 2003 Feb;90(2):182-90.
30. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. Drug Saf. 2003;26(12):863-93.
31. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2002 Nov;89(5):479-84.
32. Trangsrud AJ, Whitaker AL, Small RE. Intranasal corticosteroids for allergic rhinitis. Pharmacotherapy. 2002 Nov;22(11):1458-67.
33. Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis: superior relief? Drugs. 2001;61(11):1563-79.
34. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ. 1998 Dec 12;317(7173):1624-9.
    Nasser M, Fedorowicz Z, Aljufairi H, et al. **Antihistamines used in addition to topical nasal steroids** for intermittent and persistent allergic rhinitis in children. Cochrane Database Syst Rev. 2010 Jul 7;7:CD006989. In view of the lack of evidence for the benefit or lack of benefit of antihistamine add-on therapy with topical nasal steroids for children with intermittent or persistent allergic rhinitis, it is important that clinicians are mindful of the adverse effects of antihistamines and the additional costs that may be incurred.
35. Moayyedi P, Soo S, Deeks J, Forman D, Harris A, Innes M, Delaney B. Systematic review: Antacids, H2-receptor antagonists, prokinetics, bismuth and sucralfate therapy for non-ulcer **dyspepsia**. Aliment Pharmacol Ther. 2003 May 15;17(10):1215-27.
36. Delaney BC, Moayyedi P, Forman D. Initial management strategies for **dyspepsia**. Cochrane Database Syst Rev. 2003;(2):CD001961.
37. Lembo A, Camilleri M. Chronic **constipation**. N Engl J Med. 2003 Oct 2;349(14):1360-8.
38. Webster GF. **Acne** vulgaris. BMJ. 2002 Aug 31;325(7362):475-9.
39. Leyden JJ. A review of the use of combination therapies for the treatment of **acne** vulgaris. J Am Acad Dermatol. 2003 Sep;49(3 Suppl):S200-10.
40. Berson DS, Chalker DK, Harper JC, Leyden JJ, Shalita AR, Webster GF. Current concepts in the treatment of **acne**: report from a clinical roundtable. Cutis. 2003 Jul;72(1 Suppl):5-13.
41. Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole **anti-fungal** agents for the treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. BJOG. 2002 Jan;109(1):85-95.
42. Hart R, Bell-Syer SE, Crawford F, Torgerson DJ, Young P, Russell I. Systematic review of topical treatments for **fungal** infections of the skin and nails of the feet. BMJ. 1999 Jul 10;319(7202):79-82.
43. Gupta AK, Chow M, Daniel CR, Aly R. Treatments of **tinea pedis**. Dermatol Clin. 2003 Jul;21(3):431-62.
44. Gupta AK, Chaudhry M, Elewski B. **Tinea corporis**, tinea **cruris**, tinea **nigra**, and **piedra**. Dermatol Clin. 2003 Jul;21(3):395-400
45. Leung DY, Bieber T. **Atopic dermatitis**. Lancet. 2003 Jan 11;361(9352):151-60.
46. Correale CE, Walker C, Murphy L, Craig TJ. **Atopic dermatitis**: a review of diagnosis and treatment. Am Fam Physician. 1999 Sep 15;60(4):1191-8, 1209-10.
47. Gibbs S, Harvey I, Sterling J, Stark R. Local treatments for cutaneous **warts**: systematic review. BMJ. 2002 Aug 31;325(7362):461.
48. Stulberg DL, Hutchinson AG. Molluscum contagiosum and **warts**. Am Fam Physician. 2003 Mar 15;67(6):1233-40.
49. Bedinghaus JM, Niedfeldt MW. Over-the-counter **foot** remedies. Am Fam Physician. 2001 Sep 1;64(5):791-6.
    Gibbs S, Harvey I. T opical treatments for cutaneous **warts**. Cochrane Database Syst Rev. 2006;(3): CD001781.
    Bruggink, Sjoerd C., Gussekloo, Jacobijn, Berger, Marjolein Y., et al. **Cryotherapy** with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: a randomized controlled trial CMAJ 2010 0: cmaj.092194.
    Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. Br J Dermatol 2011; online 11 January.
    Cockayne S, Hewitt C, Hicks K, Jayakody S, Kang'ombe AR, Stamuli E, et al. **Cryotherapy versus salicylic acid** for the treatment of plantar warts (verrucae): a randomised controlled trial. BMJ 2011;342:d3271.
    Mulhem E, Pinelis S. Treatment of **nongenital cutaneous warts**. Am Fam Physician. 2011 Aug 1;84(3):288-93.
    Cockayne S, Curran M, Denby G, et al. EVerT: **cryotherapy versus salicylic acid** for the treatment of verrucae - a randomised controlled trial. Health Technol Assess. 2011 Sep;15(32):1-170.
50. Nash B. Treating **head lice**. BMJ. 2003 Jun 7;326(7401):1256-7.(Leung AK, Fong JH, Pinto-Rojas A. Pediculosis capitis. J Pediatr Health Care. 2005 Nov-Dec;19(6):369-73.)
51. Frankowski BL, Weiner LB; Committee on School Health the Committee on Infectious Diseases. American Academy of Pediatrics. **Head lice**. Pediatrics. 2002 Sep;110(3):638-43.
    Frankowski, B., & Bocchini, J. (**2010**). **Head Lice** *PEDIATRICS, 126* (2), 392-403 DOI: 10.1542/peds.2010-1308
52. Villar J, Merialdi M, et al. Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials. J Nutr. 2003 May;133(5 Suppl 2):1606S-1625S.(Fawzi WW, Msamanga GI, et al. Vitamins and perinatal outcomes among HIV-negative women in Tanzania. N Engl J Med. 2007 Apr 5;356(14):1423-31. Multivitamin supplementation reduced the incidence of low birth weight and small-for-gestational-age births but had no significant effects on prematurity or fetal death. Multivitamins should be considered for all pregnant women in developing countries.)
    Shah PS, Ohlsson A. Effects of **prenatal multimicronutrient supplementation** on pregnancy outcomes: a meta-analysis. CMAJ. 2009 Jun 9;180(12):E99-E108. Prenatal multimicronutrient supplementation was associated with a significantly reduced risk of low birth weight & with improved birth weight when compared with iron-folic acid supplementation. There was no significant effect of multimicronutrient supplementation on the risk of preterm birth or small-for-gestational-age infants.
    Catov JM, Bodnar LM, Olsen J, Olsen S, Nohr EA. **Periconceptional multivitamin** use and risk of preterm or small-for-gestational-age births in the Danish National Birth Cohort. Am J Clin Nutr. 2011 Sep;94(3):906-12.
    Persson LÅ, Arifeen S, Ekstro¨m E-C, et al. **MINIMat** Study Team. Effects of **prenatal micronutrient and early food supplementation** on maternal hemoglobin, birth weight, and infant mortality among children in Bangladesh: the MINIMat randomized trial. JAMA. 2012;307(19):2050- 2059.
53. Morris CD, Carson S. Routine **vitamin** supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2003 Jul 1;139(1):56-70.
54. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant **vitamins** for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet. 2003 Jun 14;361(9374):2017-23.
55. http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adrv13n1_e.pdf
56. Cass E. et al. Hazards of **phenylephrine** topical medication in persons taking propranolol CMAJ 1979 120: 1261-1262.
57. Veldhuyzen van Zanten SJ, Flook N, et al. An evidence-based approach to the management of uninvestigated **dyspepsia** in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ. 2000 Jun 13;162(12 Suppl):S3-23.

TOP

58. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on **irritable bowel syndrome**. Gastroenterology. 2002 Dec;123(6):2108-31.
59. Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the **irritable bowel syndrome**. Arch Intern Med. 2003 Feb 10;163(3):265-74.
60. Jones J, Boorman J, Cann P, Forbes A, Gomborone J, et al. British Society of Gastroenterology guidelines for the management of the **irritable bowel syndrome**. Gut. 2000 Nov;47 Suppl 2:ii1-19.
61. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of **irritable bowel syndrome** in family practice. IBS Consensus Conference Participants. CMAJ. 1999 Jul 27;161(2):154-60.
62. Rucker D, Allan JA, Fick GH, Hanley DA. **Vitamin D** insufficiency in a population of healthy western Canadians. CMAJ. 2002 Jun 11;166(12):1517-24.
63. Scavone JM, et al. Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. J Clin Pharmacol. 1998 Jul;38(7):603-9. (Merenstein D, et al. The Trial of Infant Response to **Diphenhydramine**: The TIRED Study--A Randomized, Controlled, Patient-Oriented Trial. Arch Pediatr Adolesc Med. 2006 Jul;160(7):707-712.)
64. Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, Morgenstern LB, Wilterdink JL, Horwitz RI. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med. 2000 Dec 21;343(25):1826-32.
65. Jones MP, Talley NJ, Nuyts G, Dubois D. Lack of objective evidence of efficacy of laxatives in chronic constipation. Dig Dis Sci. 2002 Oct;47(10):2222-30.
66. Focht DR 3rd, Spicer C, Fairchok MP. The efficacy of duct tape vs cryotherapy in the treatment of verruca vulgaris (the common wart). Arch Pediatr Adolesc Med. 2002 Oct;156(10):971-4. (de Haen M, et al. Efficacy of duct tape vs placebo in the treatment of verruca vulgaris (warts) in primary school children. Arch Pediatr Adolesc Med. 2006 Nov;160(11):1121-5.) (Wenner R, Askari SK, Cham PM, Kedrowski DA, Liu A, Warshaw EM. Duct tape for the treatment of common warts in adults: a double-blind randomized controlled trial. Arch Dermatol. 2007 Mar;143(3):309-13. (n=90) Patients were instructed to wear the pads for 7 consecutive days and leave the pad off on the seventh evening. This process was repeated for 2 months or until the wart resolved, whichever occurred first. Of patients with complete resolution, 6 (75%) in the treatment group and 3 (33%) in the control group had recurrence of the target wart by the sixth month. CONCLUSION: We found no statistically significant difference between duct tape and moleskin for the treatment of warts in an adult population. (InfoPOEMs: Occlusion with transparent duct tape is no more or less effective than occlusion with moleskin. The low success rate overall argues against any effect for occlusion. One interesting suggestion is that since hypnosis has been shown to be an effective treatment, perhaps that is the mechanism by which duct tape occlusion works, and perhaps adults are less suggestible than children. While this may not be the final word on this topic, it is discouraging news for the good folks at the American Duct Tape Council.))
Bavinck JNB, Eekhof JAH, Bruggink SC. Treatments for common and plantar warts. BMJ 2011;342:d3119.
67. Sano M, Ernesto C, Thomas RG, Klauber MR, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med. 1997 Apr 24;336(17):1216-22.
68. Tabet N, Birks J, Grimley Evans J. Vitamin E for Alzheimer's disease. Cochrane Database Syst Rev. 2000;(4):CD002854.
69. Brown BG, Zhao XQ, Chait A, Fisher LD, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001 Nov 29;345(22):1583-92.
70. Patient information & other useful links to the American Podiatric Medical Association http://www.apma.org/topics/Warts.htm
71. Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). (Cochrane Review). In: The Cochrane Library, Issue 4, 2003.
72. De Sutter AIM, Lemiengre M, Campbell H, Mackinnon HF Antihistamines for the common cold (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.
73. Taverner D, Bickford L, Draper M Nasal decongestants for the common cold (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd. (Infant Deaths Associated with Cough and Cold Medications --- Two States, 2005 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm)
Pharmacist's Letter- Efficacy of oral phenylephrine. Feb,2008
Vaidyanathan S, Williamson P, Clearie K, et al. **Fluticasone Reverses Oxymetazoline** Induced Tachyphylaxis of Response and Rebound Congestion. Am J Respir Crit Care Med. 2010 Mar 4.
Umoren R, Odey F, Meremikwu MM. **Steam inhalation or humidified oxygen** for acute bronchiolitis in children up to three years of age. Cochrane Database Syst Rev. 2011 Jan 19;1:CD006435. Steam inhalation (or cool mist therapy) is commonly used to treat acute bronchiolitis in resource-constrained settings. One study was eligible for inclusion and found that nebulised salbutamol was an effective intervention for young children with bronchiolitis but mist in a tent did not lead to a significant decrease in RDS score. Since only one study was analysed it would be misleading to conclude that mist therapy is ineffective in children with bronchiolitis. We conclude that there is insufficient evidence to inform practice regarding using steam inhalation or mist therapy for acute bronchiolitis in kids up to three year old.
74. Schroeder K, Fahey T Over-the-counter medications for acute cough in children and adults in ambulatory settings (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.
Cals JW, Francis NA. Acute cough in adults. BMJ. 2010 Feb 12;340:c574. doi:10.1136/bmj.c574.
75. Marshall I Zinc for the common cold (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.
Prasad AS, Beck FW, Bao B, Snell D, Fitzgerald JT. Duration and severity of symptoms and levels of plasma interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and adhesion molecules in patients with common cold treated with zinc acetate. J Infect Dis. 2008 Mar 15;197(6):795-802. Administration of zinc lozenges was associated with reduced duration and severity of cold symptoms. We related the improvement in cold symptoms to the antioxidant and anti-inflammatory properties of zinc.
Singh M, Das RR. **Zinc for the common cold**. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD001364. DOI: 10.1002/14651858.CD001364.pub3. Zinc administered within 24 hours of onset of symptoms reduces the duration and severity of the common cold in healthy people. When supplemented for at least five months, it reduces cold incidence, school absenteeism and prescription of antibiotics in children. There is potential for zinc lozenges to produce side effects. In view of this and the differences in study populations, dosages, formulations and duration of treatment, it is difficult to make firm recommendations about the dose, formulation and duration that should be used.
Science M, Johnstone J, Roth DE, et al. Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. CMAJ. 2012 May 7.
76. Gunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of over-the-counter cough and cold medications. Pediatrics. 2001 Sep;108(3):E52 (Hatton RC, Winterstein AG, McKelvey RP, Shuster J, Hendeles L. Efficacy and safety of oral phenylephrine: systematic review and meta-analysis. Ann Pharmacother. 2007 Mar;41(3):381-90. Epub 2007 Jan 30. There is insufficient evidence that oral phenylephrine is effective for nonprescription use as a decongestant. The Food and Drug Administration should require additional studies to show the safety and efficacy of phenylephrine.) Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Cough and cold medication use by US children, 1999-2006: results from the slone survey. Pediatrics. 2008 Aug;122(2):e323-9. Approximately 1 in 10 US children uses a cough and cold medication in a given week. The especially high prevalence of use among children of young age is noteworthy, given concerns about potential adverse effects and the lack of data on the efficacy of cough and cold medications in this age group. Rimsza ME, Newberry S. Unexpected infant deaths associated with use of cough and cold medications. Pediatrics. 2008 Aug;122(2):e318-22. Review of these infants' deaths raises concern about the role of the over-the-counter cough and cold medications in these deaths. These findings support the recommendation that such medications not be given to infants.
Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Pseudoephedrine use among US children, 1999-2006: results from the Slone survey. Pediatrics. 2008 Dec;122(6):1299-304. Pseudoephedrine exposure, mostly in the form of multiple-ingredient products, is common among US children, especially children who are younger than 2 years, who are at the highest risk for toxicity and for whom safe dosing recommendations are lacking. Concerning patterns of use include taking >1 pseudoephedrine-containing product concurrently and using pseudoephedrine for extended periods. Pediatric pseudoephedrine use seems to be declining since the institution of the 2005 Combat Methamphetamine Epidemic Act.
Dart RC, Paul IM, et al. Pediatric fatalities associated with over the counter (nonprescription) cough and cold medications. Ann Emerg Med. 2009 Apr;53(4):411-7. Epub 2008 Dec 19.
Lokker Nicole, Sanders Lee, Perrin Eliana M. et al. Parental Misinterpretations of Over-the-Counter Pediatric Cough and Cold Medication Labels. Pediatrics 2009 123: 1464-1471.
Shefrin AE, Goldman RD. Use of over-the-counter cough and cold medications in children. Can Fam Physician. 2009 Nov;55(11):1081-3.
Kuehn Bridget M. Medical News & Perspectives: Withdrawal of Infant Cold Medicines Decreases ED Visits by Half, CDC Finds. *JAMA*. 2010;304(24):2686.doi:10.1001/jama.2010.1831
Goldman RD; Canadian Paediatric Society, Drug Therapy and Hazardous Substances Committee. Treating cough and cold: guidance for caregivers of children and youth. Paediatr Child Health 2011;16:564-6. www.cps.ca/English/statements/DT/TreatingCough.htm (accessed December 12, 2011).
77. Use of codeine- and dextromethorphan-containing cough remedies in children. American Academy of Pediatrics. Committee on Drugs. Pediatrics. 1997 Jun;99(6):918-20.
78. Albanes D, Heinonen OP, Taylor PR, et al. Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance (ATBC trial).
J Natl Cancer Inst. 1996 Nov 6; 88: 1560-70.
79. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the cache county study. Arch Neurol. 2004 Jan; 61(1): 82-8.
Chan JM, Oh WK, Xie W, Regan MM, Stampfer MJ, King IB, Abe M, Kantoff PW. Plasma Selenium, Manganese Superoxide Dismutase, and Intermediate- or High-Risk Prostate Cancer. J Clin Oncol. 2009 Jun 15. [Epub ahead of print]
80. Michaelsson K, Lithell H, et al. Serum retinol levels and the risk of fracture. N Engl J Med. 2003 Jan 23; 348(4): 287-94. (Rothman KJ, Moore LL, Singer MR, Nguyen US, et al. Teratogenicity of high vitamin A intake. N Engl J Med. 1995 Nov 23;333(21):1369-73.)
81 Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. JAMA. 2002 Jun 19; 287(23): 3116-26. Review. Erratum in: JAMA 2002 Oct 9;288(14):1720.
82. Wagstaff AJ, Frampton JE, Croom KF. Tegaserod: a review of its use in the management of irritable bowel syndrome with constipation in women. Drugs. 2003;63(11):1101-20.
83. European Nicotinamide Diabetes Intervention Trial Group, European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. Lancet 2004; 363: 925-31.
84. Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. Br J Dermatol. 2002 Mar;146(3):423-31.
85. Hendry, J . Ocular Disorders Associated with Increased Risk of Mortality, But Zinc Therapy Appears to Reduce Mortality Arch Ophthalmol 2004;122:716-726.
86. Holmes R., et al. Evaluation of the Patient with Chronic Cough. Am Fam Physician. 2004 May 1;69(9):2159-66.
Bailey E, Morris P, Kruske S, Chang A. **Clinical pathways** for chronic cough in **children**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006595. Without further available evidence, recommendations for the use of clinical pathways for the treatment of chronic cough in children cannot be made. Until further evidence is available, the decision for further investigation and treatment for the child presenting with chronic cough should be made on an individual basis (i.e. dependent on symptoms and signs) with consideration for existing data from other Cochrane reviews on specific treatments for cough. Trials are required to provide evidence on the effectiveness of clinical pathways for the treatment of chronic cough in children.
Chang A, Peake J, McElrea M. **Anti-histamines** for prolonged non-specific cough in **children**. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005604. This review has significant limitations. However, our finding of uncertain efficacy of anti-histamines for chronic cough are similar to that for acute cough in children. In contrast to recommendations in adults with chronic cough, anti-histamines cannot be recommended as empirical therapy for children with chronic cough. If anti-histamines were to be trialled in these children, current data suggest a clinical response (time to response) occurs within two weeks of therapy. However the use of anti-histamines in children with non-specific cough has to be balanced against the well known risk of adverse events especially in very young children.

TOP

Barraclough K. Chronic cough in adults. BMJ. 2009 Apr 24;338:b1218. doi: 10.1136/bmj.b1218.
87. Feldman S., et al. Diagnosis and Treatment of Acne. Am Fam Physician. 2004 May 1;69(9):2123-30.
88. Haider A, Shaw JC. Treatment of acne vulgaris. JAMA. 2004 Aug 11;292(6):726-35.
89. James, W.D., Acne. N Engl J Med 2005;352:1463-72. (Ozolins M, Eady EA, et al. Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. Health Technol Assess. 2005 Jan;9(1):iii-212.)
90. Eidelman RS, Hollar D, Hebert PR, Lamas GA, Hennekens CH. Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. Arch Intern Med. 2004 Jul 26;164(14):1552-6.
91. Fawzi WW, Msamanga GI, Spiegelman D, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. N Engl J Med. 2004 Jul 1;351(1):23-32. (McGrath N, Bellinger D, Robins J, Msamanga GI, Tronick E, Fawzi WW. Effect of maternal multivitamin supplementation on the mental and psychomotor development of children who are born to HIV-1-infected mothers in Tanzania. Pediatrics. 2006 Feb;117(2):e216-25.)
Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006088. There is insufficient evidence to decide whether OTC medications for cough associated with acute pneumonia are beneficial. Mucolytics may be, but there is insufficient evidence to recommend them as an adjunctive treatment of acute pneumonia. This leaves only theoretical recommendations that OTC medications containing codeine and antihistamines should not be used in young children.
92. Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, Dilworth DA, Berlin CM Jr. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics. 2004 Jul;114(1):e85-90.
93. Sobel JD., Wiesenfeld HC., et al. Maintenance Fluconazole Therapy for Recurrent Vulvovaginal Candidiasis. N Engl J Med. 2004 Aug 26;351(9):876-83.
94. Pirotta M. et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. BMJ. 2004 Aug 27 online p 1-5.
95. Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women. JAMA. 2002 Jan 2;287(1):47-54.
96. Goodman GE, Thornquist MD, Balmes J, Cullen MR, Meyskens FL Jr, Omenn GS, Valanis B, Williams JH Jr. The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements (CARET). J Natl Cancer Inst. 2004 Dec 1;96(23):1743-50.
Benn CS, Diness BR, Roth A, Nante E, Fisker AB, Lisse IM, Yazdanbakhsh M, Whittle H, Rodrigues A, Aaby P. Effect of 50 000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial. BMJ. 2008 Jun 16. [Epub ahead of print] Vitamin A supplementation given with BCG vaccine at birth had no significant benefit in this African setting. Although little doubt exists that vitamin A supplementation reduces mortality in older children, a global recommendation of supplementation for all newborn infants may not contribute to better survival.
Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. BMJ. 2009 Mar 27;338:b919. doi: 10.1136/bmj.b919.
Benn CS, Fisker AB, Napirna BM, et al.. Vitamin A supplementation and BCG vaccination at birth in low birthweight neonates: two by two factorial randomized controlled trial. BMJ. 2010 Mar 9.
Fernandes TF, Figueiroa JN, Grande de Arruda IK, Diniz AD. Effect on Infant Illness of Maternal Supplementation With **400 000 IU Vs 200 000 IU of Vitamin A**. Pediatrics. 2012 Mar 12.
Mactier H, McCulloch DL, Hamilton R, et al. **Vitamin A** Supplementation Improves Retinal Function in Infants at Risk of Retinopathy of Prematurity. J Pediatr. 2012 Jan 25.
97. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality. Ann Intern Med. 2004 Nov 10.
98. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. Lancet. 2004 Oct 2;364(9441):1219-28. (Bjelakovic G, et al. Meta-analysis: antioxidant supplements for primary and secondary prevention of colorectal adenoma. Aliment Pharmacol Ther. 2006 Jul 15;24(2):281-91. (InfoPOEMs: Antioxidant supplementation for up to 6 years does not decrease the risk of colorectal adenomatous polyps and thus, by extension, does not reduce the risk of colorectal cancer. Vitamin E may increase the risk of colorectal adenoma. (LOE = 1a-)). (Wright ME, et al. Higher baseline serum concentrations of vitamin E are associated with lower total and cause-specific mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. (ATBC Study) Am J Clin Nutr. 2006 Nov;84(5):1200-7.) [Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention: Systematic Review and Meta-analysis. JAMA. 2007 Feb 28;297(8):842-57. Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study. (InfoPOEMs: Current evidence suggests that regular supplementation with the antioxidants beta carotene, vitamin A, and vitamin E increases mortality risk in adults. This report found no evidence of benefit or harm from supplementation with vitamin C and selenium. (LOE = 1a-))]
Slatore CG, Littman AJ, Au DH, Satia JA, White E. Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer. Am J Respir Crit Care Med. 2008 Mar 1;177(5):524-30. Epub 2007 Nov 7. Supplemental multivitamins, vitamin C, vitamin E, and folate were not associated with a decreased risk of lung cancer. Supplemental vitamin E was associated with a small increased risk. Patients should be counseled against using these supplements to prevent lung cancer.
Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD007176. We found no evidence to support antioxidant supplements for primary or secondary prevention. **Vitamin A, beta-carotene, and vitamin E may increase mortality**. Future randomised trials could evaluate the potential effects of vitamin C and selenium for primary and secondary prevention.
Schürks Markus, Glynn Robert J, Rist Pamela M, et al. Effects of **vitamin E on stroke subtypes**: meta-analysis of randomised controlled trials. BMJ 341:doi:10.1136/bmj.c5702 (Published 4 November 2010).
Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (**SELECT**). JAMA. 2011 Oct 12;306(14):1549-56.
99. Simons FE. Advances in H1-**antihistamines**. N Engl J Med. 2004 Nov 18;351(21):2203-17.(Berger WE, et al. Efficacy of desloratadine, 5 mg, compared with fexofenadine, 180 mg, in patients with symptomatic seasonal allergic rhinitis. Allergy Asthma Proc. 2006 May-Jun;27(3):214-23. & Merenstein D, et al. The trial of infant response to diphenhydramine: the TIRED study--a randomized, controlled, patient-oriented trial. Arch Pediatr Adolesc Med. 2006 Jul;160(7):707-12. (InfoPOEMs: Diphenhydramine was no more effective (and was technically less effective) than placebo in reducing parental attention in infants with frequent nocturnal awakenings. (LOE = 2b)) & Raphael GD, et al. Efficacy of diphenhydramine 50mg tid vs desloratadine 5mg od and placebo in patients with moderate-to-severe seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2006 Apr;96(4):606-14. Diphenhydramine, 50 mg, given for 1 week provided statistically significant and clinically superior improvements in symptoms compared with 5 mg of desloratadine in patients with moderate-to-severe SAR. Somnolence occurred more frequently with diphenhydramine (22.1%) compared with desloratadine (4.5%) and placebo (3.4%).)
So M, Bozzo P, Inoue M, Einarson A. Safety of **antihistamines during pregnancy** and lactation. Can Fam Physician. 2010 May;56(5):427-9.
100. The Medical Letter, Treatment Guidelines, Dec, **2009** . **Antifungal Drugs**.
Nurbhai M, Grimshaw J, Watson M, Bond C, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). Cochrane Database Syst Rev. 2007 Oct 17;(4):CD002845. No statistically significant differences were observed in clinical cure rates of anti-fungals administered by the oral and intra-vaginal routes for the treatment of uncomplicated vaginal candidiasis.
101. Muller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. Am J Gastroenterol. 2005 Jan;100(1):232-42.
102. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, Ross C, Arnold A, Sleight P, Probstfield J, Dagenais GR; HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA. 2005 Mar 16;293(11):1338-47. The HOPE and **HOPE-TOO** Trial Investigators*. Effects of Long-term **Vitamin E** Supplementation on Cardiovascular Events and Cancer
A Randomized Controlled Trial. JAMA. 2005;293:1338-1347. (InfoPOEMs: Vitamin E supplementation does not reduce the risk of cancer or major cardiovascular events in patients at high risk for vascular disease, but may increase the risk of heart failure. (LOE = 1b)) (Lonn E, Yusuf S, Arnold MJ, et al.; Heart Outcomes Prevention Evaluation **(HOPE) 2** Investigators. **Homocysteine** lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006 Apr 13;354(15):1567-77. Epub 2006 Mar 12. (InfoPOEMs: Supplementation with folic acid and B vitamins is ineffective for adults 55 years and older with known cardiovascular disease (CVD) or diabetes. A second report in the same issue found that similar supplementation in patients with a recent acute myocardial infarction was not helpful and may actually increase the risk of a bad cardiovascular outcome (relative risk = 1.22; 95% CI, 1.0 - 1.5). (LOE = 1b)))
103. El-Kadiki A, Sutton AJ. Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials. BMJ. 2005 Mar 31; [Epub ahead of print] (Hercberg S, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med. 2004 Nov 22;164(21):2335-42.)
Neuhouser ML, Wassertheil-Smoller S, Thomson C, Aragaki A, Anderson GL, Manson JE, Patterson RE, Rohan TE, van Horn L, Shikany JM, Thomas A, Lacroix A, Prentice RL. Multivitamin Use and Risk of Cancer and Cardiovascular Disease in the Women's Health Initiative Cohorts (WHI). Arch Intern Med. 2009 Feb 9;169(3):294-304. After a median follow-up of 8.0 and 7.9 years in the clinical trial and observational study cohorts, respectively, the Women's Health Initiative study provided convincing evidence that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women.
Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. Arch Intern Med. 2009 Feb 23;169(4):335-41. These randomized trial data from a large cohort of women at high risk of cardiovascular disease indicate that daily supplementation with folic acid, pyridoxine, and cyanocobalamin may reduce the risk of **AMD**.
Larsson SC, Orsini N, Wolk A. **Vitamin B6** and Risk of Colorectal Cancer: A Meta-analysis of Prospective Studies. JAMA. 2010 Mar 17;303(11):1077-83.
Kirkwood BR, Hurt L, Amenga-Etego S et al; for the ObaapaVitA Trial Team. Effect of **vitamin A** supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial. Lancet. 2010 Apr 30.
Checkley, William, West, Keith P., Jr., Wise, Robert A., et al. Maternal **Vitamin A** Supplementation and **Lung Function** in Offspring. N Engl J Med 2010 362: 1784-1794.
House AA.; Eliasziw Misha; Cattran Daniel C.; et al. Effect of **B-Vitamin** Therapy on Progression of Diabetic Nephropathy: A Randomized Controlled Trial. JAMA. 2010;303(16):1603-1609.
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (**SEARCH**) Collaborative Group. Effects of **Homocysteine-Lowering** With Folic Acid Plus Vitamin B12 vs Placebo on Mortality and Major Morbidity in Myocardial Infarction Survivors: A Randomized Trial. JAMA. 2010;303(24):2486-2494.
McCance DR, Holmes VA, Maresh MJ, et al.; for the Diabetes and **Pre-eclampsia** Intervention Trial (**DAPIT**) Study Group. Vitamins C and E for prevention of pre-eclampsia in women with type 1 diabetes (DAPIT): a randomised placebo-controlled trial. Lancet. 2010 Jun 25.
Roberts JM, Myatt L, et al. Eunice Kennedy Shriver National Institute of Child Health & Human Development Maternal-Fetal Medicine Units Network, Vitamins C & E to Prevent Complications of **Pregnancy-Associated Hypertension**. N Engl J Med 2010 362: 1282-91.
van den Broek N, Dou L, Othman M, et al. **Vitamin A supplementation during pregnancy** for maternal and newborn outcomes. Cochrane Database Syst Rev. 2010 Nov 10;11:CD008666. The pooled results of two large trials in Nepal and Ghana (with almost 95,000 women) do not currently suggest a role for antenatal vitamin A supplementation to reduce maternal or perinatal mortality. However the populations studied were probably different with regard to baseline vitamin A status and there were problems with follow-up of women. There is good evidence that antenatal vitamin A supplementation reduces maternal anaemia for women who live in areas where vitamin A deficiency is common or who are HIV-positive. In addition the available evidence suggests a reduction in maternal infection, but these data are not of a high

TOP

quality.
Imdad A, Herzer K, Mayo-Wilson E, Yakoob MY, Bhutta ZA. **Vitamin A supplementation** for preventing morbidity and mortality in children from 6 months to 5 years of age. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD008524. DOI: 10.1002/14651858.CD008524.pub2. VAS is effective in reducing all-cause mortality by about 24% compared to no treatment. In our opinion, given the evidence that VAS causes considerable reduction in child mortality, further placebo-controlled trials of VAS in children between 6 months and 5 years of age are not required.
Christian Parul, Murray-Kolb Laura E., Khatry Subarna K., et al. **Prenatal Micronutrient Supplementation (iron/folic)** and Intellectual and Motor Function in Early School-aged Children in Nepal. JAMA. 2010;304(24):2716-723.doi:10.1001/jama.2010.1861.
Mayo-Wilson E, Imdad A, Herzer K, Yakoob MY, Bhutta ZA. **Vitamin A supplements** for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis. BMJ 2011;343:d5094.
Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. Dietary supplements and mortality in older women: the Iowa Women's Health Study. Arch Intern Med. 2011;171(18):1625-1633.
Medical Letter. **Who should take vitamin supplements**. Dec 12/26, 2011.
Shankar P, Boylan M, Sriram K. Micronutrient deficiencies after bariatric surgery. Nutrition. 2010 Nov-Dec;26(11-12):1031-7.
Schmitz J, West KP Jr, Khatry SK, LeClerq SC, Karna SL, Katz J, et al. **Vitamin A** supplementation in preschool children and risk of **hearing loss** as adolescents and young adults in rural Nepal: randomised trial cohort follow-up study. BMJ 2012;344:d7962.
Andreeva VA, Touvier M, Kesse-Guyot E, et al. B Vitamin and/or ω-3 Fatty Acid Supplementation and Cancer: Ancillary Findings From the Supplementation With Folate, Vitamins B6 and B12, and/or Omega-3 Fatty Acids **(SU.FOL.OM3)** Randomized Trial. Arch Intern Med. 2012 Apr 9;172(7):540-7.
104. Andres E, Loukili NH, Noel E, et al. Vitamin B(12) (cobalamin) deficiency in elderly patients. CMAJ. 2004 Aug 3;171(3):251-259. (Butler CC, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Fam Pract. 2006 Jun;23(3):279-85. Epub 2006 Apr 3. The evidence derived from these limited studies suggests that 2000 microg doses of oral vitamin B(12) daily and 1000 microg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short-term haematological and neurological responses in vitamin B(12)-deficient patients. (InfoPOEMs: Based on 2 small studies, both oral and intramuscular (IM) vitamin B12 replacement increase serum B12 levels and improve neurological outcomes. Oral vitamin B12 replacement should be considered for patients with documented deficiency. It is available over the counter in 1000 mcg and 2000 mcg doses in the United States. (LOE = 2a)))
Castelli M. Cristina, Friedman Kristen, Sherry James, et al. Comparing the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-Label, Parallel-Group Study, Clinical Therapeutics, Volume 33, Issue 3, March 2011, Pages 358-371.e2
Malouf R, Areosa Sastre A. **Vitamin B12** for cognition. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004394. DOI: 10.1002/14651858.CD004394.
105. Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., et al., for the Alzheimer's Disease Cooperative Study Group Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment Published at www.nejm.org April 13, 2005
106. Viera AJ, Hoag S, Shaughnessy J. Management of irritable bowel syndrome. Am Fam Physician. 2002 Nov 15;66(10):1867-74. (Sharara AI, et al. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. Am J Gastroenterol. 2006 Feb;101(2):326-33. (InfoPOEMs: A 10-day course of rifaximin (Xifaxan) reduced symptoms of bloating and flatulence in patients with and without irritable bowel syndrome (IBS). Another study found a reduction in abdominal symptoms in patients with diverticulitis who were treated for 7 days each month for 1 year, suggesting that cyclic administration may be an option. Although larger, longer-term studies are needed before we widely adopt this approach for all our patients with IBS, it could be considered now for patients with especially troublesome symptoms. (LOE = 1b))) (Robinson A, et al. A randomised controlled trial of **self-help interventions** in patients with a primary care diagnosis of irritable bowel syndrome. Gut. 2006 May;55(5):643-8. Epub 2005 Aug 12.)
107. Villamor E, Saathoff E, Bosch RJ, Hertzmark E, Baylin A, Manji K, Msamanga G, Hunter DJ, Fawzi WW. Vitamin supplementation of HIV-infected women improves postnatal child growth. Am J Clin Nutr. 2005 Apr;81(4):880-8.
108. Kris-Etherton PM, Lichtenstein AH, Howard BV, et al. Nutrition Committee of the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Antioxidant vitamin supplements and cardiovascular disease. Circulation. 2004 Aug 3;110(5):637-41.
109. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of **calcium** and supplementation with **cholecalciferol (vitamin D3)** for prevention of fractures in primary care. BMJ. 2005 Apr 30;330(7498):1003.
110. Grant AM, Avenell A, et al.; Oral **vitamin D3 and calcium** for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of **Calcium Or vitamin D**, **RECORD**): a randomised placebo-controlled trial. Lancet. 2005 May;365(9471):1621-8.
111. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with **vitamin D** supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005 May 11;293(18):2257-64. (Oral vitamin D supplementation between 700 to 800 IU/d appears to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons. An oral vitamin D dose of 400 IU/d is not sufficient for fracture prevention.)(Wactawski-Wende J, Kotchen JM, Anderson GL, et al.; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006 Feb 16;354(7):684-96.)(Jackson RD, LaCroix AZ, Gass M, et al.; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006 Feb 16;354(7):669-83. Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones.) (Villar J, Abdel-Aleem Het al.; World Health Organization Calcium Supplementation for the Prevention of Preeclampsia Trial Group. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol. 2006 Mar;194(3):639-49. CONCLUSION: A 1.5-g calcium/day supplement did not prevent preeclampsia but did reduce its severity, maternal morbidity, and neonatal mortality, albeit these were secondary outcomes) & (Bischoff-Ferrari HA, et al. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Arch Intern Med. 2006 Feb 27;166(4):424-30.) Wactawski-Wende J, et al.; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006 Feb 16;354(7):684-96. Erratum in: N Engl J Med. 2006 Mar 9;354(10):1102. (InfoPOEMs: A modest dose of calcium and vitamin D does not alter the risk of colorectal cancer in healthy, normal-risk women. (LOE = 1b)) (Prince RL, et al. Effects of **calcium** supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Supplementation with calcium carbonate tablets supplying 1200 mg/d is ineffective as a public health intervention in preventing clinical fractures in the ambulatory elderly population owing to poor long-term compliance, but it is effective in those patients who are compliant. Arch Intern Med. 2006 Apr 24;166(8):869-75.)(Greer FR, Krebs NF; American Academy of **Pediatrics** Committee on Nutrition. Optimizing bone health and calcium intakes of infants, children, and adolescents. Pediatrics. 2006 Feb;117(2):578-85.) (Brown SJ. The Role of Vitamin D in Multiple Sclerosis (June). Ann Pharmacother. 2006 May 9; [Epub ahead of print]) (Medical Letter: Calcium & Vitamin D supplements July 31,2006) (Palmieri C, Macgregor T, Girgis S, Vigushin D. Serum 25 hydroxyvitamin D levels in early and advanced breast cancer. J Clin Pathol. 2006 Oct 17; [Epub ahead of print]) Winzenberg T, Shaw K, Fryer J, Jones G. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ. 2006 Sep 15; [Epub ahead of print] The small effect of calcium supplementation on bone mineral density in the upper limb is unlikely to reduce the risk of fracture, either in childhood or later life, to a degree of major public health importance. & Chan GM, et al. Effects of dietary calcium intervention on adolescent mothers and newborns: A randomized controlled trial. Obstet Gynecol. 2006 Sep;108(3 Pt 1):565-71. (Holick MF. **Vitamin D deficiency**. N Engl J Med. 2007 Jul 19;357(3):266-81.)
Autier P, Gandini S. Vitamin D Supplementation and **Total Mortality**: A Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2007 Sep 10;167(16):1730-7. Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates remains to be investigated. Population-based, placebo-controlled randomized trials with total mortality as the main end point should be organized for confirming these findings. (Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007 Aug 25;370(9588):657-66. Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older. For best therapeutic effect, we recommend minimum doses of 1200 mg of calcium, and 800 IU of vitamin D (for combined calcium plus vitamin D supplementation).) Freedman DM, Looker AC, Chang SC, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst. 2007 Nov 7;99(21):1594-602. Epub 2007 Oct 30.
Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007 Jun;85(6):1586-91.
Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab. 2002 Nov;87(11):4952-6.
Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. Arch Intern Med. 2008 Jan 14;168(1):103-8. Patients with a history of falling and vitamin D insufficiency living in sunny climates benefit from ergocalciferol supplementation in addition to calcium, which is associated with a 19% reduction in the relative risk of falling, mostly in winter.
Levine RJ, Hauth JC, Curet LB, et al. Trial of **calcium to prevent preeclampsia**. N Engl J Med 1997;337:69-76.
Zipitis CS, Akobeng AK. Vitamin D Supplementation in Early Childhood and Risk of Type 1 Diabetes: a Systematic Review and Meta-analysis. Arch Dis Child. 2008 Mar 13; [Epub ahead of print] Vitamin D supplementation in early childhood may offer protection against the development of type 1 **diabetes**.
Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. **Depression** is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008 May;65(5):508-12. The results of this large population-based study show an association of depression status and severity with decreased serum 25(OH)D levels and increased serum PTH levels in older individuals.
Ahn J, Peters U, Albanes D, et al. For the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Project Team. Serum Vitamin D Concentration and Prostate Cancer Risk: A Nested Case-Control Study. J Natl Cancer Inst. 2008 May 27. [Epub ahead of print] The findings of this large prospective study do not support the hypothesis that vitamin D is associated with decreased risk of **prostate cancer**; indeed, higher circulating 25(OH)D concentrations may be associated with increased risk of aggressive disease.
Bischoff-Ferrari HA, Rees JR, Grau MV, Barry E, Gui J, Baron JA. Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. Am J Clin Nutr. 2008 Jun;87(6):1945-51. A total of 930 participants (72% men; mean age: 61 y) were randomly assigned to receive 4 yr of treatment with 3 g CaCO(3) (1200 mg elemental Ca) daily or placebo and were followed for a mean of 10.8 yr. Calcium supplementation reduced the risk of all fractures and of minimal trauma fractures among healthy individuals. The benefit appeared to dissipate after treatment was stopped.
Sievenpiper JL, McIntyre EA, Verrill M, Quinton R, Pearce SH. **Unrecognised severe vitamin D deficiency**. BMJ. 2008 Jun 14;336(7657):1371-4.
Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of **myocardial infarction** in men: a prospective study. Arch Intern Med. 2008 Jun 9;168(11):1174-80. Low levels of 25(OH)D are associated with higher risk of myocardial infarction in a graded manner, even after controlling for factors known to be associated with coronary artery disease.
Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular **mortality**. Arch Intern Med. 2008 Jun 23;168(12):1340-9. Low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels are independently associated with all-cause and cardiovascular mortality. A causal relationship has yet to be proved by intervention trials using vitamin D.
Melamed ML, Michos ED, et al. 25-hydroxyvitamin d levels and the risk of mortality in the general population. Arch Intern Med. 2008 Aug 11;168(15):1629-37. The lowest quartile of 25(OH)D level (<17.8 ng/mL) is independently associated with **all-cause mortality** in the general population.
Cauley JA, Lacroix AZ, Wu L, Horwitz M, et al. Serum 25-hydroxyvitamin D concentrations and risk for **hip fractures**. Ann Intern Med. 2008 Aug 19;149(4):242-50. Low serum 25(OH) vitamin D concentrations are associated with a higher risk for hip fracture.
Chlebowski RT, Johnson KC, Kooperberg C, et al. for the Women's Health Initiative Investigators. (WHI) Calcium Plus Vitamin D Supplementation and the Risk of Breast Cancer. J Natl Cancer Inst. 2008 Nov 11. [Epub ahead of print] Calcium and vitamin D supplementation did **not reduce invasive breast cancer** incidence in postmenopausal women. In addition, 25-hydroxyvitamin D levels were not associated with subsequent breast cancer risk. These findings do not support a relationship between total vitamin D intake and 25-hydroxyvitamin D levels with breast cancer risk.
Bacon CJ, Gamble GD, Horne AM, Scott MA, Reid IR. High-dose oral vitamin D(3) supplementation in the elderly. Osteoporos Int. 2008 Dec 20. [Epub ahead of print] Sixty-three elderly participants were randomized to three regimens of vitamin D supplementation: a 500,000-IU loading dose; the **loading dose plus** 50,000 IU/month; or **50,000 IU/month**. Large loading doses of vitamin D(3) rapidly and safely normalize 25OHD levels in the frail elderly. Monthly dosing is similarly effective and safe, but takes 3-5 months for plateau 25OHD

TOP

levels to be reached.
Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, Reitz R, Salameh W, Ameri A, Tannenbaum AD. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab. 2008 Mar;93(3):677-81. Epub 2007 Dec 18. A 1000 IU dose of **vitamin D2 daily was as effective as 1000 IU vitamin D3** in maintaining serum 25-hydroxyvitamin D levels and did not negatively influence serum 25-hydroxyvitamin D3 levels. Therefore, vitamin D2 is equally as effective as vitamin D3 in maintaining 25-hydroxyvitamin D status.
Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics. 2008 Nov;122(5):1142-52. Erratum in: Pediatrics. 2009 Jan;123(1):197.
Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009 Mar 23;169(6):551-61. Nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older. Vitamin D at dosages **greater than 400 IU per day** is effective in decreasing nonvertebral fractures, including hip fractures.
Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and Associations of 25-Hydroxyvitamin D Deficiency in US Children: NHANES 2001-2004. Pediatrics. 2009 Aug 3. [Epub ahead of print] 25(OH)D deficiency is common in the general US pediatric population and is associated with adverse cardiovascular risks.
Bordelon P, Ghetu MV, Langan RC. Recognition and management of vitamin D deficiency. Am Fam Physician. 2009 Oct 15;80(8):841-6.
Bischoff-Ferrari H A, Dawson-Hughes B, Staehelin H B, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692, doi: 10.1136/bmj.b3692 (Published 1 October 2009)
Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med. 2009 Mar 23;169(6):626-32.
Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evid Rep Technol Assess (Summ). 2009 Jul;183: 1-342.
Palmer SC, McGregor DO, Macaskill P, et al. Meta-analysis: vitamin D compounds in chronic kidney disease. Ann Intern Med. 2007;147(12):840–853.
Pearce Simon HS, Cheetham Tim D. Diagnosis and management of vitamin D deficiency. BMJ 2010;340:b5664, doi: 10.1136/bmj.b5664 (Published 11 January 2010)
Wang, Lu, Manson, JoAnn E. Song, Yiqing et al. Systematic Review: Vitamin D and Calcium Supplementation in Prevention of Cardiovascular Events. *Ann Intern Med* March 2, 2010 152:315-323; doi:10.1059/0003-4819-152-5-201003020-00010.
Anastassios G. Pittas, Mei Chung, Thomas Trikalinos, Et al. Systematic Review: Vitamin D and Cardiometabolic Outcomes. *Ann Intern Med* March 2, 2010 152:307-314; doi:10.1059/0003-4819-152-5-201003020-00009.
Vitamin D supplementation: Recommendations for Canadian mothers and infants. Paediatr Child Health 2007;12(7):583-9. Reference No. FNIM07-01. http://www.cps.ca/english/statements/ii/fnim07-01.htm
Hofmeyr GJ, Lawrie TA, Atallah AN, et al. **Calcium supplementation during pregnancy** for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2010 Aug 4;8:CD001059.
Straube S, Derry S, Moore RA, et al. Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007771.
Casey CF, Slawson DC, Neal LR. VItamin D Supplementation in Infants, Children, and Adolescents. Am Fam Physician. 2010 Mar 15;81(6):745-8.
Bischoff-Ferrari Heike A.; Dawson-Hughes Bess; Platz Andreas; et al. Effect of **High-Dosage Cholecalciferol** (2000 vs 800 IU/day) and Extended Physiotherapy on Complications After Hip Fracture: A Randomized Controlled Trial. Arch Intern Med. 2010;170(9):813-820.
Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007 Dec;46(12):1852-7. Epub 2007 Nov 12. An **annual i.m. injection of 300 000 IU** vitamin D(2) is not effective in preventing non-vertebral fractures among elderly men and women resident in the general population.
Sanders Kerrie M.; Stuart Amanda L.; Williamson Elizabeth J.; et al. Annual **High-Dose Oral Vitamin D** (500,000IU x1/yr for 3-5yrs: increased falls & fractures) and Falls and Fractures in Older Women: A Randomized Controlled Trial. JAMA. 2010;303(18):1815-1822.
Terushkin V et al. Estimated equivalency of **vitamin D production from natural sun exposure** versus oral vitamin D supplementation across seasons at two US latitudes. J Am Acad Dermatol 2010 Jun; 62:929.e1.
Perrine, Cria G., Sharma, Andrea J., Jefferds, Maria Elena D., et al. Adherence to Vitamin D Recommendations Among US Infants. Pediatrics 2010 125: 627-632.
Llewellyn David J.; Lang Iain A.; Langa Kenneth M.; et al. Vitamin D and Risk of **Cognitive Decline** in Elderly Persons Arch Intern Med. 2010;170(13):1135-1141. Conclusion: Low levels of vitamin D were associated with substantial cognitive decline in the elderly population studied over a 6-year period, which raises important new possibilities for treatment and prevention.
Knekt Paul; Kilkkinen Annamari; Rissanen Harri; et al. Serum Vitamin D and the Risk of **Parkinson Disease** Arch Neurol. 2010;67(7):808-811.
Hanley DA, Cranney A, Jones G, et al. **Vitamin D in adult** health & disease: a review and **guideline statement from Osteoporosis Canada**–summary.CMAJ 2010 0: cmaj.091062.
Ascherio A, Munger KL, Simon KC. Vitamin D and **multiple sclerosis**. Lancet Neurol. 2010 Jun;9(6):599-612.
Bolland Mark J, Avenell Alison, Baron John A, et al, Effect of **calcium** supplements on risk of **myocardial infarction** and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.
Kalyani RR, Stein B, Valiyil R, et al. Vitamin D treatment for the prevention of **falls** in older adults: systematic review and meta-analysis. J Am Geriatr Soc. 2010 Jul;58(7):1299-310. Epub 2010 Jun 23. Vitamin D treatment effectively reduces the risk of falls in older adults.
Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces **cancer risk**: results of a randomized trial. Am J Clin Nutr. 2007 Jun;85(6):1586-91
Vatanparast H, Dolega-Cieszkowski JH, Whiting SJ. Many adult Canadians are not meeting current **calcium recommendations from food and supplement** intake. Appl Physiol Nutr Metab. 2009 Apr;34(2):191-6.
Winzenberg TM, Powell S, Shaw KA, Jones G. **Vitamin D** supplementation for improving bone mineral density in **children**. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006944. DOI: 10.1002/14651858.CD006944.pub2. These results do not support vitamin D supplementation to improve bone density in healthy children with normal vitamin Dlevels, but suggest that supplementation of deficient children may be clinically useful.
Papaioannou, Alexandra, Morin, Suzanne, Cheung, Angela M., et al. **2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada**: summary CMAJ 2010 0: cmaj.100771.
IOM (Institute of Medicine): Dietary Reference Intakes for **Calcium and Vitamin D** Nov,2010.
http://www.iom.edu/~/media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf
Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the u.s. Preventive services task force (**USPSTF**). Ann Intern Med. 2010 Dec 21;153(12):815-25.
Zhu K, Austin N, Devine A, et al. A randomized controlled trial of the effects of vitamin D on **muscle strength** and mobility in older women with vitamin D insufficiency. J Am Geriatr Soc. 2010 Nov;58(11):2063-8. doi: 10.1111/j.1532-5415.2010.03142.x.
Rosen Clifford J. **Vitamin D Insufficiency**. N Engl J Med 2011; 364:248-254.
Bosomworth, N.J. Mitigating epidemic vitamin D deficiency: The agony of evidence. Can Fam Physician 2011 57: 16-20.
Panel on Prevention of Falls in Older Persons, **American Geriatrics Society (AGS)** and British Geriatrics Society. Summary of Updated American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for **Prevention of Falls in Older Persons**. Article first published online: 13 JAN 2011 DOI: 10.1111/j.1532-5415.2010.03234.x http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2010.03234.x/pdf
Winzenberg Tania, Powell Sandi, Shaw Kelly Anne, et al. Effects of vitamin D supplementation on bone density in healthy **children**: systematic review and meta-analysis. BMJ 2011;342:doi:10.1136/bmj.c7254 (Published 25 January 2011).
Langer-Gould A, Huang S, Van Den Eeden SK, et al. Vitamin d, pregnancy, breastfeeding, and postpartum **multiple sclerosis** relapses. Arch Neurol. 2011 Mar;68(3):310-3.
Bolland MJ, Grey A, Avenell A, et al. **Calcium supplements with or without vitamin D** and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011; DOI: doi:10.1136/bmj.d2040.
Beauchet O, Annweiler C, Verghese J, et al. Biology of gait control: vitamin D involvement. Neurology 2011;76:1617–1622.
Warensjö Eva, Byberg Liisa, Melhus Håkan, et al. **Dietary calcium intake** and risk of fracture and osteoporosis: prospective longitudinal cohort study. BMJ 2011;342:doi:10.1136/bmj.d1473 (Published 24 May 2011)
Kumar Geeta Trilok, Sachdev Harshpal Singh, Chellani Harish, et al. Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. BMJ 2011;342:doi:10.1136/bmj.d2975
Holick Michael F., Binkley Neil C., Bischoff-Ferrari Heike A., et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an **Endocrine Society** Clinical Practice Guideline JCEM 2011 jc.2011-0385.
Gelfand JM, Cree BA, McElroy J, et al. **Vitamin D** in African Americans with multiple sclerosis. Neurology. 2011 May 24;76(21):1824-30.
BC Guideline: Medical Services Commission. **Vitamin D testing protocol**. British Columbia Medical Services Commission; 2010 Oct 1. http://www.bcguidelines.ca/pdf/vitamind.pdf
Bjelakovic G, Gluud LL, Nikolova D, et al. **Vitamin D supplementation for prevention of mortality** in adults. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD007470. DOI: 10.1002/14651858.CD007470.pub2. Vitamin D in the form of vitamin D3 seems to decrease mortality in predominantly elderly women who are mainly in institutions and dependent care. Vitamin D2, alfacalcidol, and calcitriol had no statistically significant effect on mortality. Vitamin D3 combined with calcium significantly increased nephrolithiasis. Both alfacalcidol and calcitriol significantly increased hypercalcaemia.
Sanders KM, Stuart AL, Williamson EJ, Jacka FN, Dodd S, Nicholson G, Berk M. Annual high-dose vitamin D3 and **mental well-being**: randomised controlled trial. Br J Psychiatry. 2011 May;198(5):357-64. (no benefit in older women)
Tang JY, Fu T, Leblanc E, et al. Calcium plus vitamin D supplementation and the risk of **nonmelanoma and melanoma skin cancer**: post hoc analyses of the women's health initiative randomized controlled trial. J Clin Oncol. 2011 Aug 1;29(22):3078-84.
Skversky AL, Kumar J, Abramowitz MK, et al. Association of **Glucocorticoid Use and Low 25-Hydroxyvitamin D Levels**: Results from the National Health and Nutrition Examination Survey (NHANES): 2001-2006. J Clin Endocrinol Metab. 2011 Sep 28.
Jacobsen RB, Hronek BW, Schmidt GA, Schilling ML. **Hypervitaminosis D Associated with a Vitamin D Dispensing Error** (October). Ann Pharmacother. 2011 Sep 13.
Buppasiri P, Lumbiganon P, Thinkhamrop J, et al. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD007079. DOI: 10.1002/14651858.CD007079.pub2. Calcium supplementation is associated with a significant protective benefit in the prevention of **pre-eclampsia**, and should be used for this indication according to a previous review. This review indicates that there are no additional benefits for calcium supplementation in prevention of preterm birth or low infant birth weight.
Stein MS, Liu Y, Gray OM, et al. A randomized trial of high-dose vitamin D2 in relapsing-remitting **multiple sclerosis**. Neurology 2011;77:1611–1618.
Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D3 and/or calcium (**RECORD** trial). J Clin Endocrinol Metab 2011; DOI:10.1210jc.2011-1309.
Chung M, Lee J, Terasawa T, et al. **Vitamin D With or Without Calcium** Supplementation for Prevention of Cancer and **Fractures**: An Updated Meta-analysis for the U.S. Preventive Services Task Force (USPSTF). Ann Intern Med. 2011 Dec 20;155(12):827-38.
Pérez-López FR, Brincat M, Erel CT, et al. **EMAS** position statement: Vitamin D and postmenopausal health. Maturitas. 2011 Nov 17.
McGreevy C, Williams D. New insights about vitamin D and **cardiovascular disease**: a narrative review. Ann Intern Med. 2011 Dec 20;155(12):820-6.
Marcus JF, Shalev SM, Harris CA, et al. **Severe hypercalcemia following vitamin d supplementation** in a patient with multiple sclerosis: a note of caution. Arch Neurol. 2012 Jan;69(1):129-32.
Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: The effect of **vitamin D on falls**: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011 Oct;96(10):2997-3006.
Thadhani R; Appelbaum E; Pritchett Y, et al. **Vitamin D** therapy (paricalcitol) and cardiac structure and function in patients with **chronic kidney disease**: The **PRIMO** randomized controlled trial. JAMA 2012; 307:674-684.
Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on **muscle strength, gait and balance** in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2011 Dec;59(12):2291-300.

TOP

De-Regil LM, Palacios C, Ansary A, et al. Vitamin D supplementation for women during **pregnancy**. Cochrane Database Syst Rev. 2012 Feb 15;2:CD008873.
Kunisaki KM, Niewoehner DE, Connett JE; COPD Clinical Research Network. Vitamin D levels and risk of acute exacerbations of **chronic obstructive pulmonary disease**: a prospective cohort study. Am J Respir Crit Care Med 2012;185:286–290.
Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J, et al. High doses of vitamin D to reduce exacerbations in **chronic obstructive pulmonary disease**. A randomized trial. Ann Intern Med. 2012;156:105-14
Manaseki-Holland S, Maroof Z, Bruce J, et al. Effect on the incidence of **pneumonia** of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial. Lancet. 2012 Apr 14;379(9824):1419-27.
de Boer IH, Levin G, Robinson-Cohen C, et al. Serum 25-hydroxyvitamin d concentration and risk for major clinical disease events in a community-based population of older adults: a cohort study. Ann Intern Med. 2012 May 1;156(9):627-34.
Barake M, Daher RT, Salti I, Cortas et al. **25-hydroxyvitamin D assay variations** and impact on clinical decision making. J Clin Endocrinol Metab. 2012 Mar;97(3):835-43.
Li Kuanrong, Kaaks R, Linseisen J, et al. Associations of **dietary calcium intake and calcium supplementation** with **myocardial infarction** and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart 2012. (In press)
Rejnmark L, Avenell A, Masud T, et al. **Vitamin D with Calcium Reduces Mortality**: Patient Level Pooled Analysis of 70,528 Patients from Eight Major Vitamin D Trials. J Clin Endocrinol Metab. 2012 May 17.

112. Stainer R, Matthews S, Arshad SH, et al. Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in **atopic dermatitis** in children aged 2 to 12 years: A double-blind, randomized, placebo-controlled trial. Br J Dermatol 2005; 152:334-41. (InfoPOEMs: Topical cromolyn lotion provides a statistically significant, but not clinically significant, benefit for children with atopic eczema. (LOE = 1b))
113. White KC. Anemia is a poor predictor of **iron** deficiency among toddlers in the United States: For heme the bell tolls. Pediatrics 2005; 115:315-20. (InfoPOEMs: These study results present a quandary: We cannot feel assured that a young child doesn't have anemia if they show a normal hemoglobin level, and we can't be sure that he or she has anemia if the hemoglobin level is low. Screening for iron deficiency in toddlers by checking serum hemoglobin misses most children with a deficiency, and most of the children with anemia do not have an iron deficiency. As the author of this study suggests, it might make more sense to continue low-dose supplementation of iron in all children rather than use a policy of screen and treat. (LOE = 1c)) (Rimon E, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med. 2005 Oct;118(10):1142-7. CONCLUSIONS: Low-dose iron treatment is effective in elderly patients with iron-deficiency anemia. It can replace the commonly used higher doses and can significantly reduce adverse effects.) Iron deficiency anemia USPSTF 2006 http://www.ahrq.gov/clinic/uspstf06/ironsc/ironrs.htm (Drueke TB, et al. Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia. N Engl J Med. 2006 Nov 16;355(20):2071-2084. In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events. & Singh AK, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. N Engl J Med. 2006 Nov 16;355(20):2085-2098. The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life. If epoetin alfa (Epogen) is used in patients with chronic kidney disease, the target hemoglobin should be 11.3 g/dL rather than 13.5 g/dL. A higher hemoglobin target was more likely to lead to death or adverse cardiac events (number needed to treat to harm [NNTH] = 25 for 16 months). (InfoPoems LOE =1b)) (Ceriani Cernadas JM, et al. The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. Pediatrics. 2006 Apr;117(4):e779-86. Epub 2006 Mar 27. & van Rheenen PF, Brabin BJ. A practical approach to timing cord clamping in resource poor settings. BMJ. 2006 Nov 4;333(7575):954-8. & Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy & low socioeconomic status: longitudinal analysis of cognitive test scores to age 19yrs. Arch Pediatr Adolesc Med. 2006 Nov;160(11):1108-13.)
Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. Dietary supplements and mortality in older women: the Iowa Women's Health Study. Arch Intern Med. 2011;171(18):1625-1633.
Baker, Robert D., Greer, Frank R., THE COMMITTEE ON NUTRITION, Clinical Report--Diagnosis and Prevention of **Iron Deficiency and Iron-Deficiency Anemia** in Infants and Young Children (0-3 Years of Age). (AAP) Pediatrics 2010 0: peds.2010-2576.
Lozoff B et al. Iron-fortified vs low-**iron infant formula: Developmental outcome at 10 years**. Arch Pediatr Adolesc Med2011 Nov 7; [e-pub ahead of print],
114. Spandorfer PR, Alessandrini EA, Joffe MD, Localio R, Shaw KN. Oral versus intravenous **rehydration** of moderately dehydrated children: A randomized, controlled trial. Pediatrics 2005; 115:295-301. *(InfoPOEMs:* In the emergency setting, oral rehydration therapy is as effective as intravenous rehydration in children with moderate dehydration. Administered every 5 minutes by parents, oral rehydration resulted in fewer hospitalizations. Most children (92%) who were placed in the oral rehydration group were able to drink the prescribed amount. (LOE = 1b)) (Hartling L, Bellemare et al. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. Cochrane Database Syst Rev. 2006 Jul 19;3:CD004390.) (Pharmacist's Letter April 2007. Oral rehydration therapy.)
Freedman SB, Cho D, Boutis K, et al. Assessing the palatability of oral rehydration solutions in school-aged children: a randomized crossover trial. Arch Pediatr Adolesc Med. 2010 Aug;164(8):696-702. Sucralose-sweetened oral rehydration solutions (Pedialyte and Pediatric Electrolyte) were significantly more palatable than was a comparable rice-based solution (Enfalyte).
Rouhani, Shada, Meloney, Laura, Ahn, Roy, et al. Alternative Rehydration Methods: A Systematic Literature Review and Lessons for Resource-Limited Care. Pediatrics 2011 0: peds.2010-0952.
115. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of **folate** and **mecobalamin** on hip fractures in patients with stroke. A randomized controlled trial. JAMA 2005; 293:1082-88. (InfoPOEMs: Combined supplementation with oral high dose folate and mecobalamin reduces the risk of hip fractures in elderly patients with stroke and elevated homocysteine levels. The baseline fracture rate in this population is higher than generally reported and all study subjects had low baseline serum levels of folate and vitamin B12. Since the adverse risk of treatment is minimal, it makes sense to consider supplementation at this time in similar patients. (LOE = 1b)) (Devalia V. Diagnosing vitamin B-12 deficiency on the basis of serum B-12 assay. BMJ. 2006 Aug 19;333(7564):385-6.) (Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B(12) deficiency in patients with Crohn's disease. Inflamm Bowel Dis. 2007 Sep 20; [Epub ahead of print] Vitamin B(12) abnormalities are common in patients with CD and patients with a prior ileal or ileocolonic resection are at particular risk.)
Eussen SJ, de Groot LC, Clarke R, Schneede J, Ueland PM, Hoefnagels WH, et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: a dose-finding trial. Arch Intern Med 2005;165(10):1167-72.
Butler CC, Vidal-Alaball J, Cannings-John R, McCaddon A, Hood K, Papaioannou A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Fam Pract 2006;23(3):279-85.
Volkov I, Rudoy I, Freud T, Sardal G, Naimer S, Peleg R, Press Y. Effectiveness of vitamin B12 in treating recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled trial. J Am Board Fam Med. 2009 Jan-Feb;22(1):9-16. Compared with placebo, sublingual vitamin B12 significantly reduced the average duration of recurrent aphthous stomatitis, the number of aphthous ulcers, and the subjective level of pain. Treatment was only effective after 5 months, so shorter treatment courses may not be effective. (LOE = 1b-)
Langan RC, Zawistoski KJ. Update on Vitamin B12 Deficiency. Am Fam Physician. 2011 Jun 15;83(12):1425-1430.
McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med. 2006;354(26):2764-2772.
Roumeliotis N, Dix D, Lipson A. Vitamin B12 deficiency in infants secondary to maternal causes. CMAJ. 2012 Jun 18.
116. Williams HC. Clinical practice. **Atopic dermatitis**. N Engl J Med. 2005 Jun 2;352(22):2314-24.
(dos Santos RV, Magerl M, Mlynek A, Lima HC. Suppression of histamine- and allergen-induced skin reactions: comparison of first- and second-generation antihistamines. Ann Allergy Asthma Immunol. 2009 Jun;102(6):495-9. These results indicate that hydroxyzine is more effective than nsAHs when given as recommended in suppressing histamine-induced or allergic skin reactions. Our results suggest that higher doses of nsAHs than those currently recommended are required for the treatment of skin responses to obtain antihistaminic and antiallergic effects that are equivalent to those of fgAHs.)
117. FDA Warns Against Abuse of **Dextromethorphan** May/05 http://origin.www.fda.gov/bbs/topics/ANSWERS/2005/ANS01360.html (Detromethorphan abuse, Pharmacist's Letter Feb 2007.)
Misuse of Over-the-Counter Cough and Cold Medications among Persons Aged 12 to 25, Jan, 2008 http://oas.samhsa.gov/2k8/cough/cough.htm
118. Eussen SJ, de Groot LC, Clarke R, Schneede J, Ueland PM, Hoefnagels WH, van Staveren WA. Oral **cyanocobalamin** supplementation in older people with vitamin B12 deficiency: a dose-finding trial. Arch Intern Med. 2005 May 23;165(10):1167-72.
119. Leung DY, Nicklas RA, Li JT, Bernstein IL, et al. Disease management of **atopic dermatitis**: an updated practice parameter. Joint Task Force on Practice Parameters. Ann Allergy Asthma Immunol. 2004 Sep;93(3 Suppl 2):S1-21.
120. Kamm MA, Muller-Lissner S, Talley NJ, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. Am J Gastroenterol 2005;100:362-72. (InfoPOEMs: Tegaserod is a safe and effective treatment for chronic **constipation**. Although some benefit was seen at a dose of 2 mg twice daily, a better treatment effect was seen at 6 mg twice daily, and the higher dose was similarly tolerated. However, tegaserod is much more expensive than alternatives like colchicine. Since pts receiving 6 mg tegaserod had a mean of 0.6 additional complete spontaneous bowel movements per week than those taking placebo, the cost for each one was more than $60. (LOE = 1b))
121. Drugs for **acne**, rosacea and psoriasis. Treat Guidel Med Lett. 2005 Jul;3(35):49-56.
122. I-Min Lee, MBBS, ScD; Nancy R. Cook, ScD; et al. **Vitamin E** in the Primary Prevention of Cardiovascular Disease and Cancer: The **Women's Health Study**: A Randomized Controlled Trial. JAMA. 2005;294:56-65.
Conclusions The data from this large trial indicated that **600 IU of natural-source vitamin E** taken every other day provided no overall benefit for major cardiovascular events or cancer, did not affect total mortality, and decreased cardiovascular mortality in healthy women. These data do **not support** recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women. (InfoPOEMs: Vitamin E does not reduce the risk of cardiovascular disease, cancer, or total mortality among healthy women 45 years or older. (LOE = 1b))
Zhang SM, Cook NR, Albert CM, Gaziano JM, Buring JE, Manson JE. Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women: a randomized trial. (WAFACS) JAMA. 2008 Nov 5;300(17):2012-21. Combined folic acid, vitamin B(6), and vitamin B(12) treatment had no significant effect on overall risk of total invasive cancer or breast cancer among women during the folic acid fortification era.
123. Ramkumar D, Rao SS. Efficacy and safety of traditional medical remedies for chronic **constipation**: a systematic review. Am J Gastroenterol 2005; 100:936-71. (InfoPOEMs: The best evidence supports polyethylene glycol, tegaserod, psyllium, and lactulose for adults with chronic constipation. Tegaserod is much more expensive than the other 3 drugs and its long-term safety data are not available. Evidence is lacking for many commonly used preparations, but the absence of evidence is not evidence of ineffectiveness. (LOE = 1a-)) (Rubin G, Dale A. Chronic constipation in children. BMJ. 2006 Nov 18;333(7577):1051-5. & Muller-Lissner S, et al. Safety, Tolerability, and Efficacy of Tegaserod over 13 Months in Patients with Chronic Constipation. Am J Gastroenterol. 2006 Nov;101(11):2558-69. Tegaserod has a favorable safety profile and is well tolerated during continuous long-term treatment in patients with CC. & Altomare DF, et al. Red hot chili pepper and hemorrhoids: the explosion of a myth: results of a prospective, randomized, placebo-controlled, crossover trial. Dis Colon Rectum. 2006 Jul;49(7):1018-23. (InfoPOEMs: This study found no evidence to support the popular contention that spicy foods, including red hot chili peppers, exacerbates hemorrhoid symptoms. Clinicians need not warn patients with hemorrhoids to avoid spicy foods. (LOE = 1b)) & Loening-Baucke V, Pashankar DS. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. Pediatrics. 2006 Aug;118(2):528-35.)
124. Hill N, Moor G, Cameron MM, Butlin A, et al. Single blind, randomised, comparative study of the **Bug Buster** kit and over the counter pediculicide treatments against head **lice** in the United Kingdom. BMJ. 2005 Aug 13;331(7513):384-7. Epub 2005 Aug 5. (InfoPOEMs: Approximately half of children using a special lice comb (Bug Buster) every 3 days for 9 days will be lice-free at a 2-week follow-up. This rate was higher than that of either of 2 commonly used pediculocides, although they were only used once instead of the frequently recommended twice. Combing is not technically difficult as long as conditioner has been used on the hair, though the squirm factor in the child and the squeamish factor in the parent who combs out live lice makes it less desirable. (LOE = 1b-)) (Thomas DR, et al. Surveillance of insecticide resistance in head lice using biochemical and molecular methods. Arch Dis Child. 2006 Jun 14; [Epub ahead of print]) (Resultz: New OTC Head Lice Treatment. Pharmacist's Letter Sept 2006)
Canadian Paediatric Society. Head lice infestations: a clinical update. http://cps.ca/English/statements/ID/id08-06.pdf
Jahnke C, et al. Accuracy of Diagnosis of Pediculosis Capitis: Visual Inspection vs Wet Combing. Arch Dermatol. 2009 Mar;145(3):309-13. Wet combing is a very accurate method to diagnose active head lice infestation. Visual inspection is the method of choice, if one aims to determine the frequency of carriers of eggs or nits.
Stough D, Shellabarger S, Quiring J, et al. Efficacy and Safety of Spinosad and Permethrin Creme Rinses for Pediculosis Capitis (Head Lice). Pediatrics. 2009 Aug 24.
Chosidow, Olivier, Giraudeau, Bruno, Cottrell, Jeremy, et al. Oral Ivermectin versus Malathion Lotion for Difficult-to-Treat Head Lice. N Engl J Med 2010 362: 896-905.
Cole SW, Lundquist LM. Spinosad for treatment of head lice infestation. Ann Pharmacother. 2011 Jul;45(7-8):954-9.
125. Salerno SM, Jackson JL, Berbano EP. Effect of oral **pseudoephedrine** on blood pressure and heart rate: a meta-analysis. Arch Intern Med. 2005 Aug 8-22;165(15):1686-94. (InfoPOEMs: Overall, immediate-release pseudoephedrine produces a small increase in systolic blood pressure (1.5 mmHg) but has no effect on diastolic blood pressure. Sustained-release products do not affect blood pressure. Both types of products increase heart rate to a small degree. Unlike its cousin phenylpropanolamine, pseudoephedrine rarely causes large increases in blood pressure, although its effect on blood pressure is dose-related and a

TOP

marked effect could occur with overdose. (LOE = 1a))
126. Avenell A, Campbell MK, Cook JA, et al. Effect of **multivitamin** and multimineral supplements on morbidity from infections in older people (MAVIS trial): pragmatic, randomised, double blind, placebo controlled trial. BMJ. 2005 Aug 6;331(7512):324-9.
127. Brooks WA, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. The Lancet Early Online Publication, 23 August 2005
Roy SK, Hossain MJ, Khatun W, et al. Zinc supplementation in children with cholera in Bangladesh: randomized controlled trial. BMJ. 2008 Jan 8; [Epub ahead of print]
Lassi ZS, Haider BA, Bhutta ZA. **Zinc** supplementation for the prevention of **pneumonia** in children aged 2 months to 59 months. Cochrane Database Syst Rev. 2010 Dec 8;12:CD005978.
Patro Bernadeta, Szymanski Henryk, Szajewska Hania, Oral Zinc for the Treatment of Acute Gastroenteritis in Polish Children: A Randomized, Double-Blind, Placebo-Controlled Trial, The Journal of Pediatrics, Volume 157, Issue 6, December 2010
Basnet S, Shrestha PS, Sharma A, et al. A Randomized Controlled Trial of **Zinc** as Adjuvant Therapy for Severe Pneumonia in Young Children. Pediatrics. 2012 Mar 5.
Bhatnagar S, Wadhwa N, Aneja S, et al. **Zinc** as adjunct treatment in infants aged between 7 and 120 days with probable serious bacterial infection: a randomised, double-blind, placebo-controlled trial. Lancet 2012. online May 31.
129. **Vitamin** Supplements. The Medical Letter. July 18,2005. (see also Pharmacist's Letter July 2006 " Multivitamins/Minerals & Chronic Disease Prevention") (Huang HY, et al. The Efficacy and Safety of Multivitamin and Mineral Supplement Use To Prevent Cancer and Chronic Disease in Adults: A Systematic Review for a National Institutes of Health State-of-the-Science Conference. Ann Intern Med. 2006 Jul 31; [Epub ahead of print])
Leung AM, Pearce EN, Braverman LE. **Iodine** content of prenatal multivitamins in the United States. N Engl J Med. 2009 Feb 26;360(9):939-40.
Kawai K, Spiegelman D, Shankar AH, Fawzi WW. Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. Bull World Health Organ. 2011 Jun 1;89(6):402-411B.
Imhoff-Kunsch B, Stein AD, Martorell R, et al. Prenatal **Docosahexaenoic Acid Supplementation** and Infant Morbidity: Randomized Controlled Trial. Pediatrics. 2011 Aug 1.
Andreeva VA, et al. **B Vitamin and/or ω-3 Fatty Acid** Supplementation and Cancer: Ancillary Findings From the Supplementation With Folate, Vitamins B6 and B12, and/or Omega-3 Fatty Acids (**SU.FOL.OM3**) Randomized Trial. Arch Intern Med. 2012 Feb 13.
130. Douglas RM, Hemila H, D'Souza R, Chalker EB, Treacy B. **Vitamin C** for preventing and treating the common cold. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD000980.
Douglas RM, Hemilä H, Chalker E, Treacy B. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD000980. (Possible benefit to reduce risk of colds if severe physical exercise or cold environment eg. marathon runners, Skiers)
Smith A, Di Primio G, Humphrey-Murto S. **Scurvy** in the developed world. CMAJ. 2011 Aug 9
131. Robertson J, Iemolo F, Stabler SP, Allen RH, Spence JD. **Vitamin B12**, homocysteine and carotid plaque in the era of folic acid fortification of enriched cereal grain products. CMAJ. 2005 Jun 7;172(12):1569-73.
132. Vidal-Alaball J, Butler C, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004655. CONCLUSIONS: The evidence derived from these limited studies suggests that 2000 mcg doses of oral vitamin B12 daily and 1000 mcg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short term haematological and neurological responses in vitamin B12 deficient patients.
133. Medical Letter, **Drugs for Head lice**. Vol 47 (Issue 1215/1216) Aug 15/29,2005. p.68-70.
134. Farvid MS, Jalali M, Siassi F, Hosseini M. Comparison of the Effects of **Vitamins and/or Mineral Supplementation** on Glomerular and Tubular Dysfunction in Type 2 Diabetes. Diabetes Care. 2005 Oct;28(10):2458-64.
135. Margolis DJ, Bowe WP, Hoffstad O, Berlin JA. Antibiotic treatment of **acne** may be associated with upper respiratory tract infections. Arch Dermatol. 2005 Sep;141(9):1132-6.
136. Bonakdar RA, Guarneri E. **Coenzyme Q10**. Am Fam Physician. 2005 Sep 15;72(6):1065-70.
137. American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic **constipation** in North America. Am J Gastroenterol 2005; 100:S1-S4. (InfoPOEMs: Diagnostic testing is not needed for most patients with chronic constipation. The evidence is strongest for the efficacy of psyllium, polyethylene glycol, lactulose, and tegaserod. Research is not available to support the routine use of stimulant laxatives, lubricants, stool softeners, calcium polycarbophil, bran, or any herbal products. (LOE = 1a)) & Hsieh C. Treatment of constipation in older adults. Am Fam Physician. 2005 Dec 1;72(11):2277-84. Radaelli F, Meucci G, Imperiali G, Spinzi G, Strocchi E, Terruzzi V, Minoli G. High-Dose **Senna Compared with Conventional PEG-ES** Lavage as Bowel Preparation for Elective Colonoscopy: A Prospective, Randomized, Investigator-Blinded Trial. Am J Gastroenterol. 2005 Dec;100(12):2674-80. (Rendeli C, et al. **Polyethylene glycol 4000** vs. lactulose for the treatment of neurogenic constipation in myelomeningocele children: a randomized-controlled clinical trial.Aliment Pharmacol Ther. 2006 Apr 15;23(8):1259-65.) (Freedman SB, Adler M, Seshadri R, Powell EC. Oral **ondansetron** for gastroenteritis in a pediatric emergency department. N Engl J Med. 2006 Apr 20;354(16):1698-705.) (**Gastrointestinal Drug Use in Pregnancy**. Pharmacist's Letter Dec/06) Di Palma JA, Cleveland MV, McGowan J, et al. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. Am J Gastro. 2007 Sep;102(9):1964-71. Epub 2007 Jun 15. (n=237 4 weeks) While PEG laxative and tegaserod are safe for their intended use in chronic constipation, **PEG had superior efficacy, caused fewer headaches**, and produced greater improvement of constipation symptoms.
Thomson MA, Jenkins HR, Bisset WM, Heuschkel R, Kalra DS, Green MR, Wilson DC, Geraint M. Polyethylene glycol 3350 (6.9 g sachet)plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study. Arch Dis Child. 2007 Nov;92(11):996-1000. Epub 2007 Jul 11. PEG+E is significantly more effective than placebo, and appears to be safe and well tolerated in the treatment of chronic constipation in children.
Candy D, Belsey J. Macrogol (polyethylene glycol) laxatives in children with functional constipation and faecal impaction: a systematic review. Arch Dis Child. 2009 Feb;94(2):156-60. Epub 2008 Nov 19. In this systematic review that only included published studies, polyethylene glycol (PEG) was effective in treating functional constipation in children. PEG was clearly better than placebo and slightly more effective than lactulose, but no better than milk of magnesia. (LOE = 1a-)
McCallum IJ, Ong S, Mercer-Jones M. **Chronic constipation** in adults. BMJ. 2009 Mar 20;338:b831. doi: 10.1136/bmj.b831.
Chung S, Cheng A, Goldman RD. **Polyethylene glycol 3350** without electrolytes for treatment of **childhood** constipation. Can Fam Physician. 2009 May;55(5):481-2.
Bekkali, Noor-L-Houda, van den Berg, Maartje-Maria, Dijkgraaf, Marcel G.W., et al. Rectal Fecal Impaction Treatment in Childhood Constipation: **Enemas Versus High Doses Oral PEG**. Pediatrics 2009 124: e1108-e1115.
Coleman J, Spurling G. Constipation in people with **learning disability**. BMJ. 2010 Jan 26;340:c222. doi: 10.1136/bmj.c222.
Matro R, Shnitser A, Spodik M, et al. Efficacy of **Morning-Only** Compared With Split-Dose **Polyethylene Glycol** Electrolyte Solution for Afternoon Colonoscopy: A Randomized Controlled Single-Blind Study. Am J Gastroenterol. 2010 Apr 20
Bardisa-Ezcurra Lauren, Ullman Roz, Gordon Jenny, on behalf of the Guideline Development Group. Diagnosis and management of idiopathic childhood constipation: summary of **NICE guidance**. BMJ 2010;340:c2585, doi: 10.1136/bmj.c2585.
Lee-Robichaud H, Thomas K, Morgan J, et al. **Lactulose versus Polyethylene Glycol** for Chronic Constipation. Cochrane Database Syst Rev. 2010 Jul 7;7:CD007570. Polyethylene Glycol should be used in preference to Lactulose in the treatment of Chronic Constipation.
Roerig JL, Steffen KJ, Mitchell JE, Zunker C. **Laxative abuse**: epidemiology, diagnosis and management. Drugs. 2010 Aug 20;70(12):1487-503. doi: 10.2165/11898640-000000000-00000.
Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in **chronic idiopathic constipation**: systematic review and meta-analysis. Gut. 2011 Feb;60(2):209-18.
Attaluri A, Donahoe R, Valestin J, Brown K, Rao SS. Randomised clinical trial: **dried plums (prunes)** vs. psyllium for constipation. Aliment Pharmacol Ther. 2011 Apr;33(7):822-8. doi: 10.1111/j.1365-2036.2011.04594.x.
Varughese S, Kumar AR, George A, et al. Morning-only one-gallon **polyethylene glycol** improves bowel cleansing for afternoon colonoscopies: a randomized endoscopist-blinded prospective study. Am J Gastroenterol. 2010 Nov;105(11):2368-74.
Tabbers Merit M., Chmielewska Ania, Roseboom Maaike G., et al. Fermented Milk Containing **Bifidobacterium lactis DN-173 010** in Childhood Constipation: A Randomized, Double-Blind, Controlled Trial. Pediatrics 2011; 127:6 e1392-e1399; May 23, 2011.
Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral **bisacodyl** is effective and well-tolerated in patients with chronic constipation. Clin Gastroenterol Hepatol. 2011 Jul;9(7):577-83.
Tabbers Merit M., Boluyt Nicole, Berger Marjolein Y.,et al. **Nonpharmacologic Treatments for Childhood Constipation**: Systematic Review. Pediatrics 2011; peds.2011-0179; published ahead of print September 26, 2011, doi:10.1542/peds.2011-0179
Aune D et al. **Dietary fibre, whole grains, and risk of colorectal cancer**: Systematic review and dose-response meta-analysis of prospective studies. BMJ 2011 Nov 10; 343:d6617.
Rowan-Legg A; Canadian Paediatric Society, Community Paediatrics Committee. Managing functional constipation in children. Paediatr Child Health 2011;16(10):661-5. www.cps.ca/english/statements/CP/Constipation.htm (accessed December 14, 2011).
Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler SM, et al. **Chronic constipation** in the elderly. Am J Gastroenterol. 2012 Jan;107(1):18-25.
Ori Y, Rozen-Zvi B, Chagnac A, et al. **Fatalities** and Severe Metabolic Disorders Associated With the Use of **Sodium Phosphate Enemas**: A Single Center's Experience. Arch Intern Med. 2012 Feb 13;172(3):263-5.
138. Bonaa KH for the NORVIT Study Group. **NORVIT**: Randomised trial of homocysteine-lowering with B vitamins for secondary prevention of cardiovascular disease after acute myocardial infarction. European Society of Cardiology, Sept 3-7, 2005, Abstract 1334.
140. Vahedi H, Merat S, et al. The effect of **fluoxetine** in patients with pain and constipation-predominant **irritable bowel syndrome**: a double-blind randomized-controlled study. Aliment Pharmacol Ther. 2005 Sep 1;22(5):381-5.
141. Gilbert C, Mazzotta P, Loebstein R, Koren G. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug Saf. 2005;28(8):707-19.
142. Plaut M, Alleric Rhinitis. N Engl J Med 2005;353:193-44. (Medical Letter. Treatment Guidelines. Drugs for **Allergic Disorders**. Feb 2010.)
Sussman G, Sussman D, Sussman A. Intermittent **allergic rhinitis**. CMAJ. 2010 Jun 15;182(9):935-7.
Sur DK, Scandale S. Treatment of **allergic rhinitis**. Am Fam Physician. 2010 Jun 15;81(12):1440-6.
So M, Bozzo P, Inoue M, Einarson A. Safety of **antihistamines during pregnancy** and lactation. Can Fam Physician. 2010 May;56(5):427-9.
Radulovic S, Calderon MA, Wilson D, Durham S. **Sublingual immunotherapy** for allergic rhinitis. *Cochrane Database of Systematic Reviews* 2010, Issue 12. Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.pub2. This updated review reinforces the conclusion of the original 2003 Cochrane Review that sublingual immunotherapy is effective for allergic rhinitis and has been proven to be a safe route of administration.
Schaefer P. **Urticaria**: evaluation and treatment. Am Fam Physician. 2011 May 1;83(9):1078-84.
Griffin G, Flynn CA. **Antihistamines and/or decongestants for otitis media with effusion (OME)** in children. Cochrane Database Syst Rev. 2011 Sep 7;9:CD003423. The pooled data demonstrate no benefit and some harm from the use of antihistamines or decongestants alone or in combination in the management of OME, therefore we recommend against their use.
143. Ullrich C, Wu A, et al. Screening healthy infants for iron deficiency using reticulocyte hemoglobin content. JAMA. 2005 Aug 24;294(8):924-30. (InfoPOEMs: A low reticulocyte hemoglobin content (RHC) has a higher sensitivity for the accurate detection of early iron deficiency in infants than a standard hemoglobin measurement. Randomized trials comparing infants undergoing screening with either technique or no screening at all are now necessary to assess the long-term value of screening. (LOE = 2b))
144. Thavendiranathan P, et al. Do blood tests cause anemia in hospitalized patients? The effect of diagnostic phlebotomy on hemoglobin and hematocrit levels. J Gen Intern Med. 2005 Jun;20(6):520-4. (InfoPOEMs: The typical patient admitted for a 6-day admission will have 75 mL of blood drawn and this will drop his or her hemoglobin by 0.79 g/dL (7.9 g/L) and hematocrit by 2.1 percentage points. As a result, 1 in 6 patients will become anemic as a result of blood draws. (LOE = 2b))
145. Kim HS, Park DH, Kim JW, Jee MG, Baik SK, Kwon SO, Lee DK. Effectiveness of **walking exercise** as a bowel preparation for colonoscopy: a randomized controlled trial. Am J Gastroenterol. 2005 Sep;100(9):1964-9.
146. Welch HG, Woloshin S, Schwartz LM. Skin biopsy rates & incidence of **melanoma**: population based ecological study. BMJ. 2005 Sep 3;331(7515):481. Epub 2005 Aug 4. (InfoPOEMs: This study provides preliminary evidence that the incidence of melanoma is increasing not because of factors such as skin burns and ozone layer holes, but simply because more dermatologists are biopsying more lesions. In a 5-year period the incidence of melanoma increased 2.4-fold, whereas the biopsy rate over this same period increased a similar 2.5 times. (LOE = 2c))
147. Benn CS, et al. Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. BMJ. 2005 Nov 23; [Epub ahead of print] CONCLUSIONS: Half the dose of vitamin A currently recommended by WHO may provide equally good or better protection against mortality but not against morbidity.
150. Ringe JD, Faber H, Fahramand P, Schacht E. **Alfacalcidol** versus plain vitamin D in the treatment of **glucocorticoid/inflammation-induced osteoporosis**. J Rheumatol Suppl. 2005 Sep;76:33-40.

TOP

151. Arroll B. Non-antibiotic treatments for upper-respiratory tract infections (common cold). Respir Med. 2005 Dec;99(12):1477-84. CONCLUSION: Most non-antibiotic treatments for the common cold are probably not effective. The most promising are dextromethorphan, bisolvon and guiaphenesin for cough, antihistamine-decongestant combinations for a wide range of symptoms, nasal decongestants (at least for the first dose) and possibly zinc lozenges.
152. Larson AM, et al, and the Acute Liver Failure Study Group. Acetaminophen-Induced Acute Liver Failure: Results of a US Muticenter, Prospective Study. Hepatology; Dec 2005. (of 662 consecutive acute liver failure pts over 6yrs: 42% from acetaminophen liver injury; 48% were unintentional overdoses; only 65% of pts survived) (Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006 Feb 16;354(7):731-9.) (Kuffner EK, Temple AR, Cooper KM, Baggish JS, Parenti DL. Retrospective analysis of transient elevations in alanine aminotransferase during long-term treatment with acetaminophen in osteoarthritis clinical trials. Curr Med Res Opin. 2006 Nov;22(11):2137-48.)
153. Bobat R, Coovadia H, Stephen C, Naidoo KL, McKerrow N, Black RE, Moss WJ. Safety and efficacy of **zinc** supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial. Lancet. 2005 Nov 26;366(9500):1862-7.
154. Health Canada warning Dec/05 Oral fleet (a concern in renal impairment or if electrolyte imbalances & if not adequate hydration): http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/phosphate_solutions_2_hpc-cps_e.pdf & Pharmacist's Letter June 2006. July/09 Health Canada: Oral sodium phosphate products are no longer authorized for purgative use - Pharmascience Inc. and Odan Laboratories Ltd.
155. Poole KE, Loveridge N, Barker PJ, et al. Reduced **Vitamin D** in Acute Stroke. Stroke. 2005 Dec 1; [Epub ahead of print]
156. Park Y, Hunter DJ, Spiegelman D, et al. Dietary **fiber** intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA. 2005 Dec 14;294(22):2849-57. (InfoPOEMs: A diet high in fiber is not independently associated with a reduced risk of colorectal cancer. Patients consuming food and nutrients high in fiber are more likely to engage in other behaviors associated with a lower cancer risk. (LOE = 2a))
157. Scharman EJ, et al. **Diphenhydramine & dimenhydrinate poisoning**: an evidence-based consensus guideline for out-of-hospital management. Washington (DC): American Association of Poison Control Centers; Aug 2005. http://www.aapcc.org/FinalizedPMGdlns/diphenhydramine%20quideline%20for%20AAPCC%20_2_.pdf
158. Manoguerra AS, et al. **Iron ingestion**: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2005;43(6):553-70 http://www.aapcc.org/FinalizedPMGdlns/iron%20guideline%20for%20AAPCC%202005-5-3.pdf
159. Berger WE. The safety and efficacy of **desloratadine** for the management of allergic disease. Drug Saf. 2005;28(12):1101-18.
160. Ryder KM, Shorr RI, Bush AJ, Kritchevsky SB, Harris T, Stone K, Cauley J, Tylavsky FA. **Magnesium** intake from food and supplements is associated with **bone mineral density** in healthy older white subjects. J Am Geriatr Soc. 2005 Nov;53(11):1875-80.
161. van Leeuwen R, Boekhoorn S, Vingerling JR, Witteman JC, Klaver CC, Hofman A, de Jong PT. Dietary intake of **antioxidants and risk of age-related macular degeneration**. JAMA. 2005 Dec 28;294(24):3101-7. (InfoPOEMs: A high dietary intake of beta carotene, vitamins C and E, and zinc reduces the risk of age-related macular degeneration (AMD). (LOE = 2b-)) (Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS; ACTS Study Group. Vitamins C and E and the risks of **preeclampsia and perinatal** complications. N Engl J Med. 2006 Apr 7;354(17):1796-806.) Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the **Women's Antioxidant Cardiovascular Study**. Arch Intern Med. 2007 Aug 13-27;167(15):1610-8. There were no overall effects of ascorbic acid, vitamin E, or beta carotene on cardiovascular events among women at high risk for CVD.
Grodstein F, Kang JH, Glynn RJ, Cook NR, Gaziano JM. A randomized trial of **beta carotene** supplementation and **cognitive** function in men: the Physicians' Health Study II. Arch Intern Med. 2007 Nov 12;167(20):2184-90. We did not find an impact of short-term beta carotene supplementation on cognitive performance, but long-term supplementation may provide cognitive benefits.
Chong EW, Wong TY, Kreis AJ, Simpson JA, Guymer RH. Dietary antioxidants and primary prevention of age-related macular degeneration: systematic review and meta-analysis. BMJ 2007;335(7623):755-763. Neither high dietary nor supplemental intake of antioxidants reduced the risk of new-onset age-related macular degeneration (AMD). (LOE = 1a) There is insufficient evidence to support the role of dietary antioxidants, including the use of dietary antioxidant supplements, for the primary prevention of early AMD.)
Ellis JM, Tan HK, Gilbert RE, et al. Supplementation with antioxidants and folinic acid for children with Down's syndrome: randomised controlled trial. BMJ. 2008 Feb 22; [Epub ahead of print] This study provides no evidence to support the use of antioxidant or folinic acid supplements in children with Down's syndrome.
Christen WG, Glynn RJ, Chew EY, et al. Vitamin E and age-related cataract in a randomized trial of women. Ophthalmology. 2008 May;115(5):822-829.e1. Epub 2007 Dec 11. These data from a large trial of apparently healthy female health professionals with 9.7 years of treatment and follow-up indicate that 600 IU natural-source vitamin E taken every other day provides no benefit for age-related cataract or subtypes.
Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD007176. We found no evidence to support antioxidant supplements for primary or secondary prevention. **Vitamin A, beta-carotene, and vitamin E may increase mortality**. Future randomised trials could evaluate the potential effects of vitamin C and selenium for primary and secondary prevention.
Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the Prevention of Cardiovascular Disease in Men: The **Physicians' Health Study II** Randomized Controlled Trial. JAMA. 2008 Nov 9. [Epub ahead of print] In this large, long-term trial of male physicians, neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events. These data provide no support for the use of these supplements for the prevention of cardiovascular disease in middle-aged and older men.
Lippman SM, Klein EA, Goodman PJ, Lucia MS, et al. Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers: The Selenium and Vitamin E Cancer Prevention Trial (**SELECT**). JAMA. 2008 Dec 9. [Epub ahead of print] Selenium 200ug or vitamin E 400IU , alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men.
Gaziano JM, Glynn RJ, Christen WG, Kurth T, et al. Vitamins E and C in the Prevention of Prostate and Total Cancer in Men: The **Physicians' Health Study II** Randomized Controlled Trial. JAMA. 2008 Dec 9. [Epub ahead of print] In this large, long-term trial of male physicians, neither vitamin E nor C supplementation reduced the risk of prostate or total cancer. These data provide no support for the use of these supplements for the prevention of cancer in middle-aged and older men.
Smedts HP, de Vries JH, Rakhshandehroo M, et al. High maternal **vitamin E** intake by diet or supplements is associated with congenital heart defects in the offspring. BJOG. 2009 Feb;116(3):416-23. High maternal vitamin E intake is associated with congenital heart defects with a dose-response gradient. Although causality has not been demonstrated, the association is biologically plausible and may be sufficient to discourage women of child-bearing age from taking vitamin E supplements. (LOE = 3b)
Ristow M et al. Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci U S A 2009 May 26; 106:8665. (http://dx.doi.org/10.1073/pnas.0903485106)
Chan JM, Oh WK, Xie W, Regan MM, Stampfer MJ, King IB, Abe M, Kantoff PW. Plasma **Selenium**, Manganese Superoxide Dismutase, and Intermediate- or High-Risk Prostate Cancer. J Clin Oncol. 2009 Jun 15. [Epub ahead of print]
Sanyal, Arun J., Chalasani, Naga, Kowdley, Kris V., et al. the NASH CRN, Pioglitazone, **Vitamin E**, or Placebo for **Nonalcoholic Steatohepatitis**. N Engl J Med 2010 0: NEJMoa0907929.
Mattias Johansson; Caroline Relton; Per Magne Ueland et al; Serum B Vitamin Levels and Risk of Lung Cancer JAMA. 2010;303(23):2377-2385. Conclusion Serum levels of **vitamin B6 and methionine** were inversely associated with risk of lung cancer.
Schürks Markus, Glynn Robert J, Rist Pamela M, et al. Effects of **vitamin E on stroke** subtypes: meta-analysis of randomised controlled trials. BMJ 341:doi:10.1136/bmj.c5702 (Published 4 November 2010).
Christen WG, Glynn RJ, Chew EY, Buring JE. **Vitamin E** and age-related macular degeneration in a randomized trial of women. Ophthalmology. 2010 Jun;117(6):1163-8.
Morris Martha Clare, Tangney Christine C. A Potential **Design Flaw of Randomized Trials of Vitamin Supplements**. JAMA. 2011;305(13):1348-1349.doi:10.1001/jama.2011.383
West KP Jr, et al. Effects of **vitamin A or beta carotene** supplementation on pregnancy-related mortality and infant mortality in rural Bangladesh: a cluster randomized trial. JAMA. 2011 May 18;305(19):1986-95. (not reduce all-cause maternal, fetal or infant mortality)
Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and **Vitamin E Cancer** Prevention Trial (**SELECT**). JAMA. 2011 Oct 12;306(14):1549-56.
Darlow BA, Graham PJ. **Vitamin A** supplementation to prevent mortality and short- and long-term **morbidity in very low birthweight infants**. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD000501.
Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. **Antioxidant supplements** for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD007176. DOI: 10.1002/14651858.CD007176.pub2. We found no evidence to support antioxidant supplements for primary or secondary prevention. **Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A.**
162. Chen SC, et al. Nonsurgical management of partial adhesive small-bowel obstruction with oral therapy: a randomized controlled trial. CMAJ. 2005 Nov 8;173(10):1165-9. (InfoPOEMs: The combination of magnesium oxide, Lactobacillus acidophilus, and simethicone appears to reduce length of stay and the need for surgery in patients with partial small bowel obstruction, although this study was limited by a failure to completely blind patients and their caregivers. (LOE = 1b))
163. Saary J, et al. A systematic review of contact dermatitis treatment and prevention. J Am Acad Dermatol. 2005 Nov;53(5):845. (InfoPOEMs: Barrier creams, high-lipid content moisturizing creams, fabric softeners, and cotton glove liners are effective for preventing irritative contact dermatitis. Rhus dermatitis can be reduced or prevented with quaternium 18 bentonite (organoclay) lotion and a topical skin protectant. The chelator diethylenetriamine pentaacetic acid is effective in preventing nickel, chrome, and copper dermatitis. Steroid preparations are effective in the treatment of both irritative and contact dermatitis. (LOE = 1a-))
Usatine RP, Riojas M. Diagnosis and management of **contact dermatitis**. Am Fam Physician. 2010 Aug 1;82(3):249-55.
164. Alonso-Coello P, Mills E, Heels-Ansdell D, Lopez-Yarto M, Zhou Q, Johanson JF, Guyatt G. **Fiber** for the treatment of **hemorrhoids** complications: a systematic review and meta-analysis. Am J Gastroenterol. 2006 Jan;101(1):181-8.
165. Tubelius P, Stan V, Zachrisson A. Increasing work-place healthiness with the probiotic **Lactobacillus** reuteri: a randomised, double-blind placebo-controlled study. Environ Health. 2005 Nov 7;4:25. (InfoPOEMs: This study provides preliminary, limited evidence for a beneficial effect of Lactobacillus reuteri in reducing sick leave among healthy adults. The sponsorship (and authorship) by the manufacturer and the lack of intention-to-treat analysis means that we should watch for confirmatory studies before broadly recommending this to our patients. (LOE = 2b)) & see Pharmacist's Letter Probiotics July 2006.
(Szajewska H, Ruszczynski M, et al. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. J Pediatr. 2006 Sep;149(3):367-372. Probiotics reduce the risk of AAD in children. For every 7 patients that would develop diarrhea while being treated with antibiotics, one fewer will develop AAD if also receiving probiotics. (InfoPOEMs: Probiotics appear to prevent antibiotic-associated diarrhea in children. However, the limited number of trials included in this study, their overall limited quality, and the potential for publication bias suggest that the data are too limited for certainty. (LOE = 1a-))
(Medical Letter. Probiotics. Aug 13,2007.) Clarification: Saccharomyces cerevisiae (including S boulardii)
Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy. 2010 Feb;30(2):119-26. The probiotic Lactobacillus is effective in preventing antibiotic-associated diarrhea (AAD) in adults, though perhaps not in children. (LOE = 1a-)
Hojsak I, Abdovic S, Szajewska H, Milosevic M, Krznaric Z, Kolacek S. Lactobacillus GG in the Prevention of Nosocomial Gastrointestinal and Respiratory Tract Infections. Pediatrics. 2010 Apr 19. [Epub ahead of print]
Deshpande G, Rao S, Patole S, et al. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics. 2010 May;125(5):921-30. Epub 2010 Apr 19
Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub3. Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.
Bernaola Aponte G, Bada Mancilla CA, Carreazo Pariasca NY, Rojas Galarza RA. Probiotics for treating persistent diarrhoea in children. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD007401. DOI: 10.1002/14651858.CD007401.pub2. There is limited evidence suggesting probiotics may be effective in treating persistent diarrhoea in children.
Coccorullo P, Strisciuglio C, Martinelli M, et al. Lactobacillus reuteri (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatr. 2010 Oct;157(4):598-602.
Thomas, Dan W., Greer, Frank R., Committee on Nutrition; Section on Gastroenterology, Hepatology, and Nutrition, Clinical Report--Probiotics and Prebiotics in Pediatrics. Pediatrics 2010 0: peds.2010-2548.
Riquelme AJ, Calvo MA, Guzmán AM, et al. Saccharomyces cerevisiae fungemia after Saccharomyces boulardii treatment in immunocompromised patients. J Clin Gastroenterol. 2003 Jan;36(1):41-3.
Elias, Jackie, Bozzo, Pina, Einarson, Adrienne. Are probiotics safe for use during pregnancy and lactation? Can Fam Physician 2011 57: 299-301.
Hao Q, Lu Z, Dong BR, Huang CQ, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD006895. DOI: 10.1002/14651858.CD006895.pub2. Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTIs, the rate ratio of episodes of acute URTI and reducing antibiotic use. This indicates that probiotics may be more beneficial than placebo for preventing acute URTIs.

TOP

Pozzoni P, Riva A, Bellatorre AG, et al. Saccharomyces boulardii for the Prevention of Antibiotic-Associated Diarrhea in Adult Hospitalized Patients: A Single-Center, Randomized, Double-Blind, Placebo-Controlled Trial. Am J Gastroenterol. 2012 Apr 3. In elderly hospitalized patients, S. boulardii was not effective in preventing the development of AAD.

Agustina R, Kok FJ, van de Rest O, et al. Randomized trial of probiotics and calcium on diarrhea and respiratory tract infections in Indonesian children. Pediatrics. 2012 May;129(5):e1155-64. RC milk, alone or with L casei, did not reduce diarrhea or ARTIs in indonesian children. L reuteri may prevent diarrhea, especially in children with lower nutritional status.

Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA. 2012 May 9;307(18):1959-69.

166. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine Lowering and Cardiovascular Events after Acute Myocardial Infarction. N Engl J Med. 2006 Mar 12; [Epub ahead of print] & Homocysteine Lowering with Folic Acid and B Vitamins in Vascular Disease. N Engl J Med. 2006 Mar 12; [Epub ahead of print]. (Folate Status in Women of Childbearing Age, by Race/Ethnicity --- United States, 1999--2000, 2001--2002, and 2003—2004 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5551a2.htm) (Durga J, van Boxtel MPJ, Schouten EG, et al. Effect of 3-year **folic acid** supplementation on **cognitive function** in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 2007; 369:208-216. Folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age. (De Wals P, Tairou F, Van Allen MI, et al. **Reduction in neural-tube defects after folic acid** fortification in Canada. N Engl J Med. 2007 Jul 12;357(2):135-42. Food fortification with folic acid was associated with a significant reduction in the rate of neural-tube defects in Canada. The decrease was greatest in areas in which the baseline rate was high.)
Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. Lancet. 2001 Dec 15;358(9298):2069-73.
Jenkins KJ, Correa A, et al. American Heart Association Council on Cardiovascular Disease in the Young. Noninherited risk factors and **congenital cardiovascular defects**: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation. 2007 Jun 12;115(23):2995-3014. Epub 2007 May 22.
Wilson RD, Johnson JA, et al. Pre-conceptional vitamin/folic acid supplementation 2007: the use of **folic acid in combination with a multivitamin** supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can 2007;29:1003-26.
Wilson RD, Johnson JA, Wyatt P, Allen V, Gagnon A, Langlois S, Blight C, Audibert F, Désilets V, Brock JA, Koren G, Goh YI, Nguyen P, Kapur B; Genetics Committee of the **Society of Obstetricians and Gynaecologists of Canada and The Motherrisk** Program. Pre-conceptional vitamin/folic acid supplementation 2007: the use of **folic acid** in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2007 Dec;29(12):1003-26.
Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004514. The small number of studies which have been done provide no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvement in the response of people with Alzheimer`s disease to cholinesterase inhibitors. In another, long-term use appeared to improve the cognitive function of healthy older people with high homocysteine levels. More studies are needed on this important issue.
Ionescu-Ittu R, Marelli AJ, Mackie AS, Pilote L. Prevalence of severe congenital heart disease **after folic acid fortification** of grain products: time trend analysis in Quebec, Canada. BMJ 2009;338:b1673
U.S. Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009 May 5;150(9):626-31. The USPSTF recommends that all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 micrograms) of folic acid.
Wolff T, Witkop CT, Miller T, Syed SB; U.S. Preventive Services Task Force. Folic acid supplementation for the prevention of neural tube defects: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009 May 5;150(9):632-9.
Ebbing Marta; Bonaa Kaare Harald; Nygard Ottar; et al. **Cancer** Incidence and Mortality After Treatment With Folic Acid and Vitamin B12 (Norvit & Wenbit). JAMA. 2009;302(19):2119-2126.
Clarke R. Halsey J, Lewington S, et al. Effects of lowering homocystein levels with B vitamins (folic acid) on cardiovascular disease, cancer, and cause-specific mortality. Meta-analysis of 8 randomized trials involving 37 485 individuals. Arch Intern Med 2010; 170:1622-1631.
Colapinto, Cynthia K., O'Connor, Deborah L., Tremblay, Mark S.**Folate status of the population in the Canadian** Health Measures Survey. CMAJ 2010 0: cmaj.100568
Nilsson Torbjörn K., Yngve Agneta, Böttiger Anna K., et al. High Folate Intake Is Related to Better **Academic Achievement** in Swedish Adolescents. Pediatrics 2011; peds.2010-1481; published ahead of print July 11, 2011, doi:10.1542/peds.2010-1481
Koren G. **Folic acid and colorectal cancer**: unwarranted fears. Can Fam Physician. 2011 Aug;57(8):889-90.
Roth C, Magnus P, Schjølberg S, et al. **Folic** acid supplements in pregnancy and **severe language delay** in children. JAMA. 2011 Oct 12;306(14):1566-73.
Sadighi Z, Butler IJ, Koenig MK. Adult-Onset **Cerebral Folate Deficiency**. Arch Neurol. 2012 Feb 27.
Kennedy D, Koren G. Identifying women who might benefit from **higher doses of folic acid in pregnancy**. Can Fam Physician. 2012 Apr;58(4):394-7.

167. Mucha SM, deTineo M, Naclerio RM, Baroody FM. Comparison of **montelukast and pseudoephedrine** in the treatment of allergic rhinitis. Arch Otolaryngol Head Neck Surg. 2006 Feb;132(2):164-72.
168. Dodd SR, et al. In a systematic review, infrared ear thermometry for fever diagnosis in children finds poor sensitivity. J Clin Epidemiol. 2006 Apr;59(4):354-7. Epub 2006 Feb 20. (InfoPOEMs: Ear thermometry will only detect approximately two thirds of febrile children. Although it is fast and easy, the use of ear thermometry should be limited to those situations in which it doesn't matter if fever is present. (LOE = 1a-))
169. Poston L, et al. Vitamins in Pre-eclampsia (VIP) Trial Consortium. **Vitamin C and vitamin E** in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. Lancet. 2006 Apr 8;367(9517):1145-54. (InfoPOEMs: Supplementation with vitamins C and E during pregnancy does not reduce the risk of preeclampsia but does increase the risk of low birth weight. (LOE = 1b))
170. DHA Supplementation during Pregnancy & Lactation. Pharmacist's Letter Aug,2006.
171. Pharmacist's Letter. **Vitamin D and Calcium**: Not just for Bones anymore . July 2007.
172. InfoPOEM Feb08: Honey for cough. {A single dose of honey is effective at decreasing cough severity and sleep disruption in children with cough due to uncomplicated upper respiratory infections. Please remember that honey should never be given to infants because of the risk of botulism. (LOE = 2b).}
173. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM Jr. Effect of **honey**, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007 Dec;161(12):1140-6.
174. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database of Systematic Reviews 1999, Issue 1. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub3. {Acute cough is a common and troublesome symptom in people who suffer from acute upper respiratory tract infection (URTI). Many people self-prescribe over-the-counter (OTC) cough preparations and health practitioners often recommend their use for the initial treatment of cough. The results of this review suggest that there is no good evidence for or against the effectiveness of OTC medications in acute cough. The results of this review have to be interpreted with caution because the number of studies in each category of cough preparations was small. Many studies were of low quality and very different from each other, making evaluation of overall efficacy difficult. http://www.cochrane.org/reviews/en/ab001831.html }
Allan G. Michael, Korownyk Christina, Kolber Michael. Do cough suppressants or honey help pediatric cough? Can Fam Physician April 2011 57: 435.
Singh M, Singh M. Heated, humidified air for the common cold. Cochrane Database Syst Rev. 2011 May 11;5:CD001728.
Boulet LP, Côté G. Cough: etiology, evaluation and treatments. Update 2012. http://www.respiratoryguidelines.ca/sites/all/files/cough_toolkit.pdf (accessed January 9, 2012).
Oduwole O, Meremikwu MM, Oyo-Ita A, et al. Honey for acute cough in children. Cochrane Database Syst Rev. 2012 Mar 14;3:CD007094. Honey may be better than `no treatment` and diphenhydramine in the symptomatic relief of cough but not better than dextromethorphan
Bettiol S, Wang K, Thompson MJ, et al. Symptomatic treatment of the cough in whooping cough. Cochrane Database Syst Rev. 2012 May 16;5:CD003257. There is insufficient evidence to draw conclusions about the effectiveness of interventions for the cough in whooping cough.
175. Pynnonen MA, Mukerji SS, Kim HM, Adams ME, Terrell JE. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. Arch Otolaryngol Head Neck Surg. 2007 Nov;133(11):1115-20. Nasal irrigation (nasal washing) using a stream of normal saline, is more effective in decreasing general nasal or sinus symptoms than saline spray. The saline can be made at home, purchased as a kit, or adminstered using a neti pot. Direct your patients to an online source of video (eg, www.youtube.com) to see how it is administered. (LOE = 1b)
176. Aisen PS, Schneider LS, Sano M, et al. Alzheimer Disease Cooperative Study (ADCS). High-dose **B vitamin supplementation** and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA. 2008 Oct 15;300(15):1774-83. This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.
177. Health Canada Releases Decision on the Labelling of Cough and Cold Products for Children Dec 2008. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php
Ostroff C, Lee CE, McMeekin J. Unapproved prescription cough, cold, and allergy drug products: recent **US Food and Drug Administration** regulatory action on unapproved cough, cold, and allergy medications. Chest. 2011;140 (2): 295-300.
178. Shaikh U, Byrd RS, Auinger P. **Vitamin and mineral supplement use by children** and adolescents in the 1999-2004 National Health and Nutrition Examination Survey: relationship with nutrition, food security, physical activity, and health care access. Arch Pediatr Adolesc Med. 2009 Feb;163(2):150-7. A large number of US children and adolescents use vitamin and mineral supplements, which for most may not be medically indicated. Such supplements contribute significantly to total dietary intakes of vitamins and minerals, and studies of nutrition should include their assessment. Since vitamin and mineral supplement users report greater health care access, health care providers may be in a position to provide screening and counseling regarding dietary adequacy and indications for supplement use.
179. Rabago D, Zgierska A. **Saline nasal irrigation** for upper respiratory conditions. Am Fam Physician. 2009 Nov 15;80(10):1117-9.
180. Eekhof JA, Neven AK, Gransjean SP, Assendelft WJ. **Minor dermatologic ailments**: how good is the **evidence** for common treatments? J Fam Pract. 2009 Sep;58(9):E2.
181. Baldwin S, Odio MR , Haines SL, et al. Skin benefits from continuous topical administration of a zinc oxide/petrolatum formulation by a novel disposable **diaper**. J Eur Acad Dermatol Venereol. 2001;15(suppl 1):S5-S11.
182. Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective alpha1-adrenergic receptor agonist, **oxymetazoline**. Arch Dermatol. 2007 Nov;143(11):1369-71.
183. Vaidyanathan S, Williamson P, Clearie K, et al. Fluticasone Reverses Oxymetazoline Induced Tachyphylaxis of Response and Rebound Congestion. Am J Respir Crit Care Med. 2010 Mar 4.
Baroody FM, Brown D, Gavanescu L, et al. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. J Allergy Clin Immunol. 2011 Apr;127(4):927-34.
184. May/10 Novartis Consumer Health Canada Inc., in consultation with Health Canada, would like to bring to your attention important safety information concerning the differences between our product Maalox Multi Action liquid and other Maalox liquid products. Maalox Multi Action contains bismuth subsalicylate, which is chemically related to acetylsalicylic acid (ASA) and can lead to similar adverse effects, such as bleeding. Other Maalox liquid products are mineral based, contain different ingredients, and are indicated for different symptoms. However, due to the similarity in the name, label and package between **Maalox Multi Action** and other Maalox liquid products, they have the potential to be confused and result in medication incidents.
185. Paul, Ian M., Beiler, Jessica S., King, Tonya S., Cet al. **Vapor Rub**, Petrolatum, and No Treatment for Children With Nocturnal Cough and Cold Symptoms. Pediatrics 2010 0: peds.2010-1601.
186. FDA Mar/11 ISSUE: Tested samples of **Soladek** contained levels of vitamin A and vitamin D that were many times the recommended daily allowances for these vitamins.
187. Anti-infective Review Panel. **Anti-infective Guidelines for Community-acquired Infections**. Canadian - New-**2012**. Toronto: MUMS Guideline Clearinghouse. http://www.mumshealth.com/
188. CDC Dec/11 Two people in Louisiana have died this year from primary amebic meningoencephalitis after using tap water to irrigate their sinuses with neti pots, prompting the state's health department to remind consumers to use only distilled, sterile, or boiled water in **neti pots**. To avoid infections caused by ***Naegleria fowleri***, the CDC also recommends thoroughly rinsing neti pots after each use and letting the devices air dry completely.
189. Reamy BV, Bunt CW, Fletcher S. A diagnostic approach to **pruritus**. Am Fam Physician. 2011 Jul 15;84(2):195-202.
190. Chalasani N et al. The diagnosis and management of **non-alcoholic fatty liver disease (NAFLD)**: Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012 Jun; 55:2005. (Vitamin E: at a dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore can be recommended in this specific NAFLD population. (Note: some evidence exists that high-dose

TOP

vitamin E intake increases risks for all-cause mortality and prostate cancer.)
191.

Additional Pediatric Dosing Information for Physicians & Pharmacists (from 2008-2009 Formulary – The Hospital for Sick Children (Toronto, Canada)

Aluminum & Magnesium Hydroxide	infant	2.5-5ml po q1-2h
	child	5-15ml po after meals & qhs
Bisacodyl		0.3mg/kg/dose po 6-12h before desired effect
Dextromethorphan		1mg/kg/day (÷ q6-8h)
Dimenhydrinate		5mg/kg/day po/IV/IM/pr (÷ q6h)
Diphenhydramine		5mg/kg/day po/IV/IM (÷ q6h)
Docusate Sodium		5mg/kg/day po (÷ q6-8h or single daily dose)
Iron – Treatment		6mg Fe++/kg/day po OD (or ÷ TID)
Iron – Prophylaxis		0.5-2mg Fe++/kg/day given OD (or ÷BID-TID)
Lactulose - for Constipation		5-10ml/day po OD (double daily dose till stool produced)
Mineral Oil (Heavy)		1ml/kg/dose po HS (Avoid in <1 yr old)
Magnesium Hydroxide (MgOH) 80mg/ml (33mg elemental Magnesium/ml)		20-40 mg elemental Magnesium/kg/day po (÷ TID) –for treatment of hypomagnesemia
Polyethylene Glycol 3350 (Lax-A-Day)		Initial up to 1-1.5 g/kg/day x ≤3 days, then 0.4-1g/kg/day po (Max 17g/day)
Pseudoephedrine:	<2yrs	4mg/kg/day (÷ q6h prn)
Ranitidine – Treatment		5-8mg/kg/day po (÷ q8-12h) x8 weeks
Ranitidine – Maintenance		2.5-5mg/kg/day (given OD or divided bid)
Senna Syrup	2-5yrs	3-5ml/dose qhs
	6-12yrs	5-10ml/dose qhs
Senna Tablet	6-12yrs	1-2 tablets/dose po qhs
Sorbitol Syrup 70%		1.5-2ml/kg/dose po (Max 150ml/dose)

Taste of some medications – MgOH, docusate, lactulose - may be masked by giving with milk (chocolate mix), juice or infant formula.

TOP

References: ADHD Treatment Chart

[1] Virani A. Attention-Deficity Hyperactivity Disorder. Therapeutic Choices 5th Edition 2007.

[2] Micromedex 2010

[3] Lexi-comp 2009

[4] Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (**CADDRA**). *Canadian ADHD Practice Guidelines 2007-2008*. Toronto (ON): CADDRA; 2007.
Available at: http://www.caddra.ca/english/2007-08_guidelines_pdfs/2007-08_Caddra_Guidelines.pdf (accessed April 22, 2008).
Feldman M, Bélanger S; Canadian Paediatric Society, Community Paediatrics Committee, Psychosocial Paediatrics Committee. Extended-release medications for children and adolescents with attention-deficit hyperactivity disorder. Paediatr Child Health 2009;14(9):593-597. http://www.cps.ca/english/statements/CP/CP09-04.pdf
Canadian ADHD Resource Alliance. CADDRA Canadian ADHD practice guidelines third edition (2011). (accessed January 28, 2011). http://www.caddra.ca/cms4/pdfs/caddraGuidelines2011.pdf

[5] Pliszka SR *et al*. AACAP Official Action. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:894-921.

[6] Virani A. Advances in ADHD Treatment: an overview for pharmacists. Canadian Pharmacists Association Advancement 2005 Learning Series.

[7] Compendium of Pharmaceuticals and Specialties 2008. Available at: http://www.e-cps.ca

[8] The Medical Letter. Drugs for the Treatment of ADHD. Treatment Guidelines from the Medical Letter. Nov 2006. Vol. 4 (Issue 51).

[9] Briggs GG, Freeman RK, Sumner JY. Drugs in Pregnancy and Lactation 9th Edition. Williams & Wilkins, Baltimore, 2011.

[10] Compendium of Pharmaceuticals and Specialties 2010. Available at: http://www.e-cps.ca

[11] Sumner, C.R., et al., Placebo-controlled study of the effects of atomoxetine on bladder control in children with nocturnal enuresis. J Child Adolesc Psychopharmacol, 2006. 16(6): p. 699-711; Shatkin, J.P., Atomoxetine for the treatment of pediatric nocturnal enuresis. J Child Adolesc Psychopharmacol, 2004. 14(3): p. 443-7.

[12] Rappley M. Attention deficit-hyperactivity disorder. NEJM 2005; 352:165-173.

[13] Daviss W B et al. Clonidine for Attention-Deficit/Hyperactivity Disorder II. ECG Changes and Adverse Events Analysis. *J Am Acad Chid Adolesc Psychiatry* 2008;47:189-198.

[14] Banaschewski T, Roessner V, Dittman RW, Santosh PJ, Rothenberger A. Non-stimulant medication in the treatment of ADHD. *Eur Child Adolesc Psychiatry* 2004;13(Suppl 1):102–116.

[15] Einarson TR, Iskedjian M. Novel antipsychotics for patients with attention-deficit hyperactivity disorder: A systematic review. 17. 2001. Ottawa, Canadian Coordinating Office for Health Technology Assessment (CCOHTA).
Available at: http://cadth.ca/media/pdf/114_antipsychotic_adhd_tr_e.pdf, (accessed on May 7, 2008).

[16] Food and Drug Administration. Modafinil Serious Skin Reactions http://www.fda.gov/cder/dsn/2007_fall/postmarketing.htm#modafinil, (accessed on May 9, 2008).

[17] Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007;164:942-8.

[18] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4 th ed, Text Revision. Arlington, VA: American Psychiatric Press, Inc.; 2000.

[19] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4 th ed, Text Revision. Arlington, VA: American Psychiatric Press, Inc.; 2000.

[20] Hallowell EM, Ratey JJ. *Driven to Distraction*

[21] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4 th ed, Text Revision. Arlington, VA: American Psychiatric Press, Inc.; 2000.

[22] Hallowell EM, Ratey JJ. *Driven to Distraction*

[23] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4 th ed, Text Revision. Arlington, VA: American Psychiatric Press, Inc.; 2000.

[24] Conners CK, March JS, Frances A, Wells KC, Ross R. The Expert Consensus Guideline Series: Treatment of Attention-Deficit/Hyperactivity Disorder. *J Attention Disord*. 2001;4(suppl 1):7-128.

[25] Safren SA. Cognitive-behavioural approaches to ADHD Treatment in adulthood. *J Clin Psychiatry* 2006;67(suppl 8):46-50.

[26] **MTA** Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;56:1073-1086. (n=579; 14months)

[27] **MTA** Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;56:1073-1086.

[28] Abikoff H, Hechtman L, Klein RG, et al. Symptomatic improvement in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. *J Am Acad Child Adolesc Psychiatry* 2004;43:802-811.

[29] Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. Evid Rep Technol Assess (Summ). 1999 Nov: 1-341. Available at: http://www.ahcpr.gov (accessed May 1, 2008).

[30] Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE et al. Clinical relevance of the primary findings of the **MTA**: success rates based on severity of ADHD and ODD symptoms at the end of treatment. *J Am Acad Child Adolesc Psychiatry*. 2001;40:168-79.
Molina BS, Hinshaw SP, Swanson JM, et al. MTA Cooperative Group. The **MTA** at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry. 2009 May;48(5):484-500.

[31] Chan E. The role of complementary and alternative medicine in attention-deficit hyperactivity disorder. *J Dev Behav Pediatr* 2002;23(1 Suppl):S37-45.
Weber W, Vander Stoep A, McCarty RL, et al. Hypericum perforatum (St John's wort) for attention-deficit/hyperactivity disorder in children and adolescents: a randomized controlled trial. JAMA. 2008 Jun 11;299(22):2633-41. In this study, use of H. perforatum for treatment of ADHD over the course of 8 weeks did not improve symptoms.
Cala S, Crismon ML, Baumgartner J. A survey of herbal use in children with attention-deficit-hyperactivity disorder or depression. Pharmacotherapy. 2003 Feb;23(2):222-30. Herbal medicines were given most frequently for a behavioral condition, with ginkgo biloba, echinacea, and St. John's wort most prevalent.
Millichap JG, Yee MM. The **Diet Factor** in Attention-Deficit/Hyperactivity Disorder. Pediatrics. 2012 Jan 9. (**additive-free, oligoantigenic/elimination diets, iron/zinc/omega-3 supplements**)

[32] Villalaba L. Follow up review of AERS search identifying cases of sudden death occurring with drugs used for the treatment of attention deficit hyperactivity disorder ADHD.
Available at: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_07_01_safetyreview.pdf (accessed May 2, 2008).
Gould, Madelyn S., Walsh, B. Timothy, et al. Sudden Death and Use of Stimulant Medications in Youths. Am J Psychiatry 2009 0: appi.ajp.2009.09040472.
Schelleman H, Bilker WB, Kimmel SE, et al. Methylphenidate and risk of serious cardiovascular events in adults. Am J Psychiatry 2012; 169:178–18. (a 1.8 fold increase in sudden death or ventricular arrhythmia, but no dose response)

[33] Villalaba L. Follow up review of AERS search identifying cases of sudden death occurring with drugs used for the treatment of attention deficit hyperactivity disorder ADHD.
Available at: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_07_01_safetyreview.pdf (accessed May 2, 2008).
Schelleman Hedi, Bilker Warren B., Strom Brian L., et al. **Cardiovascular Events** and Death in Children Exposed and Unexposed to ADHD Agents. Pediatrics 2011; peds.2010-3371.
Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and **serious cardiovascular events in children and young adults**. N Engl J Med. 2011 Nov 17;365(20):1896-904.
Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of **serious cardiovascular events** in young and middle-aged adults. [published online December 12, 2011.] JAMA. doi:10.1001/JAMA.2011.1830.

[34] a) Health Canada. Attention Deficit Hyperactivity Disorder (ADHD) Drugs: Updated and Standardized Labelling Regarding Very Rare Cardiac-Related Adverse Events. May 2006.
Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/adhd-tdah_medic_hpc-cps_e.html (accessed May 2, 2008).
b) Hecthman L, Greenfield B. Long-term use of stimulants in children with attention deficit hyperactivity disorder. *Pediatr Drugs* 2003; 5:787-794.
c) Gould, Madelyn S., Walsh, B. Timothy, et al. **Sudden Death** and Use of Stimulant Medications in Youths. Am J Psychiatry 2009 0: appi.ajp.2009.09040472.
d) Winterstein, Almut Gertrud, Gerhard, Tobias, Shuster, Jonathan, Saidi, Arwa. **Cardiac Safety** of Methylphenidate Versus Amphetamine Salts in the Treatment of ADHD Pediatrics 2009 124: e75-e80.
e) Schelleman Hedi, Bilker Warren B., Strom Brian L., et al. **Cardiovascular Events** and Death in Children Exposed and Unexposed to ADHD Agents. Pediatrics 2011; peds.2010-3371.

TOP

[35] Vetter VL *et al.* Cardiovascular Monitoring of Children and Adolescents with heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. *Circulation*. Published online April 21, 2008. DOI: 10.1161/CIRCULATIONAHA.107.189473.
(Perrin JM, Friedman RA, Knilans TK; Black Box Working Group; Section on Cardiology and Cardiac Surgery. Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. Pediatrics. 2008 Aug;122(2):451-3.)
October 27, 2009 -- Electrocardiograms (ECG) are not recommended as a routine step prior to starting medications employed to control attention deficit/hyperactivity disorder (ADHD), according to a joint statement issued by the Canadian Cardiovascular Society (CCS), the Canadian Pediatric Society (CPS), and the Canadian Academy of Child and Adolescent Psychiatry (CACAP).
Warren AE, Hamilton RM, Bélanger SA, et al. Cardiac risk assessment before the use of stimulant medications in children and youth: A joint position statement by the Canadian Paediatric Society, the Canadian Cardiovascular Society, and the Canadian Academy of Child and Adolescent Psychiatry. Can J Cardiol. 2009 Nov;25(11):625-30.
Bélanger SA, Warren AE, Hamilton RM, et al. Cardiac risk assessment before the use of stimulant medications in children and youth. A joint position statement by the Canadian Paediatric Society, the Canadian Cardiovascular Society, and the Canadian Academy of Child and Adolescent Psychiatry. Paediatr Child Health 2009;14(9):579-585. http://www.cps.ca/English/statements/PP/CPS09-02.pdf
Thomas PE et al. Impact of the American Heart Association scientific statement on screening electrocardiograms and stimulant medications. Arch Pediatr Adolesc Med 2011 Feb; 165:166.
Vitiello B, Elliott GR, Swanson JM, et al. Blood Pressure and **Heart Rate** Over 10 Years in the Multimodal Treatment Study of Children With ADHD (**MTA**) . Am J Psychiatry. 2011 Sep 2.
Leslie LK, Rodday AM, Saunders TS et al. **Cardiac Screening** Prior to Stimulant Treatment of ADHD: A Survey of US-Based Pediatricians. Pediatrics. 2012 Jan 16.

[36] Polzer J, Bangs ME, Zhang S, Dellva MA, Tauscher-Visniewski S, Acharya N, et al. Meta-Analysis of Aggression or Hostility Events in Randomized, Controlled Clinical Trials of Atomoxetine for ADHD. *Biol Psychiatry* 2007;61:713–719.

[37] Poulton A. Growth on stimulant medication; clarifying the confusion: a review. *Arch Dis Child.* 2005;90;801-806.
Swanson J, Greenhill L, Wigal T, et al. Stimulant-related reductions of growth rates in the **PATS**. J Am Acad Child Adolesc Psychiatry. 2006 Nov;45(11):1304-13. For 95 children who remained on medication, annual growth rates were 20.3% less than expected for height (5.41 cm/yr-6.79 cm/yr=-1.38 cm/yr) and 55.2% for weight (1.07 kg/yr-2.39 kg/yr=-1.32 kg/yr).
Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of Stimulants on Height and Weight: A Review of the Literature. J Am Acad Child Adolesc Psychiatry. 2008 Jun 20. [Epub ahead of print] Treatment with stimulants in childhood modestly reduced expected height and weight. Although these effects attenuate over time and some data suggest that ultimate adult growth parameters are not affected, more work is needed to clarify the effects of continuous treatment from childhood to adulthood. Although physicians should monitor height, deficits in height and weight do not appear to be a clinical concern for most children treated with stimulants.

[38] **MTA** Cooperative Group. National Institute of Mental Health multimodal treatment study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics* 2004;113:762-769.

[39] **MTA** Cooperative Group. Effects of stimulant medication on **growth rates across 3 years** in the MTA follow-up. *J Am Acad Child Adolesc Psychiatry 2007*;46:1015-1027.

[40] Wilens TE, Lenard MD, Adler A, Adams J, Sgambati S, Rotrosen J, Sawtelle R, Utzinger L, Fusillo S. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry* 2008;47:21-31.

[41] Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics* 2003;111:179-185.

[42] Biederman J, Monuteaux MC, Spencer T, Wilens TE, MacPherson HA, Faraone SV. Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. *Am J Psychiatry* 2008;165, 597–603.
Biederman, Joseph, Monuteaux, Michael C., et al. Do **Stimulants Protect Against Psychiatric Disorders** in Youth With ADHD? A 10-Year Follow-up Study Pediatrics 2009 124: 71-78

[43] Mannuzza S, Klein RG, Truong NL, Moulton JL III, Roizen ER, Howell KH, Castellanos FX. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. *Am J Psychiatry* 2008;165: 604–609.
Wilens TE, Adamson J, Monuteaux MC, et al. Effect of prior stimulant treatment for attention-deficit/hyperactivity disorder on subsequent risk for cigarette smoking and alcohol and drug use disorders in adolescents. Arch Pediatr Adolesc Med. 2008 Oct;162(10):916-21. Stimulant therapy does not increase but rather reduces the risk for cigarette smoking and SUDs in adolescents with ADHD.
Setlik J, Bond GR, Ho M. Adolescent Prescription ADHD Medication Abuse Is Rising Along With Prescriptions for These Medications. Pediatrics. 2009 Aug 24.

[44] Dopheide JA, Theesen KA, Malkin M. Chapter 61: Childhood Disorders. In: DiPirio JT, Talbert RL, Hayes PE et al, eds. Pathophysiologic Approach. 6th Edition, McGraw-Hill Co., Inc., NY, 2005.

45 Humphreys C, Garcia-Bournissen F, Ito S, Koren G. Exposure to attention deficit hyperactivity disorder medications during pregnancy. Canadian Family Physician 2011; 53:1153-55.

Acknowledgements: Contributors & Reviewers: Dr. D. Quinn (SHR-Psyc), Dr. G. Ferguson (SHR-Psych), Dr. H. McKee (SHR), Dr. P. Butt (SHR), Dr. M. Jutras (SHR), Dr. T. Laubscher (SHR), Dr. F. Remillard (PharmD, College of Pharmacy, U of S.), C. Evans (BSP,PHD Cand) & the RxFiles Advisory Committee. Prepared by: Monica Lee PharmD Cand *L. Regier* BSP, BA, B. *Jensen* BSP

Additional ADHD Treatment References:

AACAP-Practice parameter on the use of psychotropic medication in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2009 Sep;48(9):961-73.
American Academy of Pediatrics (AAP): Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2011 Oct 16.
American Psychiatric Association Brochures: http://www.healthyminds.org/Functional-Library/brochures.aspx
Bateman B, et al. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. Arch Dis Child. 2004 Jun;89(6):506-11.
Bennett, Amanda E., Power, Thomas J., Eiraldi, Ricardo B., et al. Identifying Learning Problems in Children Evaluated for ADHD: The Academic Performance Questionnaire (APQ). Pediatrics 2009 124: e633-e639.
Biederman, Joseph, Monuteaux, Michael C., et al. Do Stimulants Protect Against Psychiatric Disorders in Youth With ADHD? A 10-Year Follow-up Study Pediatrics 2009 124: 71-78
Biederman J, Spencer TJ, Monuteaux MC, et al. A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. J Pediatr. 2010 Oct;157(4):635-40, 640.e1.
Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebo-controlled study of Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics. 2008 Jan;121(1):e73-e84.
Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. J Am Acad Child Adolesc Psychiatry. 2009 Sep;48(9):884-93.
Blumer JL, Findling RL, Shih WJ, et al. Controlled clinical trial of zolpidem failed to decrease latency for the treatment of insomnia associated with attention-deficit/ hyperactivity disorder in children 6 to 17 years of age. Pediatrics. 2009 May;123(5):e770-6.
Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Attention-Deficit/Hyperactivity Disorder and Urinary Metabolites of Organophosphate Pesticides. Pediatrics. 2010 May 17.
Brinkman WB, Sherman SN, Zmitrovich AR, et al. Parental angst making and revisiting decisions about treatment of attention-deficit/hyperactivity disorder. Pediatrics. 2009 Aug;124(2):580-9. Epub 2009 Jul 27.
Candy B Jones L Williams R Tookman A King M. Psychostimulants for depression. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006722. There is some evidence that in the short-term, PS reduce symptoms of depression. Whilst this reduction is statistically significant, the clinical significance is less clear.
Castells X, Ramos-Quiroga JA, Bosch R, et al. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD007813. DOI: 10.1002/14651858.CD007813.pub2.
Amphetamines improved short-term ADHD symptom severity. MAS also increased retention in treatment. Amphetamines were associated with higher attrition due to adverse events. The short study length and the restrictive inclusion criteria limit the external validity of these findings.
CDC June/10 About one fifth of US high school students reported ever having used prescription drugs not prescribed to them, such as OxyContin, Percocet, Vicodin, Adderall, Ritalin, and Xanax. The CDC reports the first assessment of such use within the National Youth Risk Behavior Survey. In addition, prescription drug abuse was more common among white than Hispanic or black students. The agency highlighted these findings from the 2009 survey in the context of an ongoing national trend toward higher rates of nonsuicide-related overdoses and deaths associated with prescription drug abuse. 2009 National Youth Risk Behavior Survey (Free PDF)CDC news release (Free) 2007 *MMWR* article on unintentional poisoning deaths (Free)
Conklin, Heather M., Lawford, Joanne, et al. Side Effects of Methylphenidate in Childhood Cancer Survivors: A Randomized Placebo-Controlled Trial Pediatrics 2009 124: 226-233.
Conklin HM., Reddick WE., Ashford J, et al. Long-Term Efficacy of Methylphenidate in Enhancing Attention Regulation, Social Skills, and Academic Abilities of Childhood Cancer Survivors. *JCO* JCO.2010.28.4026; published online on September 13, 2010.;
Connor DF, Findling RL, Kollins SH, et al. Effects of Guanfacine extended release on oppositional symptoms in children aged 6-12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. CNS Drugs. 2010 Sep 1;24(9):755-68.
Cooper WO, Habel LA, Sox CM, et al. **ADHD drugs and serious cardiovascular events** in children and young adults. N Engl J Med2011; DOI:10.1056/NEJMoa1110212.
Davidson MA. ADHD in adults: a review of the literature. J Atten Disord. 2008 May;11(6):628-41. Epub 2007 Dec 19.

TOP

Denchev P, Kaltman J, Schoenbaum M, et a. Modeled economic evaluation of alternative strategies to reduce sudden cardiac death among children treated for attention deficit/hyperactivity disorder. Circulation 2010; DOI:10.1161/CIRCULATIONAHA.109.901256.
Epstein JN, Langberg JM, Lichtenstein PK, et al. Use of an Internet Portal to Improve Community-Based Pediatric ADHD Care: A Cluster Randomized Trial. Pediatrics. 2011 Oct 17.
Espay AJ, Dwivedi AK, Payne M, et al. Methylphenidate for gait impairment in Parkinson disease: A randomized clinical trial. Neurology. 2011 Apr 5;76(14):1256-62. (lack of benefit)
Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry. 2009 Dec 29.
FDA is warning consumers and health care professionals about a counterfeit version of Teva Pharmaceutical Industries' Adderall 30 milligram tablets that is being purchased on the Internet. FDA's preliminary laboratory tests revealed that the counterfeit version of Teva's Adderall 30 mg tablets contained the wrong active ingredients. Adderall contains four active ingredients – dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate. Instead of these active ingredients, the counterfeit product contained tramadol and acetaminophen, which are ingredients in medicines used to treat acute pain.
Findling RL, Bukstein OG, et al. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2008 Jan;69(1):149-59.
Goldman RD. ADHD stimulants and their effect on height in children. Can Fam Physician. 2010 Feb;56(2):145-6.
Greenhill LL, Posner K, Vaughan BS, Kratochvil CJ. Attention deficit hyperactivity disorder in preschool children. Child Adolesc Psychiatr Clin N Am. 2008 Apr;17(2):347-66, ix.
Health Canada Oct/11, is notifying healthcare professionals, patients and their caregivers of important safety information from clinical studies regarding the risk of increased blood pressure and increased heart rate with the use of STRATTERA (atomoxetine).
Hudak ML, Tan RC et al. Neonatal Drug Withdrawal. Pediatrics. 2012 Jan 30.
Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of attention deficit hyperactivity disorder in primary care for school-age children and adolescents. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 Mar.
Keenan HT, Hall GC, Marshall SW. Early head injury and attention deficit hyperactivity disorder: retrospective cohort study. BMJ. 2008 Nov 6;337:a1984. doi: 10.1136/bmj.a1984. Medically attended head injury before 2 years of age does not seem to be causal in the development of attention deficit hyperactivity disorder. Medically attended injury before 2 years of age may be a marker for subsequent diagnosis of attention deficit hyperactivity disorder.
King S, Griffin S, Hodges Z, Weatherly H, et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technol Assess. 2006 Jul;10(23):iii-iv, xiii-146.
Kollins SH, Jain R, Brams M, et al. Clonidine Extended-Release Tablets as Add-on Therapy to Psychostimulants in Children and Adolescents With ADHD. Pediatrics. 2011 May 9.
Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry. 2010 Sep 3;10:67. ADHD often presents as an impairing lifelong condition in adults, yet it is currently underdiagnosed and treated in many European countries, leading to ineffective treatment and higher costs of illness. Expertise in diagnostic assessment and treatment of ADHD in adults must increase in psychiatry. Instruments for screening and diagnosis of ADHD in adults are available and appropriate treatments exist, although more research is needed in this age group.
Kratochvil, Christopher J., Vaughan, Brigette S., Stoner, Julie A., et al. A Double-Blind, Placebo-Controlled Study of Atomoxetine in Young Children With ADHD. Pediatrics 2011 127: e862-e868. (age 5-6yr n=101 over 8weeks)
Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N. Meditation therapies for attention-deficit/hyperactivity disorder (ADHD). Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD006507. As a result of the limited number of included studies, the small sample sizes and the high risk of bias, we are unable to draw any conclusions regarding the effectiveness of meditation therapy for ADHD.
Kurlan R. Clinical practice. Tourette's Syndrome. N Engl J Med. 2010 Dec 9;363(24):2332-8.
Larson K, Russ SA, Kahn RS, Halfon N. Patterns of Comorbidity, Functioning, and Service Use for US Children With ADHD, 2007. Pediatrics. 2011 Mar;127(3):462-70.
Lavigne JV, Dulcan MK, LeBailly SA, Binns HJ, Cummins TK, Jha P. Computer-assisted management of attention-deficit/hyperactivity disorder. Pediatrics. 2011 Jul;128(1):e46-53.
Leslie LK, Rodday AM, Saunders TS et al. Cardiac Screening Prior to Stimulant Treatment of ADHD: A Survey of US-Based Pediatricians. Pediatrics. 2012 Jan 16.
Lindstrom, Karolina, Lindblad, Frank, Hjern, Anders. Preterm Birth and Attention-Deficit/Hyperactivity Disorder in Schoolchildren. Pediatrics 2011 127: 858-865
Martinsson L, Hårdemark H, Eksborg S. Amphetamines for improving recovery after stroke. Cochrane Database Syst Rev 2007; 1: CD002090.
May DE, Kratochvil CJ. Attention-deficit hyperactivity disorder: recent advances in paediatric pharmacotherapy. Drugs. 2010;70(1):15-40.
McCann D, Barrett A, Cooper A, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. Lancet. 2007 Nov 3;370(9598):1560-7. Erratum in: Lancet. 2007 Nov 3;370(9598):1542.
Medical Letter: Treatment Guidelines – Drugs for Treatment of ADHD. May 2011.
Millichap JG, Yee MM. The Diet Factor in Attention-Deficit/Hyperactivity Disorder. Pediatrics. 2012 Jan 9.
Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. Cochrane Database Syst Rev. 2010 Jul 7;7:CD006704. There is increasing evidence that psychostimulant trials provide evidence for improvement in CRF at a clinically meaningful level. There is still a requirement for a large scale RCT of methylphenidate to confirm the preliminary results from this review. There is new safety data which indicates that the haemopoietic growth factors are associated with increased adverse outcomes. These drugs can no longer be recommended in the treatment of CRF. Readers of the first review should re-read the document in full.
Molina BS, Flory K, Hinshaw SP, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. J Am Acad Child Adolesc Psychiatry. 2007 Aug;46(8):1028-40.
Molina BS, Hinshaw SP, Swanson JM, et al. MTA Cooperative Group. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry. 2009 May;48(5):484-500.
Morrow RL, Garland J, Wright JM et al. Influence of relative age on diagnosis and treatment of attention-deficit/hyperactivity disorder in children. CMAJ. 2012 Mar 5. (effect in age 6-12)
Mosholder AD, Gelperin K, Hammad TA, et al. Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. Pediatrics. 2009 Feb;123(2):611-6.
National Initiative for Children's Healthcare Quality Tool Kit http://www.nichq.org/adhd.html
Newcorn JH, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008 Jun;165(6):721-30. Epub 2008 Feb 15. Response was significantly greater with osmotically released methylphenidate than with atomoxetine. One-third of patients who received methylphenidate followed by atomoxetine responded better to one or the other, suggesting that there may be preferential responders.
NICE Sept/08 Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12061 Kendall T, Taylor E, Perez A, Taylor C; Guideline Development Group. Diagnosis and management of attention-deficit/hyperactivity disorder in children, young people, and adults: summary of NICE guidance. BMJ. 2008 Sep 24;337:a1239. doi: 10.1136/bmj.a1239.
Nomura Y, Marks DJ, Grossman B, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring [Jan 2,12]. Arch Pediatr Adolesc Med.
Nuwwareh, S, Cimon, K, Ford, K and Weiss, M. Pharmacological and Nonpharmacological Therapies for Adults with Attention-Deficit/Hyperactivity Disorder: Systematic Review and Meta-analysis of Clinical Evidence [Internet] Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 (Rapid Response Report: Systematic Review). [cited 2011-09-21]. Available from:http://www.cadth.ca/media/pdf/htis/sept-2011/RE0026_ADHD_in%20adults_e.pdf
Pappadopulos E et al. Medication adherence in the MTA: Saliva methylphenidate samples versus parent report and mediating effect of concomitant behavioral treatment. J Am Acad Child Adolesc Psychiatry 2009 May; 48:501.
Pasker-de Jong PC, Zielhuis GA, van Gelder MM, et al. Antihypertensive treatment during pregnancy and functional development at primary school age in a historical cohort study. BJOG. 2010 May 12. Conclusions In this hypothesis-generating study, labetalol exposure in utero seemed to increase the risk of ADHD among children of primary school age, whereas prenatal methyldopa exposure might influence sleep.
Pelsser LM, Frankena K, Toorman J, et al. Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet. 2011 Feb 5;377(9764):494-503.
Post RE, Kurlansik SL. Diagnosis and Management of Attention-Deficit/Hyperactivity Disorder in Adults. Am Fam Physician. 2012 May 1;85(9):890-896.
Pringsheim T, Steeves T. Pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev. 2011;4:CD007990. Methylphenidate, clonidine, guanfacine, desipramine and atomoxetine appear to reduce ADHD symptoms in children with tics. Although stimulants have not been shown to worsen tics in most people with tic disorders, they may nonetheless exacerbate tics in individual cases. In these instances, treatment with alpha agonists or atomoxetine may be an alternative. Although there is evidence that desipramine is effective for both tics and ADHD in children, safety concerns will likely continue to limit its use in this population.
Proal E, Reiss PT, Klein RG, et al.. Brain Gray Matter Deficits at 33-Year Follow-up in Adults With Attention-Deficit/Hyperactivity Disorder Established in Childhood. Arch Gen Psychiatry. 2011 Nov;68(11):1122-34.
Rader R, McCauley L, Callen EC. Current strategies in the diagnosis and treatment of childhood attention-deficit/hyperactivity disorder. Am Fam Physician. 2009 Apr 15;79(8):657-65.
Roessner V, Plessen KJ, Rothenberger A, et al; ESSTS Guidelines Group. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry 2011;20:173-96.
Safren SA, Sprich S, Mimiaga MJ, et al. Cognitive behavioral therapy vs relaxation with educational support for medication-treated adults with ADHD and persistent symptoms: a randomized controlled trial. JAMA. 2010 Aug 25;304(8):875-80.
Schachter HM, Pham B, King J, Langford S, Moher D. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. CMAJ. 2001 Nov 27;165(11):147
Scheffler RM, Brown TT, Fulton BD, et al. Positive association between attention-deficit/ hyperactivity disorder medication use and academic achievement during elementary school. Pediatrics. 2009 May;123(5):1273-9.

TOP

Schelleman Hedi, Bilker Warren B., Strom Brian L., et al. Cardiovascular Events and Death in Children Exposed and Unexposed to ADHD Agents. Pediatrics 2011; peds.2010-3371.
Setlik J, Bond GR, Ho M. Adolescent Prescription ADHD Medication Abuse Is Rising Along With Prescriptions for These Medications. Pediatrics. 2009 Aug 24.
Shaw P, Sharp WS, Morrison M, et al. Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. Am J Psychiatry. 2009 Jan;166(1):58-63. Epub 2008 Sep 15. These findings show no evidence that psychostimulants were associated with slowing of overall growth of the cortical mantle.
Shram MJ, Quinn AM, Chen N, et al. Differences in the In Vitro and In Vivo Pharmacokinetic Profiles of Once-Daily Modified-Release Methylphenidate Formulations in Canada: Examination of Current Bioequivalence Criteria. Clin Ther. 2012 Apr 16.
Solanto MV, Marks DJ, Wasserstein J, Mitchell K, Abikoff H, Alvir JM, Kofman MD. Efficacy of Meta-Cognitive Therapy for Adult ADHD. Am J Psychiatry. 2010 Mar 15.
Stavrinos D, Biasini FJ, Fine PR, Hodgens JB, Khatri S, Mrug S, Schwebel DC. Mediating factors associated with pedestrian injury in children with attention-deficit/hyperactivity disorder. Pediatrics. 2011 Aug;128(2):296-302.
Storebo OJ, Skoog M, Damm D, et al. Social skills training for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 5 to 18 years. Cochrane Database Syst Rev. 2011 Dec 7;12:CD008223. The review suggests that there is little evidence to support or refute social skills training for adolescents with ADHD.
Szobot CM, Bukstein O. Attention deficit hyperactivity disorder and substance use disorders. Child Adolesc Psychiatr Clin N Am. 2008 Apr;17(2):309-23, viii.
Thomson A, Maltezos S, Paliokosta E, et al. Risperidone for attention-deficit hyperactivity disorder in people with intellectual disabilities. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD007011. There is no evidence from RCTs that risperidone is effective for the treatment of ADHD in people with ID. Prescribing in this population can only be based on open-label studies or extrapolation from research in people with autism and disruptive behaviour disorders; however these studies have not investigated people with ID separately so there are reservations regarding the applicability of these findings.
Vitiello B, Elliott GR, Swanson JM, et al. Blood Pressure and Heart Rate Over 10 Years in the Multimodal Treatment Study of Children With ADHD. Am J Psychiatry. 2011 Sep 2.
Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology. 2010 Aug 3;75(5):448-55.
Westover AN, Nakonezny PA. Aortic dissection in young adults who abuse amphetamines. Am Heart J 2010; 160:315-321.
Williams NM, Zaharieva I, Martin A, et al. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. Lancet. 2010 Oct 23;376(9750):1401-8.
Winhusen TM, Somoza EC, Brigham GS, et al. Impact of attention-deficit/hyperactivity disorder (ADHD) treatment on smoking cessation intervention in ADHD smokers: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010 May 18.
Winterstein, Almut Gertrud, Gerhard, Tobias, Shuster, Jonathan, Saidi, Arwa. Cardiac Safety of Methylphenidate Versus Amphetamine Salts in the Treatment of ADHD Pediatrics 2009 124: e75-e80.
Xu, Xiaohui, Cook, Robert L., Ilacqua, Vito A., et al. Racial Differences in the Effects of Postnatal Environmental Tobacco Smoke on Neurodevelopment. Pediatrics 2010 0: peds.2009-3589
Yoshimasu K, Barbaresi WJ, Colligan RC, et al. Written-Language Disorder Among Children With and Without ADHD in a Population-Based Birth Cohort. Pediatrics. 2011 Aug 22.
Zuvekas, Samuel H., Vitiello, Benedetto. Stimulant Medication Use in Children: A 12-Year Perspective. Am J Psychiatry 2011 0: appi.ajp.2011.11030387.

TOP

ANXIETY DISORDER MEDICATION Comparison Chart

[1] Therapeutic Choices 5th Edition, 2007

[2] Ontario Guidelines for the Management of Anxiety Disorders in Primary Care Fall 2000 1st Edition

[3] Micromedex 2011

[4] Treatment Guidelines: Drugs for Psychiatric Disorders. The Medical Letter: July, 2003; p. 69-76. (**Medical Letter** "Treatment Guidelines- Drugs for Psychiatric Disorders Vol 4 (Issue 46) **June 2006**.)

[5] Modell JG, Katholi CR, Modell JD, et. al. Comparative sexual side effects of bupropion fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997;61(4):476-87.

[6] Gonzalez M, Llorca G, Izquierdo JA, et.al. J Sex Marital Ther 1997;23(3):176-94.

[7] Which SSRI? Med Lett Drugs Ther. 2003 Nov 24;45(1170):93-95.

[8] Glassman AH, O'Connor CM, Califf RM, et al.; Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA. 2002 Aug 14;288(6):701-9.

[9] Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation 9th Ed. Williams & Wilkins, Media, Pennsilvania, 2011.

[10] Fricchione G. Clinical practice. Generalized anxiety disorder. N Engl J Med. 2004 Aug 12;351(7):675-82.

[11] Jenike MA. Clinical practice. Obsessive-compulsive disorder. N Engl J Med. 2004 Jan 15;350(3):259-65.

[12] Stein DJ. Obsessive-compulsive disorder. Lancet. 2002 Aug 3;360(9330):397-405.

[13] Grinage BD. Diagnosis and management of post-traumatic stress disorder. Am Fam Physician. 2003 Dec 15; 68(12): 2401-8.

[14] Asnis GM, Kohn SR, Henderson M, Brown NL. SSRIs versus Non-SSRIs in Post-traumatic Stress Disorder : An Update with Recommendations. Drugs. 2004;64(4):383-404.

Additional articles:

AACAP-Practice parameter for assessment & treatment of children & adolescents with **obsessive-compulsive disorder**. J Am Acad Child Adolesc Psych 2012 Jan;51(1):98-113.

Abramowitz JS, Taylor S, McKay D. **Obsessive-compulsive disorder**. Lancet. 2009 Aug 8;374(9688):491-9.

Ahmadi N, Hajsadeghi F, Mirshkarlo HB, et al. **Post-traumatic stress disorder**, **coronary atherosclerosis, and mortality**. Am J Cardiol. 2011 Jul 1;108(1):29-33.

Alderman CP, McCarthy LC, Condon JT, Marwood AC, Fuller JR. **Topiramate** in combat-related posttraumatic stress disorder. Ann Pharmacother. 2009 Apr;43(4):635-41. Epub 2009 Mar 31.

Alraies C, Keller E, Shaheen K et al. A 40-year-old woman with **excoriated skin lesions**. *Cleveland Clinic Journal of Medicine* 2011; 78(3):161-163; doi:10.3949/ccjm.78a.10042

American Psychiatric Association Brochures: http://www.healthyminds.org/Functional-Library/brochures.aspx

Amsterdam JD, Li Y, Soeller I, et al. A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (**chamomile**) extract therapy for generalized anxiety disorder. J Clin Psychopharmacol. 2009 Aug;29(4):378-82. n=61 over 8 weeks. This is the first controlled clinical trial of chamomile extract for GAD. The results suggest that chamomile may have modest anxiolytic activity in patients with mild to moderate GAD

Andersson E et al. **Internet-based cognitive behaviour therapy** for **obsessive–compulsive disorder**: A randomized controlled trial.Psychol Med 2012 Feb 21.

Anthierens, Sibyl, Pasteels, Inge, Habraken, Hilde, et al. Barriers to nonpharmacologic treatments for **stress, anxiety, and insomnia**: Family physicians' attitudes toward benzodiazepine prescribing. Can Fam Physician 2010 56: e398-406.

Andrus MR, Gilbert E. Treatment of Civilian and Combat-Related Posttraumatic Stress Disorder with **Topiramate**. Ahead of Print 1Nov2010, DOI 10.1345/aph.1P163. Ann Pharmacother ;44:1810-1816.

APA 2008 Practice Guideline for the Treatment of Patients With Panic Disorder http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=PanicDisorder_2e_PracticeGuideline

Aurora RN, Zak RS, Auerbach SH, et al. Standards of Practice Committee, American Academy of Sleep Medicine. Best practice guide for the treatment of **nightmare disorder in adults**. J Clin Sleep Med 2010 Aug 15;6(4):389-401. (prazosin, ? clonidine etc)

Baldwin DS, Huusom AK, Maehlum E. **Escitalopram** (5-20mg od) and **paroxetine** (20mg od) in the treatment of **generalised anxiety disorder**: Randomised, placebo-controlled, double-blind study. Br J Psychiatry. 2006 Sep;189:264-272. 12 weeks

Baldwin David, Woods Robert, Lawson Richard, et al. Efficacy of **drug treatments for generalised anxiety disorder**: systematic review and meta-analysis. BMJ 342:doi:10.1136/bmj.d1199 (Published 11 March 2011).

Berger W et al. Pharmacologic alternatives to antidepressants in **posttraumatic stress disorder**: systematic review. Prog Neuropsychopharmacol Biol Psyc. 2009Mar17;33(2):169-80.

Berlin HA, Koran LM, Jenike MA, et al. Double-blind, placebo-controlled trial of **topiramate** augmentation in treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2010 Aug 10.

Bisson JI. **Post-traumatic stress disorder**. BMJ. 2007 Apr 14;334(7597):789-793.

Blanco C, Heimberg RG, Schneier FR, et al. A placebo-controlled trial of **phenelzine**, cognitive behavioral group therapy, and their combination for social anxiety disorder. Arch Gen Psychiatry. 2010 Mar;67(3):286-95.

Bradwejn J, et al. **Venlafaxine** extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry. 2005 Oct;187:352-9.

Bruce SE, et al. Are **benzodiazepines** still the medication of choice for patients with panic disorder with or without agoraphobia? Am J Psychiatry. 2003 Aug;160(8):14

TOP

Bryant RA, Mastrodomenico J, Felmingham KL, et al. Treatment of acute stress disorder: a randomized controlled trial. Arch Gen Psychiatry. 2008 Jun;65(6):659-67. Exposure-based therapy leads to greater reduction in subsequent PTSD symptoms in patients with ASD when compared with cognitive restructuring. **Exposure** should be used in early intervention for people who are at high risk for developing PTSD.

Canadian Anxiety Guideline July 2006 (Panic, PTSD, GAD, SAD, OCD & specific phobias) (see also Pharmacist's Letter: Management of Anxiety Disorders Nov 2006) http://www.cpa-apc.org/Publications/CJP/supplements/july2006/anxiety_guidelines_2006.pdf

Comer JS, Mojtabai R, Olfson M: **National trends in the antipsychotic treatment** of psychiatric outpatients with anxiety disorders. Am J Psychiatry 2011; 168:1057–1065.

Connolly SD, Bernstein GA, Work Group on Quality Issues. Practice parameter for the assessment and treatment of **children and adolescents with anxiety disorders**. J Am Acad Child Adolesc Psychiatry 2007 Feb;46(2):267-83.

Gao K, Muzina D, Gajwani P, Calabrese JR. Efficacy of **typical and atypical antipsychotics** for primary and comorbid **anxiety** symptoms or disorders: a review. J Clin Psychiatry. 2006 Sep;67(9):1327-40. Except for trifluoperazine, there is no large, well-designed study of antipsychotics in the treatment of primary or comorbid anxiety symptoms or disorders. The efficacy of these agents in various anxiety conditions needs to be further investigated with large, well-designed comparison studies.

Dannon PN, et al. **Three year naturalistic** outcome study of **panic** disorder patients treated with **paroxetine**. BMC Psychiatry. 2004 Jun 11;4:16.

Davidson J, et al. Treatment of **Posttraumatic Stress Disorder With Venlafaxine** Extended Release: A 6-Month Randomized Controlled Trial. Arch Gen Psychiatry. 2006 Oct;63(10):1158-1165. n=329

Denys D, Mantione M, Figee M, et al. **Deep brain stimulation** of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. 2010 Oct;67(10):1061-8.

Depping AM, Komossa K, Kissling W, Leucht S. **Second-generation antipsychotics for anxiety** disorders. Cochrane Database Syst Rev. 2010;(12):CD008120.

Dhillon S, Scott LJ, Plosker GL. **Escitalopram**: a review of its use in the management of anxiety disorders. CNS Drugs. 2006;20(9):763-90. Nevertheless, available clinical data indicate that escitalopram is an effective first-line treatment option for the management of GAD, SAD, panic disorder and OCD.

Duffy M, Gillespie K, Clark DM. Post-traumatic stress disorder in the context of terrorism and other civil conflict in Northern Ireland: randomised controlled trial. BMJ. 2007 Jun 2;334(7604):1147. Epub 2007 May 11. Cognitive therapy is an effective treatment for post-traumatic stress disorder related to terrorism and other civil conflict.

Ertl V, Pfeiffer A, Schauer E, Elbert T, Neuner F. **Community-implemented trauma therapy** for former **child soldiers** in Northern Uganda: a randomized controlled trial. JAMA. 2011;306(5):503-512.

Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry. 2008 Mar;165(3):342-51. Epub 2008 Jan 2. Adults with the combination of both anxiety and depression are significantly more difficult to successfully treat than patients with depression alone. (LOE = 1b-)

FDA Aug/11 Antidepressant **citalopram** (*Celexa*, Forest Laboratories) should not be used in doses higher than 40 mg per day because of concerns that it can cause potentially fatal changes in heart rhythm (eg. ↑ QT)

Fenske JN, Schwenk TL. **Obsessive compulsive disorder**: diagnosis and management. Am Fam Physician. 2009 Aug 1;80(3):239-45.

Fortinguerra, Filomena, Clavenna, Antonio, Bonati, Maurizio. Psychotropic Drug Use During **Breastfeeding**: A Review of the Evidence. Pediatrics 2009 124: e547-e556.

Franklin ME, Sapyta J, Freeman JB, et al. **Cognitive behavior therapy augmentation of pharmacotherapy** in pediatric obsessive-compulsive disorder: the Pediatric OCD Treatment Study II (**POTS II**) randomized controlled trial. JAMA. 2011 Sep 21;306(11):1224-32.

Gale C, Davidson O. **Generalised anxiety disorder**. BMJ. 2007 Mar 17;334(7593):579-81.

Goddard AW, et al. Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry. 2001 Jul;58(7):681-6.

Grant JE, Odlaug BL, Kim SW. **N-acetylcysteine**, a glutamate modulator, in the treatment of **trichotillomania**: a double-blind, placebo-controlled study. Arch Gen Psychiatry. 2009 Jul;66(7):756-63.

Hanna GL, Hollander E, Nestadt G, Blair Simpson H. Treatment of patients with obsessive-compulsive disorder. In: *APA practice guidelines* [database online]. Arlington(VA): American Psychiatric Association (APA) 2007. Available: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=OCDPracticeGuidelineFinal05-04-07

Hawkins EJ, Malte CA, Imel ZE, et al. Prevalence and trends of benzodiazepine use among Veterans Affairs patients with **posttraumatic stress disorder**, 2003-2010. Drug Alcohol Depend. 2012 Feb 2.

Hedman E, Andersson G, Andersson E, et al. **Internet-based cognitive-behavioural therapy** for severe health anxiety: randomised controlled trial. Br J Psychiatry. 2011 Mar;198:230-6.

Hetrick SE, Purcell R, Garner B, et al. Combined **pharmacotherapy and psychological therapies** for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2010 Jul 7;7:CD007316. There is not enough evidence available to support or refute the effectiveness of combined psychological therapy and pharmacotherapy compared to either of these interventions alone.

Herring MP, O'Connor PJ, Dishman RK. The Effect of **Exercise** Training on Anxiety Symptoms Among Patients: A Systematic Review. Arch Intern Med. 2010;170(4):321-331.

Heyman I, Mataix-Cols D, Fineberg NA. **Obsessive-compulsive disorder**. BMJ. 2006 Aug 26;333(7565):424-9.

Hodgins S, De Brito SA, Chhabra P, et al. Anxiety disorders among offenders with **antisocial** personality disorders: a distinct subtype? Can J Psychiatry. 2010 Dec;55(12):784-91.

Hodgins David C, Stea Jonathan N, Grant Jon E. **Gambling disorders**. www.thelancet.com Published online May 19, 2011 DOI:10.1016/S0140-6736(10)62185-X

Holbrook TL et al. **Morphine** use after combat injury in Iraq and **post-traumatic stress disorder**. *N Engl J Med* 2010 Jan 14; 362:110.

Ipser JC, et al. Pharmacotherapy **augmentation** strategies in treatment-resistant **anxiety** disorders. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005473.

TOP

Kavan MG. Elsasser GN et al. **Generalized Anxiety Disorder**: Practical Assessment and Management. *Am Fam Physician.* 2009;79(9):785-791.
Komossa K, Depping AM, Meyer M, et al. **Second-generation antipsychotics for obsessive compulsive disorder**. Cochrane Database Syst Rev. 2010 Dec 8;12:CD008141.
Kampman M, et al. A randomized, double-blind, placebo-controlled study of the effects of adjunctive paroxetine in panic disorder patients unsuccessfully treated with cognitive-behavioral therapy alone. J Clin Psychiatry. 2002 Sep;63(9):772-7.
Katon WJ. Clinical practice. **Panic disorder**. N Engl J Med. 2006 Jun 1;354(22):2360-7.
Kimerling R, Ouimette P, Prins A, et al. Brief report: Utility of a short **screening** scale for DSM-IV **PTSD** in primary care. J Gen Intern Med. 2006 Jan;21(1):65-7.
Kinrys G, Wygant LE, Pardo TB, Melo M. Levetiracetam for treatment-refractory posttraumatic stress disorder. J Clin Psychiatry. 2006 Feb;67(2):211-4.
Kobak KA, Taylor LV, et al. **St John's wort** versus placebo in obsessive-compulsive disorder: results from a double-blind study. Int Clin Psychopharmacol. 2005;20(6):299-304.
Komossa K, Depping AM, Meyer M, et al. **Second-generation antipsychotics** for obsessive compulsive disorder. Cochrane Database Syst Rev. 2010 Dec 8;12:CD008141. The available data of the effects of olanzapine in OCD are too limited to draw any conclusions. There is some evidence that adding quetiapine or risperidone to antidepressants increases efficacy, but this must be weighed against less tolerability and limited data.
Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB; **American Psychiatric Association**. Practice guideline for the treatment of patients with **obsessive-compulsive** disorder. Am J Psychiatry. 2007 Jul;164(7 Suppl):5-53. http://www.psych.org/psych_pract/treatg/pg/OCDPracticeGuidelineFinal05-04-07.pdf
Kurlan R. Clinical practice. **Tourette's Syndrome**. N Engl J Med. 2010 Dec 9;363(24):2332-8.
Krystal JH et al. Adjunctive **risperidone** treatment for antidepressant-resistant symptoms of chronic military service–related PTSD: randomized trial. JAMA 2011 Aug 3. (ineffective)
Lenze EJ, Rollman BL, Shear MK, et al. **Escitalopram** for **older** adults with generalized anxiety disorder: a randomized controlled trial. JAMA. 2009 Jan 21;301(3):295-303. Older adults $^{n=177}$ with GAD randomized to escitalopram 10-20mg od had a higher cumulative response rate for improvement vs placebo over 12 weeks; however, response rates were not significantly different using an intention-to-treat analysis. Further study is required to assess efficacy and safety over longer treatment durations.
Lewis C, Pearce J, et al. Efficacy, cost-effectiveness and acceptability of **self-help** interventions for anxiety disorders: systematic review. Br J Psychiatry. 2012 Jan;200(1):15-21.
Mallet L, Polosan M, Jaafari N, et al. STOC Study Group. **Subthalamic nucleus stimulation** in severe obsessive-compulsive disorder. N Engl J Med. 2008 Nov 13;359(20):2121-34. These preliminary findings suggest that stimulation of the subthalamic nucleus may reduce the symptoms of severe forms of OCD but is associated with a substantial risk of serious adverse events.
Mac Donald CL et al. Detection of **blast-related traumatic brain injury** in U.S. military personnel. *N Engl J Med* 2011 Jun 2; 364:2091.
Machado A, Fernandez HH, Deogaonkar M. Deep brain stimulation: What can patients expect from it? (OCD) Cleveland Clinic Journal of Medicine 2012; 79(2):113-120.
Maher AR et al. Efficacy and comparative effectiveness of **atypical antipsychotic medications for off-label uses in adults**. JAMA 2011 Sep 28; 306:1359.
[For generalized anxiety disorder, a pooled analysis of 3 trials showed that quetiapine was associated with a 26% greater likelihood of a favorable response (defined as at least 50%improvement on the Hamilton Anxiety Scale) compared with placebo. For obsessivecompulsive disorder, risperidone was associated with a 3.9-fold greater likelihood of a favorable response (defined as a 25% improvement on the Yale-Brown Obsessive Compulsive Scale) compared with placebo.]
McFall Miles, Saxon Andrew J., Malte Carol A., et al. for the CSP 519 Study Team. Integrating **Tobacco Cessation** Into Mental Health Care for Posttraumatic Stress Disorder: A Randomized Controlled Trial. JAMA. 2010;304(22):2485-2493.doi:10.1001/jama.2010.1769.
Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in **panic** disorder with and without agoraphobia. J Affect Disord. 2005 Sep;88(1):27-45.
Montgomery SA, et al. Efficacy and safety of **pregabalin** in the treatment of generalized anxietydisorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry. 2006 May;67(5):771-82.
Miyasaka LS, Atallah AN, Soares BG. **Valerian** for anxiety disorders. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004515.
Murphy TK, et al. Clinical Factors Associated with Pediatric Autoimmune Neuropsychiatric Disorders Associated with **Streptococcal Infections**.(PANDAS) J Pediatr.2011Aug 24.
NICE Nov 2005 :Obsessive Compulsive Disorder: Core interventions in the treatment of **OCD** and body dysmorphic disorder http://www.nice.org.uk/page.aspx?o=cg031
NICE Mar 2005 Anxiety: Management of **post-traumatic stress disorder** in adults in primary, secondary and community care http://www.nice.org.uk/page.aspx?o=CG026
NICE Dec 2004 Anxiety: Management of anxiety (**panic disorder**, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community Care http://www.nice.org.uk/page.aspx?o=cg022fullguideline
NICE: National Institute for Health and Clinical Excellence. **Generalised anxiety disorder** and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. 2011. (Clinical guideline 113.) http://guidance.nice.org.uk/CG113 .
NICE: Pilling Stephen, Whittington Craig, Taylor Clare, et al. on behalf of the Guideline Development Group. Guidelines: Identification and care pathways for common mental health disorders: summary of NICE guidance. BMJ 2011;342:doi:10.1136/bmj.d2868 (Published 24 May 2011)
NICE: National Institute for Health and Clinical Excellence. Common mental health disorders: identification and **pathways to care**. (Clinical guideline CG123. 2011. http://guidance.nice.org.uk/CG123 .
Nemeroff CB. Use of atypical antipsychotics in refractory depression and anxiety. J Clin Psychiatry. 2005;66 Suppl 8:13-21.
Parmet Sharon, Lynm Cassio, Golub Robert M. JAMA **Patient Page Obsessive-Compulsive Disorder**. *JAMA*. 2011;305(18):1926.doi:10.1001/jama.305.18.1926
Pollack MH, et al. A double-blind study of the efficacy of **venlafaxine** extended-release, **paroxetine**, and placebo in the treatment of panic disorder. Depress Anxiety. 2006 Aug 7.
Rickels K, Etemad B, Khalid-Khan S, et al. Time to relapse after 6 and **12 months' treatment** of generalized anxiety disorder with venlafaxine extended release. Arch Gen Psychiatry. 2010 Dec;67(12):1274-81.
Saeed SA, et al. **Herbal and Dietary Supplements** for Treatment of Anxiety Disorders. American Family Physician 2007;76:549-56. Kava potential for mild to moderate anxiety.

TOP

Inositol modest effects with panic or OCD disorder. Not encourage St. John's wort, valerian, Sympathyl or passionflower.
Saeed SA, Antonacci DJ, Bloch RM. **Exercise, yoga, and meditation** for depressive and anxiety disorders. Am Fam Physician. 2010 Apr 15;81(8):981-6.
Sareen J, et al. **Disability and poor quality of life** associated with comorbid **anxiety** disorders and physical conditions. Arch Intern Med. 2006 Oct 23;166(19):2109-16. After adjusting for sociodemographic factors and other common mental disorders, the presence of an anxiety disorder was significantly associated with thyroid disease, respiratory disease, gastrointestinal disease, arthritis, migraine headaches, and allergic conditions (adjusted odds ratios between 1.39 and 2.12; P<.05).
Schneier FR. Clinical practice. Social anxiety disorder. N Engl J Med. 2006 Sep 7;355(10):1029-36.
Schneier FR, Neria Y, Pavlicova M, et al. **Combined Prolonged Exposure Therapy and Paroxetine for PTSD** Related to the World Trade Center Attack: A Randomized Controlled Trial. Am J Psychiatry. 2011 Sep 9.
Schnurr PP, et al. **Cognitive behavioral therapy for posttraumatic stress disorder** in women: a randomized controlled trial. JAMA. 2007 Feb 28;297(8):820-30.
Seng J, Low L, Sperlich M, et al. Post-traumatic stress disorder, **child abuse history, birthweight & gestational age**: a prospective cohort study. BJOG.2011Oct;118(11):1329-39.
Shalev AY et al. **Prevention of posttraumatic stress disorder** by early treatment: the Jerusalem Trauma Outreach and Prevention study. Arch Gen Psychiatry 2011 Oct 3
Simeon D, Stein DJ, Gross S, et al. A double-blind trial of **fluoxetine** in pathologic skin picking (**dermatotillomania**) . J Clin Psychiatry 1997; 58:341–347.
Smith TC, Ryan MA, Wingard DL, et al. Millennium Cohort Study Team. New onset and persistent symptoms of **post-traumatic stress disorder** self reported after deployment & combat exposures: prospective population based **US military** cohort study. BMJ. 2008 Feb 16;336(7640):366-71. Epub 2008 Jan 15. After adjustment for baseline characteristics, these prospective data indicate a threefold increase in new onset self reported post-traumatic stress disorder symptoms or diagnosis among deployed military personnel who reported combat exposures.
Smoller JW, Pollack MH, Wassertheil-Smoller S, Jackson RD, Oberman A, Wong ND, Sheps D. Panic Attacks and Risk of Incident **Cardiovascular Events** Among Postmenopausal Women in the Women's Health Initiative Observational Study. Arch Gen Psychiatry. 2007 Oct;64(10):1153-60. Panic attacks are relatively common among postmenopausal women and appear to be an independent risk factor for cardiovascular morbidity and mortality in older women.
Soomro G, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (**SSRIs**) versus placebo for obsessive compulsive disorder (OCD). **Cochrane** Database Syst Rev. 2008 Jan 23;(1):CD001765. SSRIs are more effective than placebo for OCD, at least in the short-term, although there are differences between the adverse effects of individual SSRI drugs.
Sousa MB, et al. A randomized clinical trial of **cognitive-behavioral group** therapy **and sertraline** in the treatment of **OCD**. J Clin Psychiatry. 2006 Jul;67(7):1133-9.
Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief **measure** for assessing **generalized anxiety disorder**: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092-7.
Stein D, et al. Pharmacotherapy for post traumatic stress disorder (**PTSD**). *The **Cochrane** Database of Systematic Reviews* 2006, Issue 1.
Stein MB, Goin MK, Pollack MH, Roy-Byrne P, Sareen J, Simon NM, et al. Treatment of patients with **panic disorder**. In: *APA practice guidelines* [database online]. Second Edition. Arlington(VA): American Psychiatric Association (**APA**) ; 2008. http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=PanicDisorder_2e_PracticeGuideline
Stein MB, Ravindran LN, Simon NM, et al. **Levetiracetam** in generalized social anxiety disorder: a double-blind, randomized controlled trial. J Clin Psychiatry. 2009 Dec 15.
Strawn JR, Keeshin BR, et al. Psychopharmacologic treatment of **posttraumatic stress disorder in children** and adolescents: a review. J Clin Psychiatry. 2010 Apr 20.
Swedo SE, et al. The pediatric autoimmune neuropsychiatric disorders associated with **streptococcal** infection (**PANDAS**) subgroup: separating fact from fiction. Pediatrics. 2004 Apr;113(4):907-11.
Rickels K, Pollack MH, Feltner DE, et al. **Pregabalin** for Treatment of Generalized Anxiety Disorder: A 4-Week, Multicenter, Double-blind, Placebo-Controlled Trial of Pregabalin and Alprazolam. Arch Gen Psychiatry. 2005 Sep;62(9):1022-1030.
Robb AS, Cueva JE, Sporn J, et al. **Sertraline treatment of children and adolescents** with posttraumatic stress disorder: a double-blind, placebo-controlled trial. J Child Adolesc Psychopharmacol. 2010 Dec;20(6):463-71. Sertraline was a generally safe treatment in children and adolescents with PTSD, but did not demonstrate efficacy when compared to placebo during 10 weeks of treatment.
Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Systematic review and meta-analysis of multiple-session early interventions following traumatic events. Am J Psychiatry. 2009 Mar;166(3):293-301. Epub 2009 Feb 2. Identification of a traumatic stress event within 3 months and treatment using trauma-focused **cognitive behavioral therapy** is beneficial for patients who meet DSM-IV criteria for the diagnosis of posttraumatic stress disorder (PTSD). It is uncertain whether individuals would benefit if they are symptomatic but do not meet diagnostic criteria for PTSD. (LOE = 1a-)
Roy-Byrne PP, et al. A randomized effectiveness trial of **cognitive-behavioral therapy & medication** for primary care panic disorder. Arch Gen Psych. 2005 Mar;62(3):290-8.
Roy-Byrne PP, Craske MG, Stein MB. **Panic** disorder. Lancet. 2006 Sep 16;368(9540):1023-32.
Roy-Byrne P; Craske MG.; Sullivan G et al; Delivery of Evidence-Based Treatment for Multiple **Anxiety Disorders** in Primary Care: A Randomized Controlled Trial JAMA. 2010;303(19):1921-1928.
Schwartz TL, Siddiqui UA, Raza S, et al. **Acamprosate** Calcium as Augmentation Therapy for Anxiety Disorders (December). Ann Pharmacother. 2010 Nov 9.
Seitz DP, Adunuri N, Gill SS, et al. **Antidepressants for agitation and psychosis** in dementia. Cochrane Database Syst Rev. 2011 Feb 16;2:CD008191. Currently there are relatively few studies of antidepressants for the treatment of agitation and psychosis in dementia. The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies. Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics.
Sher L, Braquehais MD, Casas M. **Posttraumatic stress disorder, depression, and suicide in veterans**. Cleveland Clinic Journal of Medicine 2012; 79(2):92-97.
Stanley MA et al. **Cognitive behavior therapy** for generalized anxiety disorder among older adults in primary care: A randomized clinical trial. JAMA 2009 Apr 8; 301:1460.

TOP

Stevens LM, Burke AE, Glass RM. JAMA **patient page. Posttraumatic stress disorder**. JAMA. 2007 Aug 1;298(5):588.
Taylor CB. **Panic disorder**. BMJ. 2006 Apr 22;332(7547):951-5.
Torpy JM, Burke AE, Golub RM. JAMA **patient page. Generalized Anxiety Disorder**. JAMA. 2011 Feb 2;305(5):522.
Torpy Janet M., Burke Alison E., Golub Robert M. JAMA Patient Page : **Panic Disorder**. JAMA. 2011;305(12):1256.doi:10.1001/jama.305.12.1256
Treatment of **posttraumatic stress disorder**: an **assessment of the evidence**. Washington (DC): National Academies Home; 2008.
Tyrer P, Baldwin D. **Generalised anxiety disorder**. Lancet. 2006 Dec 16;368(9553):2156-66.
Ursano RJ, Bell C, et al. Practice guideline for the treatment of patients with acute stress disorder and **posttraumatic stress disorder**. Am J Psychiatry.2004;161(11 Suppl):i-31.
VA/DoD: Management of Post-Traumatic Stress Working Group. VA/DoD clinical practice guideline for management of post-traumatic stress. Washington (DC): Veterans Health Administration, Department of Defense; 2010.
Van Ameringen M, Mancini C, et al. A randomized, double-blind, placebo-controlled trial of **olanzapine** in the treatment of **trichotillomania**. J Clin Psychiatry. 2010 Apr 20.
Walkup JT, Albano AM, et al. **Cognitive Behavioral Therapy, Sertraline, or a Combination** in Childhood Anxiety. (**CAMS**) N Engl J Med. 2008 Oct 30. [Epub ahead of print]
Wensel TM, Powe KW, Cates ME. **Pregabalin** for the treatment of generalized anxiety disorder. Ann Pharmacother. 2012 Mar;46(3):424-9.
Xue Y, Taub PR, Iqbal N et al. **Cardiac Biomarkers, Mortality**, and Post-Traumatic Stress Disorder in Military Veterans. Am J Cardiol. 2012 Feb 2.

TOP

BENZODIAZEPINE (BZ) COMPARISON CHART

[1] Micromedex 2011; Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation 9th Ed. Williams & Wilkins, Media, Pennsilvania, 2011.

[2] Nelson J, Chouinard G. Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal. Canadian Society for Clinical Pharmacology. Can J Clin Pharmacol. 1999 Summer;6(2):69-83.

[3] Rickels K, DeMartinis N, Rynn M, Mandos L. Pharmacologic strategies for discontinuing benzodiazepine treatment. J Clin Psychopharmacol. 1999 Dec;19(6 Suppl 2):12S-16S.

[4] Teboul E, Chouinard G. A guide to benzodiazepine selection. Part II: Clinical aspects. Can J Psychiatry. 1991 Feb;36(1):62-73.

[5] Teboul E, Chouinard G. A guide to benzodiazepine selection. Part I: Pharmacological aspects. Can J Psychiatry. 1990 Nov;35(8):700-10.

[6] Baillargeon L, Landreville P, Verreault R, et al. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. CMAJ. 2003 Nov 11;169(10):1015-1020. (Benzodiazepines: How they work & how to withdraw "aka The **Ashton Manual**" protocol http://www.benzo.org.uk/manual/index.htm)

[7] Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000 Jan 25;162(2):225-33.

[8] Wagner AK, Zhang F, Soumerai SB, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? Arch Intern Med. 2004 Jul 26;164(14):1567-72.

Additional references:

Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for **alcohol withdrawal**. Cochrane Database Syst Rev. 2010 Mar 17;3:CD005063. Benzodiazepines showed a protective benefit against alcohol withdrawal symptoms, in particular seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with other drugs. Nevertheless, no definite conclusions about the effectiveness and safety of benzodiazepines was possible, because of the heterogeneity of the trials both in interventions and the assessment of outcomes.

American College of Obstetricians and Gynecologists (**ACOG**). Use of psychiatric medications during **pregnancy and lactation**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 Apr. 20 p. (ACOG practice bulletin; no. 92). [245 references]

Anthierens, Sibyl, Pasteels, Inge, Habraken, Hilde, et al. Barriers to nonpharmacologic treatments for **stress, anxiety, and insomnia**: Family physicians' attitudes toward benzodiazepine prescribing. Can Fam Physician 2010 56: e398-406.

Aurora RN, Zak RS, Maganti RK, et al. Standards of Practice Committee, American Academy of Sleep Medicine. Best practice guide for the treatment of **REM sleep behavior** disorder (RBD). J Clin Sleep Med 2010 Feb 15;6(1):85-95.

Bell CM, Fischer HD, Gill SS, Zagorski B, Sykora K, Wodchis WP, Herrmann N, Bronskill SE, Lee PE, Anderson GM, Rochon PA. Initiation of benzodiazepines in the **elderly** after hospitalization. J Gen Intern Med. 2007 Jul;22(7):1024-9. Epub 2007 Apr 24. New benzodiazepine prescription after hospitalization occurs frequently in older adults and may result in chronic use. A systemic effort to address this risky practice should be considered.

Benzodiazepine Tapering Schedules & Information: http://www.benzo.org.uk/manual/index.htm

Bezchlibnyk-Butler Clinical Handbook of Psychotropic Drugs, 17th Ed. 2007.

Calderon-Margalit R, Qiu C, Ornoy A, et al. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. Am J Obstet Gynecol. 2009 Dec;201(6):579.e1-8. Epub 2009 Aug 18. Maternal use of benzodiazepine during pregnancy was associated with an increased risk of preterm delivery (adjusted odds ratio, 6.79; 95% confidence interval, 4.01-11.5) and with increased risks of low birthweight, low Apgar score, neonatal intensive care unit admissions, and respiratory distress syndrome. Selective serotonin receptor inhibitors were associated with preterm deliveries only among women who started treatment after the first trimester. Benzodiazepine was associated highly with preterm delivery and other adverse perinatal outcomes.

CDC June/10 About one fifth of US high school students reported ever having used prescription drugs not prescribed to them, such as OxyContin, Percocet, Vicodin, Adderall, Ritalin, and Xanax. The CDC reports the first assessment of such use within the National Youth Risk Behavior Survey. In addition, prescription drug abuse was more common among white than Hispanic or black students. The agency highlighted these findings from the 2009 survey in the context of an ongoing national trend toward higher rates of nonsuicide-related overdoses and deaths associated with prescription drug abuse. 2009 National Youth Risk Behavior Survey (Free PDF) CDC news release (Free) 2007 *MMWR* article on unintentional poisoning deaths (Free)

Chen Lori, Farrell Barbara, Ward Natalie, et al. **Discontinuing benzodiazepine therapy**: An interdisciplinary approach at a geriatric day hospital. Canadian Pharmacists Journal: November 2010, Vol. 143, No. 6, pp. 286-295.e1.

Clegg A, Young JB. Which medications to avoid in people at **risk of delirium**: a systematic review. Age Ageing. 2011 Jan;40(1):23-9. (opiates and benzos)

Crockford D, White WD, Campbell B. **Gabapentin** use in benzodiazepine dependence and detoxification. Can J Psychiatry. 2001 Apr;46(3):287.

Cunningham CM, Hanley GE, Morgan S. Patterns in the **use of benzodiazepines in British Columbia**: Examining the impact of increasing research and guideline cautions against long-term use. Health Policy. 2010 Apr 20.

Denis C, Fatseas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005194. The results of this systematic review point to the potential value of carbamazepine as an effective intervention for benzodiazepine gradual taper discontinuation. Carbamazepine has shown rather modest benefit in reducing withdrawal severity, although it did significantly improve drug-free outcome. Larger controlled studies are needed to confirm these benefits, to assess adverse effects and to identify when its clinical use might be most indicated. Other suggested treatment approaches to benzodiazepine discontinuation management should be explored (antidepressants, benzodiazepine receptors modulator).

de Lusignan S, Buxton N, Kent A. **New patient asking for a benzodiazepine** prescription. BMJ. 2008 Aug 28;337:a658. doi: 10.1136/bmj.a658.

Ensrud KE, et al.; Study of Osteoporotic Fractures Research Group. CNS-active medications and **risk for falls** in older women. J Am Geriatr Soc. 2002 Oct;50(10):1629-

TOP

Fortinguerra, Filomena, Clavenna, Antonio, Bonati, Maurizio. Psychotropic Drug Use During **Breastfeeding**: A Review of the Evidence. Pediatrics 2009 124: e547-e556.
Gorevski E, Bian B, Kelton CM, et al. **Utilization, Spending, and Price Trends** for Benzodiazepines in the US Medicaid Program: 1991-2009. Ann Pharmacother. 2012 Apr;46(4):503-12.
Gray SL, et al. Benzodiazepine use and **physical disability** in community-dwelling older adults. J Am Geriatr Soc. 2006 Feb;54(2):224-30.
Hawkins EJ, Malte CA, Imel ZE, et al. Prevalence and trends of **benzodiazepine use among Veterans Affairs** patients with posttraumatic stress disorder, 2003-2010. Drug Alcohol Depend. 2012 Feb 2.
Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well Dietary Supplement** because a sample has been found to contain **estazolam.**
Health Canada Dec/06 is advising consumers not to use a product called **Eden Herbal Formulations Sleep Ease Dietary Supplement**, because it was found to contain an undeclared drug estazolam http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_127_e.html
Health Canada Feb/07 Health Canada is advising consumers not to use a product called **Sleepees**, because it was found to contain an undeclared drug **estazolam**, which can be habit-forming when used for as little as a few months. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_16_e.html
Health Canada April/07is advising consumers not to use a product called **Eden Herbal Formulations Serenity Pills II** because it contains the undeclared drug **estazolam**.
Health Canada June/07 is advising consumers not to use **Optimum Health Care SleePlus TCM** or **BYL SleePlus**, because the products contain the undeclared drug **clonazepam.**
Health Canada Aug/10 says **Fulda Unitang Herbs Sleep Plus**, an unauthorized product promoted as an herbal sleep aid, has been found to contain high levels of estazolam.
Hemmelgarn B, et al. Benzodiazepine use and the risk of **motor vehicle crash** in the elderly. JAMA. 1997 Jul 2;278(1):27-31. CONCLUSIONS: Brief or extended periods of exposure to long-half-life benzodiazepines are associated with an increased risk of motor vehicle crash involvement in the elderly population. There is no such elevated risk for short-half-life benzodiazepines.
Herrmann N, Gauthier S. **Diagnosis and treatment of dementia**: 6. Management of severe Alzheimer disease. CMAJ 2008;179(12):1279-87.
Hogan DB, Maxwell CJ, Fung TS, Ebly EM; Canadian Study of Health and Aging. Prevalence and potential consequences of benzodiazepine use in senior citizens: results from the Canadian Study of Health and Aging. Can J Clin Pharmacol. 2003 Summer;10(2):72-7.
Hudak ML, Tan RC et al. **Neonatal Drug Withdrawal**. Pediatrics. 2012 Jan 30.
Kelly LE, Poon S, Madadi P, Koren G. **Neonatal Benzodiazepines Exposure during Breastfeeding**. J Pediatr. 2012 Apr 13.
Lawlor DA, Patel R, Ebrahim S. Association between **falls** in elderly women and chronic diseases and drug use: cross sectional study. BMJ. 2003 Sep 27;327(7417):712-7.
Lonergan E, Luxenberg J, Areosa Sastre A, Wyller TB. Benzodiazepines for delirium. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006379. No adequately controlled trials could be found to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients, and at this time benzodiazepines cannot be recommended for the control of this condition. Because of the scarcity of trials with randomization of patients, placebo control, and adequate concealment of allocation of subjects, it is clear that further research is required to determine the role of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.
Mayo-Smith MF, Beecher LH, Fischer TL, et al. Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med. 2004 Jul 12;164(13):1405-12.
McCord J, Jneid H, et al**.** Management of **Cocaine-Associated Chest Pain** and Myocardial Infarction. A Scientific Statement From the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation online Mar 17,2008.
McIntosh B, Clark M, Spry C. *Benzodiazepines in Older Adults: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines* [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011 (Rapid Response Report: Peer-Reviewed Summary with Critical Appraisal). [cited 2011-01-06]. Available from: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/2773.
Moncada LV. Management of **falls in older persons**: a prescription for prevention. Am Fam Physician. 2011 Dec 1;84(11):1267-76.
Morin CM, et al. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. Am J Psychiatry. 2004 Feb;161(2):332-42.
Mugunthan K, McGuire T, Glasziou P.. **Minimal interventions** to decrease long-term use of benzodiazepines in primary care: a systematic review and meta-analysis. Br J Gen Pract. 2011 Sept; 61.
Ntais C, Pakos E, Kyzas P, Ioannidis J. Benzodiazepines for alcohol withdrawal. **Cochrane Database Syst Rev. 2005** Jul 20;(3):CD005063.
Parker AJ, Marshall EJ, Ball DM. Diagnosis and management of **alcohol use disorders**. BMJ. 2008 Mar 1;336(7642):496-501.
Rapoport MJ, Lanctôt KL, Streiner DL, et al. Benzodiazepine use and **driving**: a meta-analysis. J Clin Psychiatry. 2009 Apr 21;70(5):663-73.
Rickels K, et al. **Imipramine** and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. Am J Psychiatry. 2000 Dec;157(12):1973-9.
Substance Abuse and Mental Health Services Administration **SAMHSA**, Center for Behavioral Health Quality and Statistics. (Nov 3, 2011). The DAWN Report: **Drug-Related Emergency Department Visits Attributed to Intentional Poisoning**. Rockville, MD. http://oas.samhsa.gov/2k11/DAWN040/WEB_DAWN_040.htm
Tamblyn R, Abrahamowicz M, du Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. J Am Geriatr Soc. 2005 Feb;53(2):233-41. CONCLUSION: The risk of injury varied by benzodiazepine, independent of half-life, as did the risk associated with increasing dosage for individual products. Higher doses of oxazepam, flurazepam, and chlordiazepoxide are associated with the greatest risk of injury in the elderly.
Tiihonen J, Suokas JT, et al. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and **mortality in schizophrenia**. Arch Gen Psychiatry. 2012 May;69(5):476-83.
Treatment Guidelines from the Medical Letter. Pharmaceutical Drug Overdose. Sept 2006. (Benzodiazepines: flumazenil treatment)
U.S. Substance Abuse and Mental Health Services Administration, news release, June 9, 2011http://www.samhsa.gov/newsroom/advisories/1106082530.aspx Admissions fo

TOP

benzodiazepine abuse nearly tripled in the United States between 1998 and 2008, while overall admissions for substance abuse rose only 11 percent, according to a government study released Thursday. Benzodiazepines -- a class of drugs prescribed to treat anxiety, insomnia and seizure disorders -- include Valium, Halcion, Xanax, Ativan and Librium. Abuse of benzodiazepines, which were introduced in the 1950s to replace barbiturates, can lead to addiction, injury and death.The Substance Abuse and Mental Health Services Administration (SAMHSA) study found that admissions for treatment of benzodiazepine abuse among patients 12 and older rose from 22,400 in 1998 to 60,200 a decade later. Benzodiazepine-related admissions accounted for 3.2 percent of all substance abuse admissions in 2008, compared with 1.3 percent in 1998.

van der Hooft CS, Schoofs MW,et al. Inappropriate benzodiazepine use in older adults and the risk of fracture. Br J Clin Pharmacol. 2008 Aug;66(2):276-82. Epub 2008 May 6. These findings suggest that inappropriate benzodiazepine use according to the Beers criteria is not associated with increased risk of fracture. Daily dose and longer duration of use (>14 days) is associated with higher risk of fracture, irrespective of the type of benzodiazepine prescribed.

Vinkers DJ, Gussekloo J, van der Mast RC, et al. Benzodiazepine use and risk of mortality in individuals aged 85 years or older. JAMA. 2003 Dec 10;290(22):2942-3.

Voshaar RC, Couvée JE, van Balkom AJ, Mulder PG, Zitman FG. Strategies for **discontinuing long-term** benzodiazepine use: meta-analysis. Br J Psychiatry. 2006 Sep;189:213-20.

Wagner AK, et al. Benzodiazepine use and **hip fractures** in the elderly: who is at greatest risk? Arch Intern Med. 2004 Jul 26;164(14):1567-72.

Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry. 2001 Jun;158(6):892-8. Even at modest doses, including some low doses currently advocated in prescribing guidelines for older patients, treatment with benzodiazepines appears to increase the risk of hip fracture. Patients appear to be particularly vulnerable immediately after initiating therapy and after more than 1 month of continuous use. Benzodiazepines with shorter half-lives appear to be no safer than longer half-life agents.

Weinberg JA, Magnotti LJ, Fischer PE, et al. Comparison of intravenous ethanol versus diazepam for alcohol withdrawal prophylaxis in the trauma ICU: results of a randomized trial. J Trauma. 2008 Jan;64(1):99-104. Concerning the prophylaxis of AWS, intravenous ethanol offers no advantage over diazepam with respect to efficacy or adverse sedative effects. The purported benefit of intravenous ethanol as a prophylactic agent against AWS was not evident.

Woolcott John C.; Richardson Kathryn J.; et al. Meta-analysis of the Impact of 9 Medication Classes on **Falls** in Elderly Persons. Arch Intern Med. 2009;169(21):1952-1960.

TOP

MOOD STABILIZERS & ADJUNCT AGENTS

Other Sources:

AAN-Practice Parameter Update: Managament issues for women with epilepsy – focus on **pregnancy** (Valproate should be avoided during the first trimester of pregnancy. Among the other findings: Women with epilepsy who take antiepileptic drugs have twice the risk for delivering babies with Apgar scores under 7. Valproate is associated with increased risk for congenital malformations. Avoiding valproate, phenobarbital, and phenytoin during pregnancy may reduce the risk for poor cognitive outcomes (all are class D drugs), while carbamazepine (class C) "probably does not produce cognitive impairments." Monotherapy for epilepsy is preferable to polytherapy, if possible, to reduce poor cognitive outcomes. http://www.aan.com/globals/axon/assets/5476.pdf

Aggarwal SP, Zinman L, Simpson E et al; Northeast and Canadian Amyotrophic Lateral Sclerosis consortia. Safety and efficacy of **lithium** in combination with riluzole for treatment of **amyotrophic lateral sclerosis**: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010 May;9(5):481-8. Epub 2010 Apr 1.

American College of Obstetricians and Gynecologists (**ACOG**). Use of psychiatric medications during **pregnancy and lactation**. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 Apr. 20 p. (ACOG practice bulletin; no. 92). [245 references]

American Psychiatric Association Brochures: http://www.healthyminds.org/Functional-Library/brochures.aspx

Amsterdam JD and Shults J. Efficacy and safety of long-term **fluoxetine versus lithium monotherapy of bipolar II disorder**: A randomized, double-blind, placebo-substitution study. Am J Psychiatry. 2010 Jul;167(7):792-800.

Angstman K, Rasmussen NH. **Personality disorders**: review and clinical application in daily practice. Am Fam Physician. 2011 Dec 1;84(11):1253-60.

Artama M, Auvinen A, Raudaskoski T, et al. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology. 2005 Jun 14;64(11):1874-8.
CONCLUSION: Excess risk was confined to patients using **valproate** during pregnancy. The risk for malformations was not elevated in offspring of mothers using carbamazepine, oxcarbazepine, or phenytoin (as monotherapy or polytherapy without valproate).

BALANCE investigators and collaborators. **Lithium plus valproate** combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2009; published online Dec 23. DOI:10.1016/S0140-6736(09)61828-6.

Bates DE, Herman RJ. **Carbamazepine** toxicity induced by **lopinavir/ritonavir** and nelfinavir. Ann Pharmacother. 2006 Jun;40(6):1190-5. Epub 2006 May 23.

Bauer M, Ritter P, Grunze H, Pfennig A. Treatment options for **acute depression in bipolar disorder**. Bipolar Disord. 2012 May;14 Suppl 2:37-50.

Bekkelund SI, Lilleng H, Tonseth S. **Gabapentin** may cause reversible **visual field constriction**. BMJ. 2006 May 20;332(7551):1193.

Bendz H, Schön S, Attman PO, Aurell M. **Renal failure** occurs in chronic **lithium** treatment but is uncommon. Kidney Int. 2009 Nov 25. [Epub ahead of print]

Berk M, Dodd S. Efficacy of **atypical antipsychotics** in bipolar disorder. **Drugs. 2005**;65(2):257-69.

Beynon S, Soares-Weiser K, et al. **Psychosocial interventions** for the prevention of relapse in bipolar disorder: systematic review of controlled trials. Br J Psychiatry. 2008 Jan;192(1):5-11.**Cognitive behavioral therapy** and group **psychoeducation** reduce the risk of relapse in patients with stable bipolar disorder. (LOE = 1a)

Bezchlibnyk-Butler Clinical Handbook of Psychotropic Drugs, 17th Ed. 2007.

Bialer M, et al. Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. 2004;43(12):763-80.

Bond DJ, Noronha MM, Kauer-Sant'anna M, Lam RW, Yatham LN. Antidepressant-Associated Mood Elevations in Bipolar II Disorder Compared With Bipolar I Disorder and Major Depressive Disorder: A Systematic Review and Meta-Analysis. J Clin Psychiatry. 2008 Jul 15:e1-e13. [Epub ahead of print] The risk of antidepressant-associated mood elevations in bipolar II disorder is intermediate between that in bipolar I disorder and MDD.

Bowden CL, et al. Impact of **lamotrigine** and **lithium** on **weight** in obese and nonobese patients with bipolar I disorder. Am J Psychiatry. 2006 Jul;163(7):1199-201. (InfoPOEMs: Obese patients with bipolar disorder may be more likely to maintain weight or lose weight while taking long-term lamotrigine (Lamictal) than while taking lithium. No significant differences in weight occurred among nonobese patients treated with either medication. Because of concerns about cost and about the quality of these 2 trials, it makes sense to begin treatment with lithium and consider changing to lamotrigine only if individuals begin to gain weight. (LOE = 2b))

Bowden CL, et al. A randomized, double-blind, placebo-controlled study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry. 2005 Jan;66(1):111-21.

Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. Arch Gen Psychiatry. 2000 May;57(5):481-9.

Bowden CL, et al.; Lamictal 606 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry. 2003 Apr;60(4):392-400. Erratum in: Arch Gen Psychiatry. 2004 Jul;61(7):680.

Brooks JO 3rd, Goldberg JF, Ketter TA, et al. Safety and tolerability associated with **second-generation antipsychotic** polytherapy in bipolar disorder: findings from the systematic Treatment enhancement program for bipolar disorder. J Clin Psychiatry. 2010 Sep 7. [Epub ahead of print]

Brown EB, et al. A 7-week, randomized, double-blind trial of **olanzapine/fluoxetine combination versus lamotrigine** in the treatment of bipolar I depression. J Clin Psychiatry. 2006 Jul;67(7):1025-33.

Calabrese JR, Huffman RF, White RL, et al. **Lamotrigine** in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disord.2008 Mar;10(2):323-33. Lamotrigine monotherapy did not demonstrate efficacy in the acute treatment of bipolar depression in four out of five placebo-controlled clinical studies. Lamotrigine was well tolerated in the acute treatment of bipolar depression.

Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of **lamotrigine monotherapy in outpatients with bipolar I depression**. Lamictal 602 Study Group. J Clin Psychiatry. 1999 Feb;60(2):79-88.

TOP

Calabrese JR, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry. 2005 Jul;162(7):1351-60.(InfoPOEMs: In this short-term study, quetiapine was more effective than placebo in treating patients with a bipolar I or II disorder experiencing a major depressive episode. Because of the risk of extrapyramidal side effects, however, other treatment agents should be considered first. (LOE = 1b))

Calabrese JR, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry. 2003 Sep;64(9):1013-24.

Calabrese JR, et al. A 20-month, double-blind, maintenance trial of **lithium versus divalproex** in rapid-cycling bipolar disorder. Am J Psychiatry. 2005 Nov;162(11):2152-61.

Chen Pei, Lin Juei-Jueng, et al. Taiwan SJS Consortium. Carbamazepine-Induced Toxic Effects and **HLA-B*1502** Screening in Taiwan. N Engl J Med 2011; 364:1126-1133.

Chiesa A, Chierzi F, De Ronchi D, Serretti A. **Quetiapine for bipolar depression**: a systematic review and meta-analysis. Int Clin Psychopharmacol. 2011 Nov 19.

Chiu, John F., Chokka, Pratap R. **Prevalence of Bipolar Disorder symptoms in Primary Care** (ProBiD-PC): A Canadian study. Can Fam Physician 2011 57: e58-67.

Cipriani A, Pretty H, Hawton K, Geddes JR. **Lithium** in the prevention of **suicidal** behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry. 2005 Oct;162(10):1805-19. CONCLUSIONS: Lithium is effective in the prevention of suicide, deliberate self-harm, and death from all causes in patients with mood disorders.

Cipriani A, Rendell JM, Geddes J. **Olanzapine** in long-term treatment for bipolar disorder. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD004367. Though based on a limited amount of information, there is evidence that olanzapine may prevent further mood episodes in patients who have responded to olanzapine during an index manic or mixed episode and who have not previously had a satisfactory response to lithium or valproate. However, notwithstanding these positive results, the current evidence is stronger for lithium as first line maintenance treatment of bipolar disorder.

Cipriani A, Barbui C, et al. Comparative efficacy and acceptability of **anti-manic drugs in acute mania**: a multiple-treatments meta-analysis. Lancet 2011; published online Aug 17. Overall, antipsychotic drugs were significantly more effective than mood stabilisers. Risperidone, olanzapine, and haloperidol should be considered as among the best of the available options for the treatment of manic episodes. But see editorial: Berk M, Malhi GS. Should antipsychotics take pole position in mania treatment? Lancet. 2011 Aug 16.

Clinical Handbook of Psychotropic Drugs 13th Edition 2003, Bezchlibnyk-Butler,Jeffries

Cunnington M, et al; International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. Neurology. 2005 Mar 22;64(6):955-60.

Cutler AJ, Datto C, Nordenhem A, et al. **Extended-Release Quetiapine** as Monotherapy for the Treatment of Adults With Acute Mania: A Randomized, Double-Blind, 3-Week Trial. Clin Ther. 2011 Nov 3.

de Haan GJ, Edelbroek P, Segers J, et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology. 2004 Aug 10;63(3):571-3.

Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT; EUROCAT Antiepileptic Drug Working Group. Does **lamotrigine** use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology. 2008 Sep 2;71(10):714-22. Epub 2008 Jul 23. We find no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine (LTG) monotherapy. Our study is not designed to assess whether there is a generalized increased risk of malformations with LTG exposure.

Doose DR, et al. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. Epilepsia. 2003 Apr;44(4):540-9.

Drug Information Handbook 10th Edition 2002-2003.

Drugs in Pregnancy & Lactation 9th Edition 2011.

Eberhard-Gran M, Eskild A, Opjordsmoen S. Treating mood disorders during pregnancy: safety considerations. Drug Saf. 2005;28(8):695-706.

Eberhard-Gran M, Eskild A, Opjordsmoen S. Use of Psychotropic Medications in Treating Mood Disorders during Lactation:Practical Recommendations.CNS Drugs.2006;20(3):187-98.

Fardet L et al. Suicidal behavior and severe **neuropsychiatric disorders following glucocorticoid** therapy in primary care. Am J Psychiatry 2012 May 1; 169:491.

FDA Dec/09 notified health care professionals and patients about the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular **malformations**, in babies exposed to **valproate** sodium and related products (valproic acid and divalproex sodium) during pregnancy.

FDA June/11 notified healthcare professionals that children born to mothers who take the anti-seizure medication **valproate** sodium or related products (valproic acid and divalproex sodium) during pregnancy have an increased risk of **lower cognitive test scores** than children exposed to other anti-seizure medications during pregnancy.

Findling RL, et al. Double-blind 18-month trial of lithium vs divalproex maintenance treatment in pediatric bipolar disorder.J Am Acad Child Adolesc Psychiatry.2005May;44(5):409-17.

Fleisher AS, Truran D, Mai JT, et al. For the Alzheimer's Disease Cooperative Study. Chronic **divalproex** sodium use and brain atrophy in **Alzheimer** disease. Neurology. 2011 Sep 27;77(13):1263-1271.

Fortinguerra, Filomena, Clavenna, Antonio, Bonati, Maurizio. Psychotropic Drug Use During **Breastfeeding**: A Review of the Evidence. Pediatrics 2009 124: e547-e556.

Frye Mark A., **Bipolar Disorder — A Focus on Depression**. N Engl J Med 2011; 364:51-59.

Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a **critical overview**. **CMAJ**. **2005** Jun 21;172(13):1703-11.

Geddes JR, Calabrese JR, Goodwin GM. **Lamotrigine** for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry. 2009 Jan;194(1):4-9. There is consistent evidence that lamotrigine has a beneficial effect on depressive symptoms in the depressed phase of bipolar disorder. The overall pool effect was modest, although the advantage over placebo was larger in more severely depressed participants.

Geller B, Luby JL, Joshi P, et al. A Randomized Controlled Trial of **Risperidone, Lithium, or Divalproex** Sodium for Initial Treatment of Bipolar I Disorder, Manic or Mixed Phase, in **Children and Adolescents**. Arch Gen Psychiatry. 2012 Jan 2.

Geriatric Dosage Handbook 7th Edition 2002

Gerrett D, Lamont T, Paton C, et al. Prescribing and **monitoring lithium therapy**: summary of a safety report from the National Patient Safety Agency. BMJ. 2010 Nov 19;341:c6258.

Gibbons RD.; Hur Kwan; et al. Relationship Between Antiepileptic Drugs and **Suicide** Attempts in Patients With Bipolar Disorder. Arch Gen Psychiatry. 2009;66(12):1354-1360.

Gilron I, Bailey JM, Tu D, Holden RR, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005 Mar 31;352(13):1324-34.

TOP

Gijsman HJ, Geddes JR, Rendell JM, et al. **Antidepressants** for bipolar depression: a **systematic review** of randomized, controlled trials. Am J Psychiatry. 2004 Sep;161(9):1537-47.
Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of **pramipexole** added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry. 2004 Mar;161(3):564-6.
Goldsmith D, Wagstaff A, Ibbotson T, Perry C. Lamotrigine: A Review of its Use in Bipolar Disorder. Drugs. 2003;63(19):2029-2050.
Goodwin GM, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry. 2004 Mar;65(3):432-41.
Goodwin FK, Fireman B, Simon GE, et al. **Suicide risk** in bipolar disorder during treatment with lithium and divalproex. JAMA. 2003 Sep 17;290(11):1467-73.
Goodwin GM, Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating **bipolar disorder**: revised second edition recommendations from the **British Association for Psychopharmacology**. J Psychopharmacol [Internet]. June 2009 [cited 2011 Feb 18]; 23(4):346-388. http://www.bap.org.uk/pdfs/Bipolar_guidelines.pdf
Grunze H, Vieta E, Goodwin GM, et al. The **World Federation of Societies of Biological Psychiatry (WFSBP)** Guidelines for the Biological Treatment of Bipolar Disorders: **Update 2010 on the treatment of acute bipolar depression**. World J Biol Psychiatry 2010;11:81-109.
Gulack BC, Puri NV, Kim WJ. **Stutter Exacerbated by Lithium** in a Pediatric Patient with Bipolar Disorder (October). Ann Pharmacother. 2011 Sep 13.
Haas M, Delbello MP, Pandina G, et al. **Risperidone** for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2009 Nov;11(7):687-700.
Handbook of Clinical Drug Data 10th Edition 2002
Hartong EG, et al.; LitCar Group. Prophylactic efficacy of lithium versus carbamazepine in treatment-naïve bipolar patients. J Clin Psychiatry. 2003 Feb;64(2):144-51.
Health Canada Sept/04 Lamictal warning with birth control pills http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_pa-ap_e.pdf
Health Canada Aug/06 Lamictal warning with non-syndromic oral clefts. Emerging data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry suggest an association between LAMICTAL® (lamotrigine) and an increased risk of non-syndromic oral clefts over the reference population for the registry (ie. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston, USA)1. Recently published data from the Registry report three cases of isolated, non syndromic cleft palate and two cases of isolated, non syndromic cleft lip without cleft palate in infants from 564 first trimester lamotrigine monotherapy exposures giving a rate of 8.9 per 1,000, as compared to 0.37 per 1000 in the reference population for that registry. The prevalence of oral clefts noted in the NAAED registry is also higher than the background prevalence of non-syndromic oral clefts reported in the literature, including studies from the United States, Australia and Europe. While different studies have differing results due to geographic and case ascertainment variations, the reported range is 0.50 to 2.16/1000 3-17. To assist with the assessment of risk, analysis of data from additional pregnancy registries, with approximately 2200 additional lamotrigine monotherapy first trimester exposures has been conducted, and 4 additional non-syndromic cases of oral cleft have been identified.
http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/lamictal_2_hpc-cps_e.html
Health Canada Jan/10 is advising consumers not to use any unauthorized health products sold under **Natural Choice Lithium Orotate**.
Hirschfeld RM, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. Am J Psychiatry. 2004 Jun;161(6):1057-65.
Hoang U, Stewart R, Goldacre MJ. **Mortality after hospital discharge** for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006. BMJ 2011;343:d5422.
Holtzheimer PE, Kelley ME, Gross RE et al. **Subcallosal Cingulate Deep Brain Stimulation** for Treatment-Resistant Unipolar and Bipolar Depression. Arch Gen Psychiatry. 2012Jan2.
Jefferson JW. A clinician's guide to **monitoring kidney function in lithium**-treated patients. J Clin Psychiatry. 2010 Sep;71(9):1153-7.
Jentink, Janneke, Loane, Maria A., Dolk, Helen, et al. the EUROCAT Antiepileptic Study Working Group, **Valproic** Acid Monotherapy in Pregnancy and Major **Congenital** Malformations. N Engl J Med 2010 362: 2185-2193.
Jentink Janneke, Dolk Helen, Loane Maria A, et al., for the EUROCAT Antiepileptic Study Working Group. Intrauterine exposure to **carbamazepine** and specific congenital **malformations**: systematic review and case-control study. BMJ 341:doi:10.1136/bmj.c6581 (Published 2 Dec 2010). (eg. **spina bifida**, but less than valproate)
Kazmin, Aleksey, Wong, Renee C., Sermer, M, et al. **Antiepileptic drugs in pregnancy** and hemorrhagic disease of the newborn: An update. Can Fam Physician 2010 56: 1291-1292
Kessing LV, Sondergard L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. Arch Gen Psychiatry. 2005 Aug;62(8):860-6.
Kessing LV, Hellmund G, Geddes JR, et al. Valproate vs. **lithium** in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study. Br J Psychiatry. 2011 May 18.
Kowatch RA, Fristad M, Birmaher B, et al.; Child Psychiatric Workgroup on Bipolar Disorder. Treatment **guidelines for children and adolescents** with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005 Mar;44(3):213-35.
Kripalani M, Shawcross J, Reilly J, Main J. **Lithium** and chronic kidney disease. BMJ. 2009 Jul 3;339:b2452. doi: 10.1136/bmj.b2452.
Leverich GS, et al. Risk of **switch in mood polarity to hypomania or mania** in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry. 2006 Feb;163(2):232-9.
Lichtenstein P, Yip BH, Bjork C, et al. **Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study.** Lancet. 2009 Jan 17;373(9659):234-239. Similar to molecular genetic studies, we showed evidence that schizophrenia and bipolar disorder partly share a common genetic cause. These results challenge the current nosological dichotomy between schizophrenia and bipolar disorder, and are consistent with a reappraisal of these disorders as distinct diagnostic entities.
Madadi P, Ito S. **Perinatal exposure to maternal lamotrigine**: Clinical considerations for the mother and child. Can Fam Physician. 2010 Nov;56(11):1132-4.
Maher AR et al. Efficacy and comparative effectiveness of **atypical antipsychotic medications for off-label uses in adults**. JAMA 2011 Sep 28; 306:1359.
Martin A, Young C, Leckman JF, et al. Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med. 2004 Aug;158(8):773-80.
McIntyre RS, Cohen M, et al. **Asenapine** versus olanzapine in acute mania: a double-blind extension study. Bipolar Disord. 2009 Oct 14.

TOP

McClellan J, Kowatch R, Findling RL, Work Group on Quality Issues. Practice parameter for the assessment and treatment of **children and adolescents with bipolar disorder**. J Am Acad Child Adolesc Psychiatry 2007 Jan;46(1):107-25.

McCormack Mark, Alfirevic Ana, Bourgeois S, et al. **HLA-A*3101** and Carbamazepine-Induced Hypersensitivity Reactions in Europeans. N Engl J Med 2011; 364:1134-1143.

McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. **Lithium toxicity profile**: a systematic review and meta-analysis. Lancet 2012.

MDQ Mood Disorder **Questionaire** http://www.dbsalliance.org/pdfs/MDQ.pdf

Meador KJ, Baker GA, Browning N, et al. **Cognitive function** at 3 years of age after **fetal exposure** to antiepileptic drugs. N Engl J Med. 2009 Apr 16;360(16):1597-605.

Medical Letter "Treatment Guidelines- Drugs for Psychiatric Disorders Vol 4 (Issue 46) June 2006.

Medical Letter. Treatment Guidelines. Drugs for Depression and Bipolar Disorder. May 2010.

Merideth CH. A single-center, double-blind, placebo-controlled evaluation of lamotrigine in the treatment of obesity in adults. J Clin Psychiatry. 2006 Feb;67(2):258-62.

Micromedex 2010

Mindikoglu AL, King D, Magder LS, et al. **Valproic Acid-associated acute liver failure in children**: case report and analysis of liver transplantation outcomes in the United States. J Pediatr. 2011 May;158(5):802-7.

Mølgaard-Nielsen D, Hviid A. **Newer-generation antiepileptic drugs and the risk of major birth defects**. JAMA. 2011 May 18;305(19):1996-2002.

Muzina DJ, Gao K, Kemp DE, et al. Acute efficacy of **divalproex** sodium versus placebo in mood stabilizer-naive bipolar i or ii depression: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2010 Aug 24.

Navarro VJ, Senior JR. Drug-related **hepatotoxicity**. N Engl J Med. 2006 Feb 16;354(7):731-9. (Bohan TP, et al. Effect of L-carnitine treatment for valproate-induced hepatotoxicity. Neurology. 2001 May 22;56(10):1405-9.)

Nierenberg AA, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with **lamotrigine**, inositol, or risperidone. Am J Psychiatry. 2006 Feb;163(2):210-6.

Newport DJ, et al. **Lithium** Placental Passage and Obstetrical Outcome: Implications for Clinical Management During Late **Pregnancy**. Am J Psychiatry. 2005 Nov;162(11):2162-2170. (CONCLUSIONS: Lithium completely equilibrates across the placenta; Withholding lithium therapy for 24-48 hours before delivery resulted in a 0.28 meq/liter reduction in maternal lithium concentration.)

Newport DJ, Stowe ZN, Viguera AC, et al. **Lamotrigine** in bipolar disorder: efficacy during **pregnancy**. Bipolar Disord. 2008 May;10(3):432-6.

NICE: National Collaborating Centre for Mental Health. **Bipolar disorder**: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care London: National Institute for Health and Clinical Excellence; 2006 Jul [cited 2011 Feb 18]. (NICE clinical guideline 38). http://www.nice.org.uk/nicemedia/pdf/CG38niceguideline.pdf

Nicolaidou P, et al. Effects of **anticonvulsant** therapy on **vitamin D** status in children: prospective monitoring study. J Child Neurol. 2006 Mar;21(3):205-9.

Oquendo, Maria A., Galfalvy, Hanga C., Currier, Dianne, et al. Treatment of Suicide Attempters With Bipolar Disorder: A Randomized Clinical Trial Comparing **Lithium and Valproate** in the Prevention of Suicidal Behavior. Am J Psychiatry 2011 0: appi.ajp.2011.11010163.

Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol. 2003 Jun;2(6):347-56.

Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. Lancet Neurol. 2003 Aug;2(8):473-81.

Perucca E. **Birth defects** after prenatal exposure to antiepileptic drugs. Lancet Neurol. 2005 Nov;4(11):781-6.

Pharmacotherapy Handbook 2nd Edition (Wells,Dipiro et al.)

Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry. **2002** Apr;159(4 Suppl):1-50.

Price A, Marzani-Nissen G. **Bipolar Disorders**: A Review. Am Fam Physician. 2012 Mar 1;85(5):483-493.

Rendell JM, Gijsman HJ, Keck P, Goodwin GM, Geddes JR. Olanzapine alone or in combination for acute mania. Cochrane Database Syst Rev. 2003;(3):CD004040.

Sachs G, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2004 Jun;6(3):213-23.

Sachs GS, Nierenberg AA, Calabrese JR, et al. (**STEP-BD** trial) Effectiveness of **Adjunctive Antidepressant** Treatment for Bipolar Depression. N Engl J Med. 2007 Mar 28; [Epub ahead of print] The use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch. Longer-term studies are needed to fully assess the benefits & risks of antidepressant therapy for bipolar disorder.

Sanford M, Keating GM. **Quetiapine**: a review of its use in the management of bipolar depression. CNS Drugs. 2012 May 1;26(5):435-60.

Schroeder SA. A 51-year-old woman with bipolar disorder who wants to **quit smoking**. JAMA. 2009 Feb 4;301(5):522-31. Epub 2009 Jan 6.

Scherk H, Pajonk FG, Leucht S. Second-generation **antipsychotic** agents in the treatment of **acute mania**. A systematic review and meta-analysis of randomized controlled trials. Arch Gen Psychiatry 2007;64:442-455. (InfoPOEMs: Antipsychotic agents plus mood stabilizers are superior to either group of medications alone in the treatment of acute mania. This review found no evidence of a superiority of second-generation antipsychotics over first-generation antipsychotics. (LOE = 1a))

Shorvon Simon, Tomson Torbjorn. **Sudden unexpected death** (SUDEP) in epilepsy. www.thelancet.com Online July 6, 2011. (↑: GTC, Males, long-duration hx & on polytherapy)

Sidor MM., MacQueen GM., **Antidepressants for the Acute** Treatment of Bipolar Depression: A Systematic Review & Meta-Analysis. J Clin Psychiatry doi:10.4088/JCP.09r05385gre .

Spencer JP, Gonzalez LS 3rd, Barnhart DJ. Medications in the breast-feeding mother. Am Fam Physician. 2001 Jul 1;64(1):119-26.

Spina E, et al. Effect of Adjunctive **Lamotrigine** Treatment on the Plasma Concentrations of **Clozapine**, **Risperidone** and **Olanzapine** in Patients With Schizophrenia or Bipolar Disorder. Ther Drug Monit. 2006 Oct;28(5):599-602. These findings indicate that lamotrigine, at the dosages recommended for use as a mood stabilizer, does not affect the plasma levels of clozapine, risperidone, and

TOP

their active metabolites. The modest elevation in plasma olanzapine concentration, possibly due to inhibition of UGT1A4-mediated olanzapine glucuronidation, is unlikely to be of clinical significance.
Srivastava S, Ketter TA. Clinical relevance of treatments for **acute bipolar disorder**: balancing therapeutic and adverse effects. Clin Ther. 2011 Dec;33(12):B40-8.
Stoffers J, Vollm BA, Rucker G, et al. Pharmacological interventions for **borderline personality disorder**. Cochrane Database Syst Rev. 2010 Jun 16;6:CD005653.
Suppes T, et al. Clinical outcome in a randomized 1-year trial of **clozapine** versus treatment as usual for patients with treatment-resistant illness and a history of mania. Am J Psychiatry. 1999 Aug;156(8):1164-9.
Swartz HA, Thase ME. Pharmacotherapy for the treatment of **acute bipolar ii depression**: current evidence. J Clin Psychiatry. 2010 Aug 10.
Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR; for the **BOLDER II** Study Group. Efficacy of **Quetiapine** Monotherapy in Bipolar I and II **Depression**: A Double-blind, Placebo-controlled Study (The BOLDER II Study). J Clin Psychopharmacol. 2006 Dec;26(6):600-609. The incidence of treatment-emergent mania or hypomania was lower with quetiapine treatment than placebo. This study demonstrates that quetiapine monotherapy is an effective and well-tolerated treatment for depressive episodes in bipolar disorder, confirming the results observed from a previous study (BipOLar DEpRession [BOLDER] I).
Therapeutic Choices 5th edition 2007.
Tohen M, Goldberg JF, et al. A 12-week, double-blind comparison of **olanzapine vs haloperidol** in the treatment of acute mania. Arch Gen Psychiatry. 2003 Dec;60(12):1218-26.
Tohen M, et al. Relapse prevention in bipolar I disorder: 18-month comparison of **olanzapine** plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry. 2004 Apr;184:337-45.
Tohen M, Greil W et al. **Olanzapine vs lithium** in the maintenance treatment of bipolar disorder: a 12-month double-blind RCT trial. Am J Psychiatry. 2005 Jul;162(7):1281-90.
Tohen M, et al. Randomized, placebo-controlled trial of **olanzapine** as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry. 2006 Feb;163(2):247-56.
Tohen, Mauricio, Bowden, Charles L., et al. Olanzapine plus carbamazepine v. **carbamazepine** alone in treating manic episodes. The British Journal of Psychiatry 2008 192: 135-143.
Tomson T, et al. **Valproate** effects on **kinetics of lamotrigine** in pregnancy and treatment with oral contraceptives. Neurology. 2006 Oct 10;67(7):1297-9. Valproate seems to reduce the induction of lamotrigine metabolism associated with pregnancy or use of contraceptives.
Torpy JM, Lynm C, Glass RM. JAMA **patient page. Bipolar disorder**. JAMA. 2009Feb 4;301(5):564.
Treatment Guidelines: Drugs for Psychiatric Disorders. **The Medical Letter**: July, **2003**; p. 69-76. (**Medical Letter "Treatment Guidelines- Drugs for Psychiatric Disorders** Vol 4 (Issue 46) **June 2006**.) **Medical Letter. Treatment Guidelines. Drugs for Depression and Bipolar Disorder. May 2010.**
Truman CJ, Goldberg JF, Ghaemi SN, et al. Self-reported **history of manic/hypomanic switch associated with antidepressant use**: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry. 2007 Oct;68(10):1472-9.
Tsai AC, Rosenlicht NZ, Jureidini JN, et al. **Aripiprazole** in the maintenance treatment of bipolar disorder: a **critical** review of the evidence and its dissemination into the scientific literature. PLoS Med 2011;8:e1000434.

van der Lee MJ, et al. **Lopinavir/ritonavir** reduces **lamotrigine** plasma concentrations in healthy subjects. Clin Pharmacol Ther. 2006 Aug;80(2):159-68.
van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of **lamotrigine** as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry. 2008 Dec 30. pii: ej08m04152. [Epub ahead of print]
Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of **mood stabilisers** in the treatment of **acute bipolar depression**: systematic review. Br J Psychiatry. 2010Apr;196:266-73. Mood stabilizers have an effect in some people with acute bipolar depression, decreasing depression symptoms by at least 50% in at least 1 additional patient of every 10 patients (NNT=10) who are given treatment instead of placebo. The mood stabilizers in the studies were the anticonvulsants carbamazepine (Tegretol), valproic acid (Depakote), and lamotrigine (Lamictal), and the atypical antipsychotics olanzapine (Zyprexa) and quetiapine (Serroquel). (LOE = 1a)
Varghese SP, et al. **Lamotrigine**-induced toxic **epidermal necrolysis** in three patients treated for bipolar disorder. Pharmacotherapy. 2006 May;26(5):699-704.
Viguera AC, Newport DJ, Ritchie J, et al. **Lithium in breast milk** and nursing infants: clinical implications. Am J Psychiatry. 2007 Feb;164(2):342-5. Serum lithium levels in nursing infants were low and well tolerated. No significant adverse clinical or behavioral effects in the infants were noted. These findings encourage reassessment of recommendations against lithium during breast-feeding and underscore the importance of close clinical monitoring of nursing infants.
Ward RK, Zamorski MA. Benefits and risks of psychiatric medications during **pregnancy**. Am Fam Physician. 2002 Aug 15;66(4):629-36.
Weisler RH, Nolen WA, Neijber A, Hellqvist A, Paulsson B; for the Trial 144 Study Investigators. Continuation of **quetiapine versus switching to placebo or lithium** for maintenance treatment of bipolar I disorder (trial 144: a randomized controlled study). J Clin Psychiatry. 2011 Oct 18.
Wilding J, Van Gaal L, Rissanen A, Vercruysse F, Fitchet M; OBES-002 Study Group. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of **topiramate** in the treatment of **obese** subjects. Int J Obes Relat Metab Disord. 2004 Nov;28(11):1399-410.
Wyszynski DF, et al.; Antiepileptic Drug Pregnancy Registry. Increased rate of major **malformations** in offspring exposed to **valproate** during pregnancy. Neurology. 2005 Mar 22;64(6):961-5.
Yatham LN, Calabrese JR, Kusumakar V. **Bipolar depression**: criteria for treatment selection, definition of refractoriness, and treatment options. Bipolar Disord. 2003 Apr;5(2):85-97.
Yatham LN et al. Canadian Network for Mood & Anxiety Treatments (**CANMAT**) **guidelines** for the management of patients with bipolar disorder: update 2006. Bipolar Disorders **2006**:8: 1-19
Young LT, Joffe RT, Robb JC, et al. Double-blind comparison of **addition of a second mood stabilizer versus an antidepressant** to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry. 2000 Jan;157(1):124-6.

TOP

- Assess the patient's status regularly, beginning within 2 weeks after starting therapy.
- Modify treatment if there's no response within 2 months.
- Successful treatments of first episodes of major depression should continue for about 6 months; patients with a history of two or more episodes should undergo treatment for much longer periods.

Qaseem A, Snow V, Denberg TD, et al; Clinical Efficacy Assessment Subcommittee of American College of Physicians. (ACP) Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008 Nov 18;149(10):725-33.

ANTIDEPRESSANT COMPARISON CHART - References

[1] Jefferson J, Greist JH. Mood Disorders in Textbook of Psychiatry, 2nd Ed. Editors: Hales RE, Yudofsky SC, Talbot JA. American Psychiatric Press, Washington, 1994.

[2] Micromedix Drug Information, 2011.

[3] Geddes JR, Carney SM, Davies C, et al. **Relapse prevention** with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003 Feb 22;361(9358):653-61.

[4] Treatment Guidelines: Drugs for Psychiatric Disorders. The Medical Letter: July, 2003; p. 69-76. (**Medical Letter** "Treatment Guidelines- Drugs for Psychiatric Disorders Vol 4 (Issue 46) **June 2006**.)
Medical Letter. Treatment Guidelines. Drugs for Depression and Bipolar Disorder. May 2010.

[5] Remick RA. Diagnosis and management of depression in primary care: a clinical update and review. CMAJ. 2002 Nov 26;167(11):1253-60.

[6] Practice guideline for the treatment of patients with major depressive disorder (revision). **American** Psychiatric Association. Am J Psychiatry. **2000** Apr;157(4 Suppl):1-45.
http://www.psych.org/psych_pract/treatg/pg/Practice%20Guidelines8904/MajorDepressiveDisorder_2e.pdf

[7] Trindade E, Menon D, Topfer LA, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ. 1998 Nov 17;159(10):1245-52.

[8] Modell JG, Katholi CR, Modell JD, et. al. Comparative sexual side effects of bupropion fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997;61(4):476-87.

[9] Gonzalez M, Llorca G, Izquierdo JA, et.al. J Sex Marital Ther 1997;23(3):176-94.

[10] Ditto KE. SSRI discontinuation syndrome. Awareness as an approach to prevention. Postgrad Med. 2003 Aug;114(2):79-84.

[11] Glassman AH, O'Connor CM, Califf RM, et al.; Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA. 2002 Aug 14;288(6):701-9. (Taylor CB, Youngblood ME, Catellier D, et al.; ENRICHD Investigators. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry. 2005 Jul;62(7):792-8 -Observational secondary analysis)(Lesperance F, et al. CREATE Investigators. Effects of citalopram 20-40mg/d and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. JAMA. 2007 Jan 24;297(4):367-79. (n=284 12weeks)Based on these results and those of previous trials, citalopram or sertraline plus clinical management should be considered as a first-step treatment for patients with CAD and major depression.)
Pizzi C, Rutjes AW, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-Analysis of Selective Serotonin Reuptake Inhibitors in Patients With Depression and Coronary Heart Disease. Am J Cardiol. 2011 Jan 20.

[12] Grady-Weliky TA. Clinical practice. Premenstrual dysphoric disorder. N Engl J Med. 2003 Jan 30;348(5):433-8.

[13] Pearlstein T. Selective serotonin reuptake inhibitors for premenstrual dysphoric disorder: the emerging gold standard? Drugs. 2002;62(13):1869-85.

[14] Which SSRI? Med Lett Drugs Ther. 2003 Nov 24;45(1170):93-95.

[15] Glassman AH, O'Connor CM, Califf RM, et al.; Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA. 2002 Aug 14;288(6):701-9. (Taylor CB, Youngblood ME, Catellier D, et al.; ENRICHD Investigators. Effects of antidepressant medication on morbidity and mortality in **depressed patients after myocardial infarction**. Arch Gen Psychiatry. 2005 Jul;62(7):792-8 -Observational secondary analysis)
Glassman AH, Bigger JT Jr, Gaffney M. Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants. Arch Gen Psychiatry. 2009 Sep;66(9):1022-9.
O'Connor CM, Jiang W, Kuchibhatla M, et al. SADHART-CHF Investigators. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. J Am Coll Cardiol. 2010 Aug 24;56(9):692-9.

[16] Bezchlibnyk-Butler K. Serotonergic antidepressants: Drug response and drug-drug interactions. Pharmacy Practice:National CE Program 1998;Aug:1-8.

[17] Stewart DE. Hepatic adverse reactions associated with nefazodone. Can J Psychiatry. 2002 May;47(4):375-7.

[18] Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. BMJ. 2002 Dec 7;325(7376):1332-3.
Hamer Mark, Batty G. David, Seldenrijk Adrie, et al. Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Survey. Eur Heart J ehq438 first published online November 30, 2010 doi:10.1093/eurheartj/ehq438

[19] Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. BMJ. 2002 Nov 2;325(7371):991.

[20] Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. Am Fam Physician. 2005 Feb 1;71(3):483-90.

[21] Houdenhove BV, Onghena P. Pain and Depression in Depression and Physical Illness. Editors: Robertson MM, Katona CLE. Wiley & Sons, New York, 1997.

[22] Pryse-Phillips WEM, Dodick DW, Edmeads JG. Guidelines for the diagnosis and management of migraine in clinical practice. Can Med Assoc J 1997;156:1273-87.

[23] Wells BG, Mandos LA, Hayes PE. Depressive Disorders in Pharmacotherapy: A Pathophysiologic Approach 3rd Ed., 1996.

[24] Tollefson GD. Antidepressant treatment and side effect considerations. J Clin Psychiatry 1991;52(5-suppl):4-13.

[25] Cole JO, Bodkin JA. Antidepressant side effects. J Clin Psychiatry 1990;51(1):21-26

[26] Nurnberg HG, Hensley PL, Gelenberg AJ, Fava M, Lauriello J, Paine S. Treatment of antidepressant-associated **sexual dysfunction with sildenafil**: a randomized controlled trial. JAMA. 2003 Jan 1;289(1):56-64. (Taylor MJ, Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. J Affect Disord. 2005 Nov;88(3):241-54. Epub 2005 Sep 12.)(Basson R. Clinical practice. Sexual desire and arousal disorders in women. N Engl J Med. 2006 Apr 6;354(14):1497-506.) (Fava M, et al. Efficacy and safety of **sildenafil** in men with serotonergic antidepressant-associated erectile dysfunction: results from a randomized, double-blind, placebo-controlled trial.J Clin Psychiatry.2006Feb;67(2):240-6.)
Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial.JAMA. 2008 Jul 23;300(4):395-404.
In this study population, sildenafil treatment of sexual dysfunction in women taking SRIs was associated with a reduction in adverse sexual effects.

[27] Boyer EW, Shannon M. The **serotonin syndrome**. N Engl J Med. 2005 Mar 17;352(11):1112-20. (Pharmacist's Letter: Serotonin Syndrome Sept 2006)
Frank C. Recognition and treatment of **serotonin syndrome**. Can Fam Physician. 2008 Jul;54(7):988-92.
Ables AZ. Prevention, Diagnosis, and Management of **Serotonin Syndrome**. American Family Pysician. May 1, 2010.
FDA has received reports of serious central nervous system (CNS) reactions when the drug methylene blue is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications).
FDA July/11 has received reports of serious central nervous system (CNS) reactions when the antibacterial drug linezolid (Zyvox) is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications.

[28] Bhatia SC, Bhatia SK. Major Depression: Selecting Safe and Effective Treatment. Am Family Physician 1997;55(5):1683-1694.

[29] Watson CPN. Antidepressant Drugs as Adjuvant Analgesics. J Pain Symptom Manage 1994;9:392-405.

[30] The Medical Letter: Drugs that may cause Psychiatric Symptoms. July 8, 2002; (1134) pp. 59-62.

[31] Birrer RB, Vemuri SP. Depression in later life: a diagnostic and therapeutic challenge. Am Fam Physician. 2004 May 15;69(10):2375-82.

TOP

[32] Finkel SI. Efficacy and tolerability of antidepressant therapy in the **old-old**. J Clin Psychiatry 1996;57(suppl 5):23-8.
Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in **older people**: population based cohort study. BMJ. 2011 Aug 2;343:d4551.
[33] Menting JEA, Honig A, Verhey FRJ, et. al. Int Clin Psychophamacology 1996;11:165-175.
[34] Pryse-Phillips WEM, Dodick DW, Edmeads JG. Guidelines for the diagnosis and management of migraine in clinical practice. Can Med Assoc J 1997;156:1273-87.
[35] Reite M, Ruddy J, Nagel K. Evaluation and management of sleep disorders, 2nd Ed. Am Psychiatric Press, Washington, 1997.
[36] Hughes J, Stead L, Lancaster T. Antidepressants for **smoking cessation**. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD000031. Review.
[37] Drugs and Therapy Perspectives 1998;12(7):14-15.
[38] AHFS (American Hospital Formulary System) Drug Information: Antidepressants. 2005.
[39] Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ. 2005 Feb 19;330(7488):385.
[40] Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and **rate of suicide**. Arch Gen Psychiatry. 2005 Feb;62(2):165-72.
[41] Birmes P, Coppin D, Schmitt L, Lauque D. Serotonin syndrome: a brief review. CMAJ. 2003 May 27;168(11):1439-42.
[42] Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2008.
[43] Stahl MM, Lindquist M, Pettersson M, et.al. Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. Eur J clin Pharmacol 1997;53(3-4):163-9.
[44] Bleeding: Meijer WE, Heerdink ER, Nolen WA, et al. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Arch Intern Med. 2004 Nov 22;164(21):2367-70. (Benazzi F. Hemorrhages during escitalopram-venlafaxine-mirtazapine combination treatment of depression. Can J Psychiatry. 2005 Mar;50(3):184.) (Ziegelstein RC, Meuchel J, Kim TJ, et al. Selective serotonin reuptake inhibitor use by patients with acute coronary syndromes. Am J Med. 2007 Jun;120(6):525-30. Epub 2007 Apr 30. Selective serotonin reuptake inhibitor use during a hospitalization for an acute coronary syndrome is associated with reduced rates of recurrent ischemia, heart failure, or cardiac enzyme elevation at the expense of increased bleeding in patients receiving maximal conventional antiplatelet medications and heparin.) FRACTURES: Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the **risk of fracture**. Arch Intern Med. 2007 Jan 22;167(2):188-94. Daily SSRI use in adults 50 years and older remained associated with a 2-fold increased risk of clinical fragility fracture after adjustment for potential covariates. Depression and fragility fractures are common in this age group, and the elevated risk attributed to daily SSRI use may have important public health consequences. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Haney EM, Bliziotes MM, Ensrud KE. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med. 2007 Jun 25;167(12):1240-5. Use of SSRIs but not TCAs is associated with an increased rate of bone loss at the hip in this cohort of older women. Haney EM, Chan BK, Diem SJ, Ensrud KE, Cauley JA, Barrett-Connor E, Orwoll E, Bliziotes MM; for the Osteoporotic Fractures in Men Study Group. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. Arch Intern Med. 2007 Jun 25;167(12):1246-51. In this population of men, BMD was lower among those reporting current SSRI use, but not among users of other antidepressants.
Loke YK, Trivedi AN, Singh S. Meta-analysis: Gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther. 2007 Oct 5; [Epub ahead of print]) Upper gastrointestinal (GI) bleeding is associated with the use of selective serotonin reuptake inhibitors (SSRIs); the risk is increased when patients are also taking nonsteroidal anti-inflammatory drugs (NSAIDS). The risk for each individual is still low; but given the number of people taking SSRIs, the impact across a population may be noticeable. (LOE = 3a)
Schalekamp T, Klungel JH, Souverein PC, de Boer A. Increased bleeding risk with concurrent use of selective serotonin reuptake inhibitors and coumarins. Arch Intern Med. 2008 Jan 28;168(2):180-5. In users of coumarins, SSRI usage was associated with increased risk of hospitalization because of nongastrointestinal bleeding but not because of gastrointestinal bleeding.
de Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. Arch Gen Psychiatry. 2008 Jul;65(7):795-803. Antidepressants with a relevant blockade action on the serotonin reuptake mechanism increase the risk of upper gastrointestinal tract bleeding. The increased risk may be of particular relevance when these drugs are associated with nonsteroidal anti-inflammatory drugs. Our study findings also provide evidence that use of acid-suppressing agents limits such increased risk.
Targownik LE, Bolton JM, Metge CJ, et al. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol. 2009 Jun;104(6):1475-82. Epub 2009 Apr 28. SSRI use is associated with a modestly increased risk of UGIB, which may be significantly reduced with PPI co-therapy. SSRI use is not a major risk factor for NSAID-related UGIB.
Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry. 2010 Dec;71(12):1565-75.
Labos C, Dasgupta K, Nedjar H, et al. Risk of bleeding associated with combined use of selective serotonin reuptake inhibitors and antiplatelet therapy following acute myocardial infarction. CMAJ 2011; DOI:10.1503/cmaj.100912.
[45] Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. BMJ. 2004 Apr 10;328(7444):879-83.
[46] Gunnell D, Ashby D. Antidepressants and suicide: what is the balance of benefit and harm. BMJ. 2004 Jul 3;329(7456):34-8.
[47] Whittington CJ, Kendall T, Fonagy P, Cottrell D, et al. Selective serotonin reuptake inhibitors in **childhood** depression: systematic review of **published versus unpublished** data. Lancet. 2004 Apr 24;363(9418):1341-5.
Ryan ND. Treatment of **depression in children** and adolescents. Lancet. **2005** Sep 10-16;366(9489):933-40.
[48] The American Academy of Child and Adolescent Psychiatry: http://www.aacap.org/Announcements/pdfs/physiciansmedguide.pdf .
American College of Neuropsychopharmacology: SSRIs & Suicidal Behavior in youth Jan/04: http://www.acnp.org/exec_summary.pdf **Final Nov/05** http://www.nature.com/npp/journal/vaop/ncurrent/pdf/1300958a.pdf
Sept/05 Nice:Depression in children & young people http://www.nice.org.uk/pdf/CG028NICEguideline.pdf ; (Simon GE, Savarino J, Operskalski B, Wang PS. **Suicide risk during antidepressant treatment**. Am J Psychiatry. 2006 Jan;163(1):41-7. CONCLUSIONS: The risk of suicide during acute-phase antidepressant treatment is approximately one in 3,000 treatment episodes, and risk of serious suicide attempt is approximately one in 1,000. Available data do not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs.)(Cheung AH, et al. The use of antidepressants to treat depression in children and adolescents. CMAJ. 2006 Jan 17;174(2):193-200.) & (Hammad TA, et al. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006 Mar;63(3):332-9. CONCLUSION: Use of antidepressant drugs in pediatric patients is associated with a modestly increased risk of suicidality. InfoPOEMs: The use of antidepressant medications in children is associated with an increased risk of suicidal ideation and suicide-related behaviors. It is uncertain what overall effect antidepressant medications have on the morbidity and mortality of treated children. Close monitoring of patients using these medications regarding the risk of suicidality is recommended. (LOE = 1a-)) (Glaxo May/06 Meta analysis: 8958 paroxetine & 5953 placebo pts; suicidal behavior aged 18-24yrs (2.19 vs 0.92%); all ages (0.32 vs 0.05%); all were nonfatal suicide attempts; 8 of 11 attempts were in aged 18-30yrs) Emslie GJ, et al. Paroxetine Treatment in Children and Adolescents With Major Depressive Disorder: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2006 Jun;45(6):709-719. Paroxetine was not shown to be more efficacious than placebo for treating pediatric major depressive disorder. (Misri S, et al. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. Am J Psychiatry. 2006 Jun;163(6):1026-32.) (Dubicka B, Hadley S, Roberts C. Suicidal behaviour in youths with depression treated with new-generation antidepressants: meta-analysis. Br J Psychiatry. 2006 Nov;189:393-8. Self-harm or suicide-related events occurred in 71 of 1487 (4.8%) of depressed youths treated with antidepressants v. 38 of 1254 (3.0%) of those given placebo (fixed effects odds ratio 1.70, 95% CI 1.13-2.54, P=0.01).) (Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry. 2006 Nov;163(11):1898-904. The aggregate nature of these observational data precludes a direct causal interpretation of the results. More SSRI prescriptions are associated with lower suicide rates in children and may reflect antidepressant efficacy, treatment compliance, better quality mental health care, and low toxicity in the event of a suicide attempt by overdose.) (Juurlink DN, et al. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. Am J Psychiatry. 2006 May;163(5):813-21. Initiation of SSRI therapy is associated with an increased risk of suicide during the first month of therapy compared with other antidepressants. The absolute risk is low, suggesting that an idiosyncratic response to these agents may provoke suicide in a vulnerable subgroup of patients.) (Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults: A case-control study. Arch Gen Psychiatry. 2006 Aug;63(8):865-72. In these high-risk patients, antidepressant drug treatment does not seem to be related to suicide attempts and death in adults but might be related in children and adolescents. These findings support careful clinical monitoring during antidepressant drug treatment of severely depressed young people.) (Tiihonen J, et al. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry. 2006 Dec;63(12):1358-67. Among suicidal subjects who had ever used antidepressants, the current use of any antidepressant was associated with a markedly increased risk of attempted suicide and, at the same time, with a markedly decreased risk of completed suicide and death. Lower mortality was attributable to a decrease in cardiovascular- and cerebrovascular-related deaths during selective serotonin reuptake inhibitor use.) (Simon GE. The antidepressant quandary--considering suicide risk when treating adolescent depression. N Engl J Med. 2006 Dec 28;355(26):2722-3.)
(Bhatia SK, Bhatia SC. Childhood and adolescent depression. Am Fam Physician. 2007 Jan 1;75(1):73-80.) (Bridge JA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007 Apr 18;297(15):1683-96. Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.) (Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the veterans health administration data sets. Am J Psychiatry. 2007 Jul;164(7):1044-9. These findings suggest that SSRI treatment has a protective effect in all adult age groups. They do not support the hypothesis that SSRI treatment places patients at greater risk of suicide.)
Gibbons RD, Brown CH, Hur K, et al. Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents. Am J Psychiatry. 2007 Sep;164(9):1356-63. In both the

TOP

United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after U.S. and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents.

Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004851. There was also evidence of an increased risk of suicidal ideation and behaviour for those prescribed SSRIs (RR 1.80, 95% CI 1.19 to 2.72). Fluoxetine was the only SSRI where there was consistent evidence from three trials that it was effective in reducing depression symptoms in both children and adolescents (CDRS-R treatment effect -5.63, 95% CI -7.38 to -3.88), and 'response' to treatment (RR 1.86, 95% CI 1.49 to 2.32). Where rates of adverse events were reported, this was higher for those prescribed SSRIs. While untreated depression is associated with the risk of completed suicide and impacts on functioning, it is unclear whether SSRIs would modify this risk in a clinically meaningful way. (Cheung AH, Zuckerbrot RA, Jensen PS, Ghalib K, Laraque D, Stein RE; GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and ongoing management. Pediatrics. 2007 Nov;120(5):e1313-26.)

Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial.JAMA. 2008 Feb 27;299(8):901-13. For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of cognitive behavioral therapy and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine and resulted in fewer adverse effects.

Tsapakis EM, et al. Efficacy of antidepressants in juvenile depression: meta-analysis.. Br J Psychiatry. 2008 July:193;10-17. Antidepressants of all types showed limited efficacy in juvenile depression, but fluoxetine might be more effective, especially in adolescents. Studies in children & in severely depressed, hospitalised or suicidal juvenile patients are needed, and effective, safe and readily accessible treatments for juvenile depression are urgently required. This meta-analysis found that selective serotonin reuptake inhibitors (SSRIs) -- fluoxetine, in particular -- are modestly effective for depression in adolescents. Tricyclic antidepressants (TCAs) were not effective. Antidepressants were not effective in younger children. (LOE = 1a)

Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. BMJ. 2008 Mar 8;336(7643):542-5. Epub 2008 Feb 14. The noticeable reduction in prescribing of antidepressants since regulatory action in 2003 to restrict the use of SSRIs in under 18s does not seem to have been associated with changes in suicidal behaviour in young people. Specifically, these data for England do not indicate that reductions in antidepressant use have led to an increase in suicidal behaviour.

Biddle L, Brock A, Brookes ST, Gunnell D. Suicide rates in young men in England and Wales in the 21st century: time trend study. BMJ. 2008 Mar 8;336(7643):539-42. Epub 2008 Feb 14. Suicide rates in young men have declined markedly in the past 10 years in England and Wales. Reductions in key risk factors for suicide, such as unemployment, might be contributing to lower rates.

Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. CMAJ. 2009 Feb 3;180(3):291-7. Based on data from observational studies, use of SSRIs may be associated with a reduced risk of suicide in adults with depression. Among adolescents, use of SSRIs may increase suicidality.

Stone Marc, Laughren Thomas, Jones M Lisa, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880, doi: 10.1136/bmj.b2880 (Published 11 August 2009) Findings showed eight completed suicides, 134 suicide attempts, 10 patients who had made preparations without attempting suicide, and 378 patients who had thoughts about suicide but had not acted on them. These results suggest that, compared with placebo, the risks of suicidality associated with antidepressants are strongly age dependent - the risk is raised in people under 25, not affected in those aged 25-64, and reduced in those aged 65 and older, say the authors.

AACAP-Practice parameter on the use of psychotropic medication in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2009 Sep;48(9):961-73.

Thapar Anita, Collishaw Stephan, Potter Robert, et al. Managing and preventing depression in adolescents. BMJ 2010;340:c209, doi: 10.1136/bmj.c209 (Published 22 January 2010)

Oberlander TF, Papsdorf M, Brain UM, Misri S, Ross C, Grunau RE. Prenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (SLC6A4), and maternal mood on child behavior at 3 years of age. Arch Pediatr Adolesc Med. 2010 May;164(5):444-51.

Schneeweiss S, Patrick AR, Solomon DH, et al. Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults: a propensity score-adjusted analysis of 9 years' data. Arch Gen Psychiatry. 2010 May;67(5):497-506.

Schneeweiss S, Patrick AR, Solomon DH, et al. Comparative Safety of Antidepressant Agents for Children and Adolescents Regarding Suicidal Acts. Pediatrics. 2010 Apr 12.

Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet. 2012 Feb 1.

[49] Treatment for Adolescents with Depression Study (**TADS**). **Fluoxetine**, Cognitive-Behavioral Therapy, & their Combination for Adolescents with Depression. JAMA. 2004 Aug 18;292(7):807-820. (Kennard B, Silva S, Vitiello B, et al. TADS Team. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry. 2006 Dec;45(12):1404-11. The combination of FLX and CBT was superior to both monotherapy and PBO in terms of remission rates, but overall rates of remission remain low and residual symptoms are common at the end of 12 weeks of treatment.) (March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007 Oct;64(10):1132-43. In adolescents with moderate to severe depression, treatment with fluoxetine alone or in combination with CBT accelerates the response. Adding CBT to medication enhances the safety of medication. Taking benefits & harms into account, combined treatment appears superior to either monotherapy as a treatment for major depression in adolescents.)

Emslie GJ, Kennard BD, Mayes TL, et al. Fluoxetine Versus Placebo in Preventing Relapse of Major Depression in Children and Adolescents. Am J Psychiatry. 2008 Feb 15; [Epub ahead of print] Continuation treatment with fluoxetine was superior to placebo in preventing relapse and in increasing time to relapse in children and adolescents with major depression.

Goodyer I, Dubicka B, Wilkinson P, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in **adolescents** with major depression: randomised controlled trial. BMJ. 2007 Jul 21;335(7611):142. (**ADAPT**). For adolescents with moderate to severe major depression there is no evidence that the combination of CBT plus an SSRI in the presence of routine clinical care contributes to an improved outcome by 28 weeks compared with the provision of routine clinical care plus an SSRI alone.

Rohde P, Silva SG, Tonev ST, et al. Achievement and maintenance of sustained response during the Treatment for Adolescents With Depression Study continuation and maintenance therapy.Arch Gen Psychiatry. 2008 Apr;65(4):447-55. Most adolescents with depression who had not achieved sustained response during acute treatment did achieve that level of improvement during continuation and maintenance therapies. The possibility that CBT may help the subset of adolescents with depression who achieve early sustained response maintain their response warrants further investigation.

Hysinger EB, Callahan ST, Caples TL, et al. Suicidal Behavior Differs Among Early and Late Adolescents Treated With Antidepressant Agents. Pediatrics. 2011 Aug 8.

[50] Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA. 2004 Oct 27;292(16):1969-76.

Gibbons RD, Brown CH, Hur K, et al. **Suicidal** Thoughts & Behavior With Antidepressant Treatment: Reanalysis of the Randomized Placebo-Controlled Studies of **Fluoxetine and Venlafaxine**. Arch Gen Psychiatry. 2012 Feb 6

[51] Paxil (Paroxetine) and Birth Defects Pharmacist's Letter October 2005. (First trimester: Paxil any malformations 4% vs $^{\sim 3\%\ \text{general population}}$; cardiac 2% vs $^{\sim 1\%\ \text{general population}}$; most common cardiac malformation was ventricular septal defects) See also: Hallberg P, Sjoblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breast-feeding: a review and clinical aspects. J Clin Psychopharmacol. 2005 Feb;25(1):59-73. & Health Canada warning Oct/05 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/paxil_3_hpc-cps_e.pdf (Preliminay report of retrospective epidemiological study of 3,581 pregnant women). Dec/05 Health Canada update http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/paxil_4_hpc-cps_e.html (An independent epidemiological study of delivery outcome following maternal use of SSRI antidepressants in early pregnancy has been conducted utilizing the Swedish national registry data (n=5,123 women). The findings show an approximate 2-fold increased risk of cardiac malformations in infants exposed to paroxetine, compared with the total registry population (approximately 2% incidence vs. 1%, respectively).) (Use of SSRIs During Pregnancy Pharmacist's Letter April 2006) **(ACOG** Publications: Committee Opinion No. 354: Treatment With **Selective Serotonin Reuptake Inhibitors** During **Pregnancy** Obstet Gynecol 2006 108: 1601-1604.) (Djulus J, Koren G, et al. Exposure to **Mirtazapine** During **Pregnancy**: A Prospective, Comparative Study of Birth Outcomes. J Clin Psychiatry. 2006 Aug;67(8):1280-1284. Mirtazapine does not appear to increase the baseline rate of major malformations of 1% to 3%. However, the higher number of spontaneous abortions in the antidepressant groups confirms the higher rates of spontaneous abortions in pregnant women taking antidepressant medications found in previous studies.) (Kristensen JH, et al. Transfer of the antidepressant **mirtazapine** into **breast milk**. Br J Clin Pharmacol. 2006 Sep 13; [Epub ahead of print] Results Mean (95% confidence interval) relative infant doses for mirtazapine and desmethylmirtazapine (n = 8) were 1.5% (0.8, 2.2) and 0.4% (0.2, 0.6) respectively.) (Thormahlen GM. **Paroxetine** Use During **Pregnancy**: Is it Safe? (October). Ann Pharmacother. 2006 Aug 22; [Epub ahead of print]) (Wogelius P, et al. Maternal Use of Selective **Serotonin Reuptake Inhibitors** and Risk of **Congenital Malformations**. Epidemiology. 2006 Nov;17(6):701-704. The 150,780 women with no SSRI prescriptions gave birth to 5112 (3.4%) children with congenital malformations. The 1051 women with SSRI prescriptions any time during early pregnancy gave birth to 51 (4.9%) children with congenital malformations.)

Einarson A, Pistelli A, Desantis M, Malm H, Paulus WD, Panchaud A, Kennedy D, Einarson TR, Koren G. Evaluation of the Risk of Congenital Cardiovascular Defects Associated With Use of Paroxetine During Pregnancy. Am J Psychiatry. 2008 Apr 1; [Epub ahead of print] Paroxetine does not appear to be associated with an increased risk of cardiovascular defects following use in early pregnancy, as the incidence in more than 3,000 infants was well within the population incidence of approximately 1%.

Bakker MK, Kölling P, van den Berg PB, de Walle HE, et al. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. Br J Clin Pharmacol. 2008 Apr;65(4):600-6. Epub 2007 Oct 22.

Medical Letter Nov 17, 2008. Safety of SSRIs in Pregnancy.

American College of Obstetricians and Gynecologists (ACOG). Use of psychiatric medications during pregnancy and lactation. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 Apr. 20 p. (ACOG practice bulletin; no. 92). [245 references]

Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. Can J Psychiatry. 2009 Apr;54(4):242-6. As a group, antidepressant use in the first trimester of pregnancy

TOP

is not associated with an increased risk for major malformation above the baseline. In addition, no individual antidepressant was associated with an increased risk of a specific malformation.
Einarson A. Paroxetine use in pregnancy and increased risk of heart defects: Evaluating the evidence. Can Fam Physician. 2010 Aug;56(8):767-8.
Hirst KP, Moutier CY. Postpartum major depression. Am Fam Physician. 2010 Oct 15;82(8):926-33.
Grote NK, Bridge JA, Gavin AR, et al. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry. 2010 Oct;67(10):1012-24.
Patel BN, Beste J, Blackwell JC. Antidepressant use during pregnancy. Am Fam Physician. 2011 May 15;83(10):1211-5.
Malm H, Artama M, Gissler M, Ritvanen A. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstet Gynecol. 2011 Jul;118(1):111-20.
Stewart DE. Clinical practice. Depression during Pregnancy. N Engl J Med. 2011 Oct 27;365(17):1605-11.
Croen LA et al. Antidepressant use during pregnancy and childhood autism spectrum disorders. Arch Gen Psychiatry 2011 Jul 4.
Jefferies AL; Canadian Paediatric Society, Fetus and Newborn Committee. Selective serotonin reuptake inhibitors in pregnancy and infant outcomes. Paediatr Child Health 2011;16(9):562. http://www.cps.ca/english/statements/FN/fn11-02.pdf
De Vera MA, Bérard A. Antidepressant Use During Pregnancy and the Risk of Pregnancy Induced Hypertension. Br J Clin Pharmacol. 2012 Mar 21.
Koren G, Nordeng H. Antidepressant use during pregnancy: the benefit-risk ratio. Am J Obstet Gynecol. 2012 Feb 21.
El Marroun H, Jaddoe VW, Hudziak JJ, et al. Maternal Use of Selective Serotonin Reuptake Inhibitors, Fetal Growth, and Risk of Adverse Birth Outcomes. Arch Gen Psychiatry. 2012 Mar 5.

[52] Kulin AK, Pastuszak A, Sage SR, et.al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998;279:609-610.
Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation 9th Ed. Williams & Wilkins, Media, Pennsilvania, 2011.
Loughhead AM, et al. Antidepressants in Amniotic Fluid: Another Route of Fetal Exposure. Am J Psychiatry. 2006 Jan;163(1):145-147.
Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. Am J Psychiatry. 2002 Dec;159(12):2055-61.
Ward RK, Zamorski MA. Benefits and risks of psychiatric medications during pregnancy. Am Fam Physician. 2002 Aug 15;66(4):629-36. (Cohen LS, et al. Relapse of major depression during **pregnancy** in women who maintain or discontinue antidepressant treatment. JAMA. 2006 Feb 1;295(5):499-507. CONCLUSIONS: Pregnancy is not "protective" with respect to risk of relapse of major depression. Women with histories of depression who are euthymic in the context of ongoing antidepressant therapy should be aware of the association of depressive relapse during pregnancy with antidepressant discontinuation. (InfoPOEMs: Nearly 50% of women currently receiving antidepressant medication will experience a relapse of major depression during pregnancy. The risk is highest for those discontinuing their medication (68% relapse rate). It is likely that this study sample consists of patients with a higher severity of illness than those found in a routine community practice, so the findings may not generalize to other settings. (LOE = 1b))) {Wen SW, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Obstet Gynecol. 2006 Apr;194(4):961-6. (InfoPOEMs: The use of selective serotonin reuptake inhibitors (SSRIs) in the year before giving birth is associated with increased risk of prematurity, fetal death, and neonatal seizures. However, these observational data are weakened by the need to make difficult adjustments for other important factors thought to be causally related to the outcomes studied, such as poverty and drug dependence. (LOE = 2b) }
Altshuler LL, Cohen LS, Moline ML, et al. Expert Consensus Panel for Depression in Women. The Expert Consensus Guideline Series. Treatment of depression in women. Postgrad Med. 2001 Mar;(Spec No):1-107.
Nordeng H, Spigset O. Treatment with selective serotonin reuptake inhibitors in the third trimester of pregnancy: effects on the infant. Drug Saf. 2005;28(7):565-81.
Sivojelezova A, Shuhaiber S, Sarkissian L, et al. **Citalopram** use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. Am J Obstet Gynecol. 2005 Dec;193(6):2004-9. InfoPOEMs: Citalopram (Celexa) does not appear to be teratogenic. Exposure near the time of birth, however, was associated with increased risk of a diagnosis of fetal distress in labor and neonatal admission to special care nursery. (LOE = 1b))
O'Keane V, Marsh MS. Depression during pregnancy. BMJ. 2007 May 12;334(7601):1003-5.
Alwan S et al. Use of selective serotonin- reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007Jun 28; 356:2684-92.)
Louik C et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007 Jun 28; 356:2675-83.)
Dietz PM, Williams SB, Callaghan WM, Bachman DJ, Whitlock EP, Hornbrook MC. Clinically identified maternal depression before, during, and after pregnancies ending in live births. Am J Psychiatry. 2007 Oct;164(10):1515-20. n=4398. Among 4,398 continuously enrolled women with eligible pregnancies ending in live births, 678 (15.4%) had depression identified during at least one pregnancy phase; 8.7%, 6.9%, and 10.4% had depression identified before, during, and/or after pregnancy, respectively. Approximately one in seven women was identified with and treated for depression during 39 weeks before through 39 weeks after pregnancy, and more than half of these women had recurring indicators for depression.)
Toh S, Mitchell AA, Louik C, Werler MM, Chambers CD, Hernández-Díaz S. Selective Serotonin Reuptake Inhibitor Use and Risk of Gestational Hypertension. Am J Psychiatry. 2009 Jan 2. [Epub ahead of print] SSRI exposure during late pregnancy-whether a causal factor or not-might identify women who are at an increased risk for gestational hypertension and preeclampsia. Further investigation is needed in order to separate the effects of treatment with SSRIs from those of underlying mood disorders.
Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG). Gen Hosp Psychiatry. 2009 Sep-Oct;31(5):403-13.
Tuccori M, Testi A, et al.Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during pregnancy: a review. Clin Ther. 2009 Jun;31(Pt 1):1426-53.
Pedersen Lars Henning, Henriksen Tine Brink, Vestergaard Mogens, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ 2009;339:b3569, doi: 10.1136/bmj.b3569 (Published 23 September 2009) There is an increased prevalence of septal heart defects among children whose mothers were prescribed an SSRI in early pregnancy, particularly sertraline and citalopram. The largest association was found for children of women who redeemed prescriptions for more than one type of SSRI.
Briggs GG, Ambrose PJ, Ilett KF, Hackett LP, Nageotte MP, Padilla G. Use of Duloxetine in Pregnancy and Lactation (November). Ann Pharmacother. 2009 Oct 6.
Pedersen LH, Henriksen TB, Olsen J. **Fetal Exposure** to Antidepressants and Normal Milestone Development at 6 and 19 Months of Age. Pediatrics. 2010 Feb 22.
Nakhai-Pour HR, Broy P, Bérard A. Use of antidepressants during pregnancy and the risk of **spontaneous abortion**. CMAJ. 2010 May 31.
Croen Lisa A.; Grether Judith K.; Yoshida Cathleen K.; et al. Antidepressant Use During Pregnancy and Childhood **Autism Spectrum Disorders**. Arch Gen Psychiatry. 2011;0(2011):archgenpsychiatry.2011.73.
Patil AS, Kuller JA, Rhee EH. Antidepressants in pregnancy: a review of commonly prescribed medications. Obstet Gynecol Surv. 2011 Dec;66(12):777-87.

[53] Emilio J Sanz, Carlos et al. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis Lancet 2005; 365: 482-87 **& ALSO** Moses-Kolko EL, Bogen D, Perel J, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA. 2005 May 18;293(19):2372-83.(InfoPOEMs: Late third trimester exposure to maternal use of SSRIs increases the risk of neonatal behavioral abnormalities. Since the symptoms and signs were relatively benign and short lived, it makes sense to individualize the risks and benefits of continuing SSRI treatment throughout pregnancy. (LOE = 2a-)) (Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med. 2006 Feb;160(2):173-6.) (Oberlander TF, et al. **Neonatal outcomes** after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry. 2006 Aug;63(8):898-906. With linked population health data and propensity score matching, prenatal SE-D exposure was associated with an increased risk of low birth weight and respiratory distress, even when maternal illness severity was accounted for.)
Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med. 2009 Oct;163(10):949-54.
Hudak ML, Tan RC et al. **Neonatal Drug Withdrawal**. Pediatrics. 2012 Jan 30.

[54] Chambers CD, et al. Selective serotonin-reuptake inhibitors and risk of persistent **pulmonary hypertension** of the newborn. N Engl J Med. 2006 Feb 9;354(6):579-87. (InfoPOEMs: The use of selective serotonin-reuptake inhibitors (SSRIs) during the second half of pregnancy is associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). This type of study cannot establish causation, untreated depression is a serious condition, and 99% of women would give birth to infants unaffected by PPHN, so the potential benefits and harms of continuing SSRIs in these patients should be carefully weighed. (LOE = 3b)) Health Canada Mar/06 warning http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_11_e.html
FDA Dec/11 notified healthcare professionals and the public on the use of selective serotonin reuptake inhibitor (SSRI) antidepressants by women during pregnancy and the potential risk of a rare heart and lung condition known as **Persistent Pulmonary Hypertension of the Newborn** (PPHN). FDA has reviewed the additional new study results and has concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN.
Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent **pulmonary hypertension** in the newborn: population based cohort study from five Nordic countries. BMJ 2012;344:d8012.
Occhiogrosso M, Omran SS, Altemus M: **Persistent pulmonary hypertension** of the newborn and selective serotonin reuptake inhibitors: lessons from clinical and translational studies. Am J Psychiatry 2012;169:134–140

[55] Misri S, Burgmann A, Kostaras D. Are SSRIs safe for pregnant and breastfeeding women? Can Fam Physician. 2000 Mar;46:626-8, 631-3.
Spencer JP, Gonzalez LS 3rd, Barnhart DJ. Medications in the breast-feeding mother. Am Fam Physician. 2001 Jul 1;64(1):119-26.
Wisner KL, Parry BL, Piontek CM. Clinical practice. **Postpartum depression**. N Engl J Med. 2002 Jul 18;347(3):194-9. (Wisner KL, et al. Postpartum depression: a randomized trial of sertraline versus nortriptyline. J Clin Psychopharmacol. 2006 Aug;26(4):353-60. n=95 24week Times to response and remission also did not differ. Breast-fed infant serum levels were near or below the level of quantifiability for both agents.)
Altshuler LL, Cohen LS, Moline ML, Kahn DA, et al; Expert Consensus Panel for Depression in Women. The Expert Consensus Guideline Series. Treatment of depression in women. Postgrad Med. 2001 Mar;(Spec No):1-107.

TOP

Fortinguerra, Filomena, Clavenna, Antonio, Bonati, Maurizio. Psychotropic Drug Use During **Breastfeeding**: A Review of the Evidence. Pediatrics 2009 124: e547-e556.
Ng RC, Hirata CK, Yeung W, Haller E, Finley PR. Pharmacologic treatment for postpartum depression: a systematic review. Pharmacotherapy. 2010 Sep;30(9):928-41.
Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #18: use of antidepressants in nursing mothers. [Internet] Breastfeed Med 2008 Mar; [cited 2011 Feb 14] (1):44-52. Summary available from: http://www.guideline.gov/content.aspx?id=13409&search=antidepressants
American College of Obstetricians and Gynecologists (ACOG). Use of psychiatric medications during pregnancy and lactation. [Internet] Washington (DC): American College of Obstetricians and Gynecologiscs (ACOG); 2008 Apr. [cited 2011 Feb 14] (ACOG practice bulletin; no. 92). Summary available from: http://www.guideline.gov/content.aspx?id=12490
CG45 Antenatal and postnatal mental health: full guideline [Internet]. London: National Institute for Clinical Excellence; 2007 Apr 24 [cited 2011 Feb 14]. Available from: http://www.nice.org.uk/nicemedia/live/11004/30431/30431.pdf *See: Management of depression, page 10 and Chapter 7: Pharmacological Treatment of Mental disorders in Pregnant and Breastfeeding Women.*
[56] Skowron DM, Stimmel GL. Antidepressants and the risk of seizures. Pharmacotherapy 1992;12(1):18-22.
[57] **Clinical Guidelines** for the Treatment of Depressive Disorders. The Canadian Journal of Psychiatry June 2001.
(Prescribing Antidepressants for Depression in **2005**: Recent Concerns & Recommendations http://www.cpa-apc.org/Publications/Position_Papers/2004-23s-en.pdf)
Patten SB, Kennedy SH, Lam RW, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Major Depressive Disorder in Adults. I. **Classification, Burden and Principles of Management**. J Affect Disord. 2009 Aug 10. [Epub ahead of print]
Parikh SV, Sega ZV, Grigoriadis S, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. **Psychotherapy** alone or in combination with antidepressant medication. J Affect Disord. 2009 Aug 12. [Epub ahead of print] CBT and IPT are the only first-line treatment recommendations for acute MDD and remain highly recommended for maintenance. Both computer-based and telephone-delivered psychotherapy-primarily studied with CBT and IPT-are useful second-line recommendations.
Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, Parikh SV, Patten SB, Ravindran AV. **Canadian Network for Mood and Anxiety Treatments** (**CANMAT**) clinical guidelines for the management of major depressive disorder in adults. III. **Pharmacotherapy**. J Affect Disord. 2009 Aug 10. [Epub ahead of print]
Kennedy SH, Milev R, Giacobbe P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. IV. **Neurostimulation** therapies. J Affect Disord. 2009 Aug 4. [Epub ahead of print] There is most evidence to support ECT as a first-line treatment under specific circumstances and rTMS as a second-line treatment. Evidence to support VNS is less robust and DBS remains an investigational treatment.
Ravindran AV, Lam RW, Filteau MJ, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. V. **Complementary and alternative** medicine treatments. J Affect Disord. 2009 Aug 8. [Epub ahead of print] There is Level 1 evidence to support light therapy in seasonal MDD and St. John's wort in mild to moderate MDD. There is also some evidence for the use of exercise, yoga and sleep deprivation, as well as for omega-3 fatty acids and SAM-e (but with some potential safety concerns with the latter).
Tess AV, Smetana GW. Medical evaluation of patients undergoing **electroconvulsive** therapy. N Engl J Med. 2009 Apr 2;360(14):1437-44.
APA 2010: Practice Guidelines for Treatment of **Major Depressive Disorder** - American Psychiatric Association http://www.psych.org/guidelines/mdd2010
[58] Clinically significant drug interactions with antidepressants in the elderly. Spina E, Scordo MG. Drugs Aging 2002;19(4):299-320.
[59] Product monographs 2004 & Pharmacists Letter: How to Switch Antidepressants June 2006.
Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Illness risk following rapid versus gradual discontinuation of antidepressants. Am J Psychiatry. 2010 Aug;167(8):934-41.
[60] Bezchlibnyk-Butler K, Jeffries JJ, eds. Clinical handbook of psychotropic drugs, 17th ed. Toronto: Hogrefe & Huber, 2007.
[61] Bezchlibnyk-Butler K. Serotonergic antidepressants: Drug response and drug-drug interactions. Pharmacy Practice:National CE Program 1998;Aug:1-8.

Additional references:

AACAP-Practice parameter on the use of **psychotropic medication in children and adolescents**. J Am Acad Child Adolesc Psychiatry. 2009 Sep;48(9):961-73.
AACAP-Practice parameter for assessment & treatment of **children & adolescents with obsessive-compulsive disorder**. J Am Acad Child Adolesc Psych 2012 Jan;51(1):98-113.
Adams SM, Miller KE et al. Pharmacologic **Management of Adult Depression**. American Family Physician 2008; 77 (6): 785-792,795-796.
Alexopoulos GS. **Depression in the elderly**. Lancet. 2005 Jun 4-10;365(9475):1961-70.
Allan GM, Virani AS, Ivers N. **Second-generation antidepressants**. Can Fam Physician. 2011 Oct;57(10):1143.
Almeida OP, Waterreus A, Hankey GJ. Preventing depression after stroke: Results from a randomized (**sertaline NS**) placebo-controlled trial. J Clin Psychiatry. 2006 Jul;67(7):1104-9.
Alwan S, Reefhuis J, Botto LD, Rasmussen SA, Correa A, Friedman JM; National Birth Defects Prevention Study. Maternal use of **bupropion** and risk for **congenital heart defects**. Am J Obstet Gynecol. 2010 Apr 22.
American Psychiatric Association Brochures: http://www.healthyminds.org/Functional-Library/brochures.aspx
Angstman K, Rasmussen NH. **Personality disorders**: review and clinical application in daily practice. Am Fam Physician. 2011 Dec 1;84(11):1253-60.
Appelhof BC, et al. Triiodothyronine (T3) addition to paroxetine in the treatment of major depressive disorder. J Clin Endocrinol Metab. 2004 Dec;89(12):6271-6.
Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of **PHQ-2 and PHQ-9 to screen** for major depression in the primary care population. Ann Fam Med. 2010 Jul-Aug;8(4):348-53.
Attia E. **Eating disorders**. Ann Intern Med. 2012 Apr 3;156(7):ITC41.
Ballard C, Corbett A. Management of **neuropsychiatric symptoms** in people with **dementia**. CNS Drugs. 2010 Sep 1;24(9):729-39. doi:10.2165/11319240-000000000-00000.
Bambauer KZ, et al. **Physician alerts** to increase antidepressant adherence: fax or fiction? Arch Intern Med. 2006 Mar 13;166(5):498-504.
Barak Y, Plopski I, et al. **Escitalopram versus risperidone** for the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease: randomized double-blind pilot study. Int Psychogeriatr. 2011 Apr 15:1-5.
Barber JP, Barrett MS, Gallop R, et al. **Short-term dynamic psychotherapy versus pharmacotherapy** for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012 Jan;73(1):66-73.
Barbui C, Cipriani A, Patel V, Ayuso-Mateos JL, van Ommeren M. Efficacy of **antidepressants and benzodiazepines in minor depression**: systematic review and meta-analysis. Br J Psychiatry. 2011 Jan;198:11-6.
Barbui C, Hotopf M, Freemantle N, et al. Selective serotonin reuptake inhibitors versus tricyclic and heterocyclic antidepressants: comparison of drug adherence. Cochrane Database Syst Rev. 2000;(4):CD002791.
Barnes TR, Paton C. Do **antidepressants improve negative symptoms in schizophrenia**? BMJ. 2011 Jun 10;342:d3371. doi: 10.1136/bmj.d3371.
Barnes DE, Yaffe K, Byers AL, et al. Midlife vs Late-Life Depressive Symptoms and **Risk of Dementia**: Differential Effects for Alzheimer Disease and Vascular Dementia. Arch Gen Psychiatry. 2012 May;69(5):493-8.
Beck CA, Williams JV, Wang JL, et al. **Psychotropic medication use in Canada**. Can J Psychiatry. 2005 Sep;50(10):605-13. RESULTS: Overall psychotropic drug utilization was 7.2%. Utilization was higher for women and with increasing age. With any lifetime CIDI-diagnosed disorder assessed in the CCHS 1.2, utilization was 19.3%, whereas without such disorders, it was 4.1%. Selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants for those with a past-year major depressive episode (17.8%), followed by venlafaxine (7.4%). Among people aged 15 to 19 years, antidepressant use was 1.8% overall and 11.7% among those with past-year depression; SSRIs made up the majority of use. Sedative-hypnotics were used by 3.1% overall, increasing with age to 11.1% over 75 years.
Beltman MW, Voshaar RC, Speckens AE. **Cognitive-behavioural therapy** for depression in people with a somatic disease: meta-analysis of randomised controlled trials. Br J Psychiatry. 2010 Jul;197(1):11-9.
Bergh S, Selbæk G, Engedal K. **Discontinuation of antidepressants** in people with **dementia** and neuropsychiatric symptoms (**DESEP** study): double blind, randomised, parallel group, placebo controlled trial. BMJ. 2012 Mar 9;344:e1566.
Bezchlibnyk-Butler Clinical Handbook of Psychotropic Drugs, 17th Ed. 2007.
Biggs WS, Demuth RH, **Premenstrual Syndrome and Premenstrual Dysphoric Disorder**. Am Fam Physician. 2011 Oct 15;84(8):918-924.

TOP

Blier P, Ward HE, Tremblay P, et al. **Combination of antidepressant medications** from treatment initiation for major depressive disorder: a double-blind randomized study. Am J Psychiatry. 2010 Mar;167(3):281-8.
Bombardier Charles H.; Fann Jesse R.;. Temkin Nancy R et al; Rates of Major Depressive Disorder and Clinical Outcomes Following **Traumatic Brain Injury** JAMA. 2010;303(19):1938-1945.
Boulenger JP, et al. A comparative study of the efficacy of long-term treatment with **escitalopram** and **paroxetine** in severely depressed patients. Curr Med Res Opin. 2006 Jul;22(7):1331-41.
Braun UK, Pham C, Kunik ME. Recognizing and managing **depression at end of life**. Geriatrics. 2008 Jun;63(6):25-7.
Breen G, Webb BT, Butler AW, et al. A Genome-Wide Significant Linkage for Severe Depression on **Chromosome 3**: The Depression Network Study. Am J Psychiatry. 2011 May 15.
Brown GK, Ten Have T, Henriques GR, Xie SX, Hollander JE, Beck AT. **Cognitive therapy** for the prevention of suicide attempts: a randomized controlled trial. JAMA. 2005 Aug 3;294(5):563-70.
Brown J, O' Brien PM, Marjoribanks J, Wyatt K. **Selective serotonin reuptake inhibitors for premenstrual syndrome**. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD001396.
Brunzell JD. Clinical practice. **Hypertriglyceridemia**. N Engl J Med. 2007 Sep 6;357(10):1009-17.
Canadian Anxiety Guideline July 2006 (Panic, PTSD, GAD, SAD, OCD & specific phobias)
http://www.cpa-apc.org/Publications/CJP/supplements/july2006/anxiety_guidelines_2006.pdf
Canadian Coalition for Seniors' Mental Health (**CCSMH**) National **Guidelines for Mental Health** 2006: http://www.ccsmh.ca/en/default.cfm http://www.ccsmh.ca/pdf/final%20supplement.pdf
Candy B Jones L Williams R Tookman A King M. Psychostimulants for depression. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006722. There is some evidence that in the short-term, PS reduce symptoms of depression. Whilst this reduction is statistically significant, the clinical significance is less clear.
Carney RM.; et al. **Omega-3 Augmentation** of Sertraline in Treatment of Depression in Patients With Coronary Heart Disease: A Randomized Controlled Trial. JAMA. 2009;302(15):1651-1657.
Charles H. Bombardier; Jesse R. Fann; Nancy R. Temkin et al; Rates of Major Depressive Disorder and Clinical Outcomes Following **Traumatic Brain Injury** JAMA. 2010;303(19):1938-1945.
Carrasco M, Volkmar FR, Bloch MH. Pharmacologic Treatment of Repetitive Behaviors in Autism Spectrum Disorders: Evidence of **Publication Bias**. Pediatrics. 2012 Apr 23. (serotonin receptor inhibitors –SRIs)
Chalder M, Wiles NJ, Campbell J, et al. **Facilitated physical activity** as a treatment for depressed adults: randomised controlled trial. BMJ. 2012 Jun6;344:e2758.
Chaudron, Linda H., Szilagyi, Peter G., Tang, Wan, et al. Accuracy of Depression **Screening Tools** for Identifying **Postpartum Depression** Among Urban Mothers. Pediatrics 2010 125: e609-e617.
Choi-Kwon S, Han SW, Kwon SU, et al. **Fluoxetine Treatment in Poststroke** Depression, Emotional Incontinence, and Anger Proneness. A Double-Blind, Placebo-Controlled Study. Stroke. 2005 Nov 23; [Epub ahead of print]
Choi-Kwon S, Han K, Choi S, et al. **Poststroke depression** and emotional incontinence: Factors related to acute and subacute stages. Neurology. 2012 Apr 10;78(15):1130-7.
Chollet F et al. **Fluoxetine for motor recovery after acute ischaemic stroke** (**FLAME**): A randomised placebo-controlled trial. Lancet Neurol 2011 Feb; 10:123.
Chun-Fai-Chan B, Koren G, Fayez I, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: A prospective comparative study. Am J Obstet Gynecol 2005; 192:932-36. (InfoPOEMs: Bupropion is not associated with increased rates of major malformations. It may be associated with an increase in spontaneous abortions. (LOE = 1b))
Cipriani A, Brambilla P, Furukawa T, et al.Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev. 2005 Oct 19;4:CD004185. AUTHORS' CONCLUSIONS: There are statistically significant differences in terms of efficacy and tolerability between fluoxetine and certain ADs, but the clinical meaning of these differences is uncertain, and no definitive implications for clinical practice can be drawn. From a clinical point of view the analysis of antidepressants' safety profile (adverse effect and suicide risk) remains of crucial importance and more reliable data about these outcomes are needed. Waiting for more robust evidence, treatment decisions should be based on considerations of clinical history, drug toxicity, patient acceptability, and cost. We need for large, pragmatic trials, enrolling heterogeneous populations of patients with depression to generate clinically relevant information on the benefits and harms of competitive pharmacological options. A meta-analysis of individual patient data from the randomised trials is clearly necessary.
Cipriani A, Furukawa TA, Salanti G, Geddes JR, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a **multiple-treatments meta-analysis**. Lancet. 2009 Jan 28. [Epub ahead of print] Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.
Cipriani A, La Ferla T, Furukawa TA, et al. **Sertraline** versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006117. This systematic review and meta-analysis highlighted a trend in favour of sertraline over other antidepressive agents both in terms of efficacy and acceptability, using 95% confidence intervals and a conservative approach, with a random effects analysis. However, the included studies did not report on all the outcomes that were pre-specified in the protocol of this review. Outcomes of clear relevance to patients and clinicians were not reported in any of the included studies.
Coelho HF, Boddy K, Ernst E. **Massage therapy** for the treatment of depression: a systematic review. Int J Clin Pract. 2008 Feb;62(2):325-33. Epub 2007 Dec 11. This review found no robust evidence supporting a recommendation for deep (Swedish) massage therapy as a sole or additive modality for treating unipolar depression. (LOE = 1a-)
Cohen LS, et al. Relapse of major depression during **pregnancy** in women who maintain or discontinue antidepressant treatment. JAMA. 2006 Feb 1;295(5):499-507. CONCLUSIONS: Pregnancy is not "protective" with respect to risk of relapse of major depression. Women with histories of depression who are euthymic in the context of ongoing antidepressant therapy should be aware of the association of depressive relapse during pregnancy with antidepressant discontinuation.{InfoPOEMs Mar 2006: Nearly 50% of women currently receiving antidepressant medication will experience a relapse of major depression during pregnancy. The risk is highest for those discontinuing their medication (68% relapse rate). It is likely that this study sample consists of patients with a higher severity of illness than those found in a routine community practice, so the findings may not generalize to other settings. (LOE = 1b). Women maintaining their medication during pregnancy relapsed significantly less often than those who discontinued medication (26% vs 68%; number needed to treat (NNT)= 2; 95% CI, 1.8 - 4).}
Colfax GN, Santos GM, Das M, et al. **Mirtazapine to reduce methamphetamine use**: a randomized controlled trial. Arch Gen Psychiatry. 2011 Nov;68(11):1168-75.
Colman I, Naicker K, Zeng Y, et al. Predictors of long-term **prognosis of depression**. CMAJ 2011;183:1969-76.
Colucci VJ, Berry BD. **Heart failure** worsening and exacerbation after venlafaxine and duloxetine therapy. Ann Pharmacother. 2008 Jun;42(6):882-7. Epub 2008 Apr 29.
Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for **antidepressant augmentation , combination and switching strategies**. Drugs 2011;71(1):43-64.
Coogan PF, Palmer JR, Strom BL, Rosenberg L. Use of selective serotonin reuptake inhibitors and the risk of **breast cancer**. Am J Epidemiol. 2005 Nov 1;162(9):835-8. Epub 2005 Sep 21.
Cooper C, Katona C, Lyketsos K, et al. A Systematic Review of Treatments for **Refractory Depression in Older People**. Am J Psychiatry. 2011 Mar 31.
Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of **adverse outcomes in older people**: population based cohort study. BMJ. 2011 Aug 2;343:d4551. doi: 10.1136/bmj.d4551.
Coupland CA, Dhiman P, Barton G, et al. A study of the **safety and harms of antidepressant drugs for older people**: a cohort study using a large primary care database. Health Technol Assess. 2011 Aug;15(28):1-202, iii-iv.
Crawford MJ, Thana L, Methuen C, et al. Impact of **screening for risk of suicide**: randomised controlled trial. Br J Psychiatry. 2011 May;198(5):379-84.
Croen LA et al. Antidepressant use during **pregnancy and childhood autism spectrum disorders**. Arch Gen Psychiatry 2011 Jul 4
Cronholm PF, Fogarty CT, Ambuel B, Harrison SL. **Intimate partner violence**. Am Fam Physician. 2011 May 15;83(10):1165-72.
Cuijpers P, van Straten A, Smit F, Mihalopoulos C, Beekman A. Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions. Am J Psychiatry. 2008 Oct;165(10):1272-80. Epub 2008 Sep 2. Prevention of new cases of depressive disorders does seem to be possible. Prevention may become an important way, in addition to treatment, to reduce the enormous public health burden of depression in the coming years.
Davidson J, et al. Treatment of **Posttraumatic Stress Disorder With Venlafaxine** Extended Release: A 6-Month Randomized Controlled Trial. Arch Gen Psychiatry. 2006 Oct;63(10):1158-1165. n=329
Davidson KW, Rieckmann N, Clemow L, et al. Enhanced **depression care for patients with acute coronary syndrome** and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. Arch Intern Med. 2010 Apr 12;170(7):600-8.
Davis RN, Davis MM, Freed GL, Clark SJ. **Fathers' Depression** Related to Positive and Negative Parenting Behaviors With 1-Year-Old Children. Pediatrics. 2011 Mar 14.
de Graaf LE, Gerhards SA, Arntz A, et al. Clinical effectiveness of online computerised **cognitive-behavioural therapy** without support for depression in primary care: randomised trial. Br J Psychiatry. 2009 Jul;195(1):73-80.
Dennis CL, et al. **Psychosocial and psychological interventions** for treating postpartum depression. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006116. Although the methodological quality of the majority of trials was, in general, not strong, the meta-analysis results suggest that psychosocial and psychological interventions are an effective treatment option for women suffering from postpartum depression.
Dennis M, Kadri A, Coffey J. Depression in **older people in the general hospital: a systematic review of screening** instruments. Age Ageing. 2012 Mar;41(2):148-54.
Depression scales The PHQ-9 is the 9 item depression scale of the Patient Health Questionnaire. The PHQ-9 is a powerful tool for assisting primary care clinicians in diagnosing depression as well as selecting and monitoring

TOP

treatment. http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/ **PHQ-2 Patient Health Questionnaire 2** about depressed mood and anhedonia: http://www.aafp.org/afp/20040915/1101.html
Deshauer D, Moher D, Fergusson D, et al. Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic **long-term randomized controlled trials**. CMAJ. 2008 May 6;178(10):1293-301. There is a lack of classic randomized controlled trials of serotonin reuptake inhibitors lasting more than 1 year for the treatment of depression. The results of our systematic review support current recommendations for 6-8 months of antidepressant treatment following initial recovery but provide no guidance for longer treatment.
De Vera MA, Bérard A. Antidepressant Use During **Pregnancy and the Risk of Pregnancy Induced Hypertension**. Br J Clin Pharmacol. 2012 Mar 21.
Dhillon S, Scott LJ, Plosker GL. **Escitalopram**: a review of its use in the management of anxiety disorders. CNS Drugs. 2006;20(9):763-90. Nevertheless, available clinical data indicate that escitalopram is an effective first-line treatment option for the management of GAD, SAD, panic disorder and OCD.
Diez-Quevedo C, Masnou H, Planas R, et al. Prophylactic treatment with **escitalopram of pegylated interferon** alfa-2a-induced depression in hepatitis c: a 12-week, randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010 Oct 5.
Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist (**ketamine**) in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010 Aug;67(8):793-802.
Dobkin RD, Menza M, Allen LA, et al. **Cognitive-behavioral therapy for depression in Parkinson's** disease: a random ized, controlled trial. Am J Psychiatry 2011; 168:1066–1074.
Dowlati Y, Herrmann N, Swardfager WL, Reim EK, Lanctôt KL. Efficacy and tolerability of antidepressants for treatment of depression in **coronary artery disease**: a meta-analysis. Can J Psychiatry. 2010 Feb;55(2):91-9.
Drug and Therapeutics Bulletin. Management of **seasonal affective disorder.** BMJ. 2010 May 21;340:c2135. doi: 10.1136/bmj.c2135.
Durand JP, Deplanque G, Montheil V, et al. Efficacy of **venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity**: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2011 Mar 22.
Eating Disorder Treatment. Pharmacist's Letter. Aug 2006.
Earls, Marian F., THE COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, Clinical Report--Incorporating Recognition and Management of **Perinatal and Postpartum Depression** Into Pediatric Practice. Pediatrics 2010 0: peds.2010-2348.
Eberhard-Gran M, Eskild A, Opjordsmoen S. Use of Psychotropic Medications in Treating Mood Disorders during **Lactation** : Practical Recommendations. CNS Drugs. 2006;20(3):187-98.

Elderly

[Baldwin RC, Anderson D, Black S, et al; Faculty of Old Age Psychiatry Working Group, Royal College of Psychiatrists. Guideline for the management of late-life depression in primary care. Int J Geriatr Psychiatry. 2003 Sep;18(9):829-38.
Charney et al. Depression and Bipolar Support Alliance. Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. Arch Gen Psychiatry. 2003 Jul;60(7):664-72.
Cooper C, Katona C, Lyketsos K, et al. A Systematic Review of Treatments for Refractory Depression in Older People. Am J Psychiatry. 2011 Mar 31.
Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of **adverse outcomes in older people**: population based cohort study. BMJ. 2011 Aug 2;343:d4551. doi: 10.1136/bmj.d4551.
Coupland CA, Dhiman P, Barton G, et al. A study of the **safety and harms of antidepressant drugs for older people**: a cohort study using a large primary care database. Health Technol Assess. 2011 Aug;15(28):1-202, iii-iv.
Cuijpers P, van Straten A, Smit F. Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. Int J Geriatr Psychiatry. 2006 Dec;21(12):1139-49.
Dombrovski AY, Mulsant BH. The evidence for electroconvulsive therapy (ECT) in the treatment of severe late-life depression. ECT: the preferred treatment for severe depression in late life. Int Psychogeriatr. 2007 Feb;19(1):10-4, 27-35; discussion 24-6.
Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med. 2000 May 18;342(20):1462-70.
Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003491. Our findings suggest that SSRIs and TCAs are of the same efficacy. However, we have found some evidence suggesting that TCA related antidepressants and classical TCAs may have different side effect profiles and are associated with differing withdrawal rates when compared with SSRIs.
Mukai Y, Tampi RR. Treatment of depression in the elderly: A review of the recent literature on the efficacy of single- versus dual-action antidepressants. Clin Ther. 2009 May;31(5):945-61. The available data, although limited, suggest that the dual-action agents (TCAs and SNRIs) do not appear to confer any additional benefits in efficacy over single-action agents (SSRIs) in the treatment of depression in the elderly.
Pinquart M, Duberstein PR, Lyness JM. Treatments for later-life depressive conditions: a meta-analytic comparison of pharmacotherapy and psychotherapy. Am J Psychiatry. 2006 Sep;163(9):1493-501. Given that psychotherapy and pharmacotherapy did not show strong differences in effect sizes, treatment choice should be based on other criteria, such as contraindications, treatment access, or patient preferences.
Reynolds CF 3rd, Frank E, Perel JM, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA. 1999 Jan 6;281(1):39-45.
Rodda J, Walker Z, Carter J. Depression in **older adults**. BMJ. 2011 Sep 28;343:d5219. doi: 10.1136/bmj.d5219.
Sjösten N, Kivelä SL. The effects of physical exercise on depressive symptoms among the aged: a systematic review. Int J Geriatr Psychiatry. 2006 May;21(5):410-8.
Unützer J. Clinical practice. **Late-life depression**. N Engl J Med. 2007 Nov 29;357(22):2269-76.
Wilson K, Mottram P. A comparison of side effects of selective serotonin reuptake inhibitors and tricyclic antidepressants in older depressed patients: a meta-analysis. Int J Geriatr Psychiatry. 2004 Aug;19(8):754-62.]

Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. **Escitalopram in the Treatment of Adolescent Depression**: A Randomized Placebo-Controlled Multisite Trial. J Am Acad Child Adolesc Psychiatry. 2009 May 20. [Epub ahead of print]. In this study, escitalopram was effective and well tolerated in the treatment of depressed adolescents.
Emslie GJ, Mayes T, Porta G, et al. Treatment of **Resistant Depression in Adolescents** (**TORDIA**): Week 24 Outcomes. Am J Psychiatry. 2010 May 17.
Ensrud KE, et al. for Study of Osteoporotic Fractures Research Gp. Use of **selective serotonin reuptake inhibitors** and **sleep** disturbances in community-dwelling older women. J Am Geriatr Soc 2006 Oct;54(10):1508-15.
Erkkilä J, Punkanen M, Fachner J, et al. Individual **music therapy** for depression: randomised controlled trial. Br J Psychiatry. 2011 Aug;199(2):132-9.
Etminan M, Mikelberg FS, Brophy JM. Selective **Serotonin Reuptake Inhibitors** and the Risk of **Cataracts** A Nested Case-Control Study. Ophthalmology. 2010 Mar 6.
Eyding D, Lelgemann M, Grouven U, et al. **Reboxetine** for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010 Oct 12;341:c4737. doi: 10.1136/bmj.c4737.
Fancher TL, Kravitz RL. **In the clinic. Depression**. Ann Intern Med. 2010 May 4;152(9):ITC51-15; quiz ITC5-16.
Fang F et al. **Suicide and cardiovascular death after a cancer diagnosis**. N Engl J Med 2012 Apr 5; 366:1310.
Fardet L et al. Suicidal behavior and severe **neuropsychiatric disorders following glucocorticoid** therapy in primary care. Am J Psychiatry 2012 May 1; 169:491.
Fava M, et al. Efficacy and safety of **sildenafil** in men with **serotonergic antidepressant-associated erectile dysfunction**: results from a randomized, double-blind, placebo-controlled trial.J Clin Psychiatry.2006Feb;67(2):240-6.
Fava M, Rush AJ, Wisniewski SR, et al. A Comparison of Mirtazapine and Nortriptyline Following Two Consecutive Failed Medication Treatments for Depressed Outpatients: A **STAR*D** Report. Am J Psychiatry. 2006 Jul;163(7):1161-72. Following lack of remission or an inability to tolerate an initial trial of citalopram for up to 12 weeks (first step) and a second trial with either monotherapy involving another antidepressant or augmentation of citalopram with bupropion or buspirone (second step), adult outpatients (N=235) with nonpsychotic major depressive disorder were randomly assigned to 14 weeks of treatment with mirtazapine (up to 60 mg/day) (N=114) or nortriptyline (up to 200 mg/day) (N=121). For mirtazapine, remission rates were 12.3% and 8.0% per the Hamilton and QIDS-SR(16) scores, respectively. For nortriptyline, remission rates were 19.8% and 12.4%, respectively
FDA: Oct/06 Letter regarding venlafaxine overdose concern http://www.fda.gov/medwatch/safety/2006/effexor_DHCPletter.pdf
FDA: Aug/11 Antidepressant citalopram (Celexa, Forest Laboratories) should not be used in doses higher than 40 mg per day because of concerns that it can cause potentially fatal changes in heart rhythm.
FDA: Dec/11 Selective Serotonin Reuptake Inhibitor Antidepressants: Use During Pregnancy & Potential Risk of Persistent Pulmonary Hypertension of the Newborn http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm283696.htm
Fink M, Taylor MA. **Electroconvulsive therapy**: evidence and challenges. JAMA. 2007 Jul 18;298(3):330-2.

TOP

Fisher HL, Moffitt TE, Houts RM, et al. **Bullying victimisation** and risk of **self harm** in early adolescence: longitudinal cohort study. BMJ. 2012 Apr 26;344:e2683.
Fournier Jay C.; DeRubeis Robert J.; Hollon Steven D.; et al. **Antidepressant Drug Effects and Depression Severity**: A Patient-Level Meta-analysis. JAMA. 2010;303(1):47-53.
Freeman MP, Mischoulon D, Tedeschini E, et al. **Complementary and alternative medicine for major depressive** disorder: a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. J Clin Psychiatry. 2010 Jun;71(6):682-8. Participants in CAM trials were more likely to be female and to have a lower placebo-response rate compared to those in standard antidepressant trials for MDD. Trials of standard antidepressants and CAM therapies were composed of patients with similar depression severity.
Freeman Ellen W., Guthrie Katherine A., Caan Bette, et al. Efficacy of **Escitalopram for Hot Flashes** in Healthy Menopausal Women: A Randomized Controlled Trial. JAMA. 2011;305(3):267-274.doi:10.1001/jama.2010.2016.
Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug **scopolamine**: a randomized, placebo-controlled clinical trial. Arch Gen Psychiatry. 2006 Oct;63(10):1121-9.
Gamble J, Creedy D, Moyle W, Webster J, McAllister M, Dickson P. Effectiveness of a counseling intervention after traumatic childbirth: A randomized trial. Birth 2005; 32:11-19. (InfoPOEMs: Women with trauma symptoms who receive face-to-face counseling during their hospital stay and phone counseling at 4 to 6 weeks postpartum are less likely to have persistent trauma symptoms or postpartum depression at 3 months. (LOE = 1b-))
Garber J et al. Prevention of **depression in at-risk adolescents**: A randomized controlled trial. *JAMA* 2009 Jun 3; 301:2215. The **CB prevention program** had a significant prevention effect through the 9-month follow-up period based on both clinical diagnoses and self-reported depressive symptoms, but this effect was not evident for adolescents with a currently depressed parent.
Garland J, Virani A, Kutcher S. **CACAP 2008** position paper on using **SSRIs in children and adolescents** [Internet]. Ottawa: Canadian Academy of Child and Adolescent Psychiatry; 2008
Gartlehner G, Gaynes BN, Hansen RA, et al. Comparative **benefits and harms of second-generation antidepressants**: background paper for the American College of Physicians. Ann Intern Med. 2008 Nov 18;149(10):734-50.
Gartlehner G, Thaler K, Hansen RA, Gaynes BN. The general and comparative efficacy and safety of **duloxetine** in major depressive disorder: a systematic review and meta-analysis. Drug Saf. 2009;32(12):1159-73. doi: 10.2165/11318930-000000000-00000.
Gartlehner G, Hansen RA, Morgan LC, et al. Comparative Benefits and Harms of **Second-Generation Antidepressants** for Treating Major Depressive Disorder: An Updated Meta-analysis. Ann Intern Med. 2011 Dec 6;155(11):772-85. Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy. Differences in onset of action and adverse events may be considered when choosing a medication.
George MS, Lisanby SH, Avery D, et al. Daily left prefrontal **transcranial magnetic stimulation** (TMS) therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010 May;67(5):507-16.
Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative Care for Depression: A Cumulative Meta-analysis and Review of **Longer-term Outcomes**. Arch Intern Med. 2006 Nov 27;166(21):2314-21.
Gilbody S, House A, Sheldon T, Gilbody S. **Screening** and case finding instruments for depression. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD002792. AUTHORS' CONCLUSIONS: There is substantial evidence that routinely administered case finding/screening questionnaires for depression have minimal impact on the detection, management or outcome of depression by clinicians. Practice guidelines and recommendations to adopt this strategy, in isolation, in order to improve the quality of healthcare should be resisted. The longer term benefits and costs of routine screening/case finding for depression have not been evaluated. A two stage procedure for screening/case finding may be effective, but this needs to be evaluated in a large scale cluster randomised trial, with a prospective economic evaluation.
Gibbons RD, Brown CH, Hur K, et al. **Suicidal** Thoughts & Behavior With Antidepressant Treatment: Reanalysis of the Randomized Placebo-Controlled Studies of **Fluoxetine and Venlafaxine**. Arch Gen Psychiatry. 2012 Feb 6
Gibbons RD, Hur K, Brown CH, et al. **Benefits From Antidepressants**: Synthesis of 6-Week Patient-Level Outcomes From Double-blind Placebo-Controlled Randomized Trials of Fluoxetine and Venlafaxine. Arch Gen Psychiatry. 2012 Mar 5.
Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry. 2004 Sep;161(9):1537-47.
Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of **light therapy** in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry. 2005 Apr;162(4):656-62. (InfoPOEMs: The available published research literature provides very weak evidence that light therapy is effective for seasonal affective disorder (SAD) or nonseasonal depression. There seems to be a large acute effect of light therapy on symptoms of SAD in the first week of treatment but this effect disappears quickly thereafter. Light therapy has a moderate effect on patients with nonseasonal depression when studied for only 7 days. Light therapy does not produce an additional effect when combined with pharmacologic therapy. Light boxes are expensive and may not provide the results desired by patients with SAD. (LOE = 1a-))
Goodman WK. **Electroconvulsive therapy (ECT)** in the spotlight. N Engl J Med. 2011 May 12;364(19):1785-7.
Goodyer I, Dubicka B, Wilkinson P, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in **adolescents** with major depression: randomised controlled trial. BMJ. 2007 Jul 21;335(7611):142. (ADAPT). For adolescents with moderate to severe major depression there is no evidence that the combination of CBT plus an SSRI in the presence of routine clinical care contributes to an improved outcome by 28 weeks compared with the provision of routine clinical care plus an SSRI alone.
Gordon PR, et al. **Sertraline** to treat **hot flashes**: a randomized controlled, double-blind, crossover trial in a general population. Menopause. 2006 Jul-Aug;13(4):568-75.
Gram L. Fluoxetine. *N Engl J Med* 1994;331:1354-61. (**low dose ~5mg effective**)
Green JM, Wood AJ, Kerfoot MJ, Trainor G, Roberts C, Rothwell J, et al. Group therapy for **adolescents with repeated self harm**: randomised controlled trial (ASSIST) with economic evaluation. BMJ 2011;342:d682.
Guaiana G, Barbui C, Hotopf M. **Amitriptyline for depression**. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004186. This present systematic review indicates that amitriptyline is at least as efficacious as other tricyclics or newer compounds. However, the burden of side-effects in patients receiving it was greater. In comparison with selective serotonin reuptake inhibitors amitriptyline was less well tolerated, and although counterbalanced by a higher proportion of responders, the difference was not statistically significant.
Gunderson JG, Morey LC, Stout RL, et al. Major depressive disorder and **borderline personality disorder** revisited: longitudinal interactions. J Clin Psychiatry 2004;65:1049-56.
Gunderson John G., **Borderline Personality Disorder**. N Engl J Med 2011; 364:2037-2042.
Hackett ML, Anderson CS, House A, et al. Interventions for treating **depression after stroke**. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD003437.
Hamer M, David Batty G, Seldenrijk A, Kivimaki M. **Antidepressant** medication use and future **risk of cardiovascular disease**: the Scottish Health Survey. Eur Heart J. 2010 Nov 30.
Hansen RA, Gartlehner G, Lohr KN, et al. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann Intern Med. 2005 Sep 20;143(6):415-26. CONCLUSIONS: Overall, second-generation antidepressants probably do not differ substantially for treatment of major depressive disorder. Choosing the agent that is most appropriate for a given patient is difficult. (InfoPOEMs: When it comes to the new, nontricyclic antidepressants, the medical literature does not give us any clear guidance as to which one is more effective, of faster onset, safer, or better tolerated. Sexual side effects are lower with bupropion and nausea seems to occur more often with venlafaxine. Other research has shown these new drugs to be no more effective or better tolerated than tricyclic antidepressants. For now, start your patient on your favorite antidepressant, with the realization that most patients will need to switch to another drug at least once. (LOE = 1a))
Hatcher S, Arroll B. **Newer antidepressants** for the treatment of depression in adults. BMJ 2012; 344 doi: 10.1136/bmj.d8300 (19 January 2012).
Häuser W, Wolfe F, Tölle T, Uçeyler N, Sommer C. The role of **antidepressants in the management of fibromyalgia** syndrome: a systematic review and meta-analysis. CNS Drugs. 2012 Apr 1;26(4):297-307.
Hawton K, Bergen H, Simkin S, Cooper J, Waters K, Gunnell D, et al. **Toxicity of antidepressants**: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry 2010;196:354-8.
Health Canada Oct/08 Venlafaxine overdose warning http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/venlaflaxine_hpc-cps-eng.php
Health Canada Feb/11 **Methylene blue injectable** in combination with serotonin reuptake inhibitors - Association with serotonin toxicity Cases of serotonin toxicity have been reported and published in association with the use of methylene blue injectable in patients exposed to drugs with serotonin reuptake inhibition properties.
Health Canada Jan/12: Lundbeck Canada, in collaboration with Health Canada, would like to inform you that the antidepressant **Celexa® (citalopram** hydrobromide; also marketed as generics), should no longer be used at doses greater than **40 mg per day** due to study results indicating a dose-dependent potential for QT prolongation.
Health Canada May/12 is informing Canadians of a labelling update for the prescription drug **Cipralex** (the brand name of the drug **escitalopram**) regarding a dose-related risk of abnormal heart rhythms. Cipralex is used to treat depression and belongs to a family of drugs known as Selective Serotonin Reuptake Inhibitors (SSRIs). 10 mg per day is the maximum recommended dose for patients who: are 65 years of age or older, or have liver problems, or are taking the heartburn drugs omeprazole or cimetidine which can increase the blood level of Cipralex. 20 mg per day is still the maximum recommended dose for most other patients.
Hedayati S. Susan; Minhajuddin Abu T.; Afshar Masoud et al.Association Between Major Depressive Episodes in Patients With **Chronic Kidney Disease** and Initiation of Dialysis, Hospitalization, or Death JAMA. 2010;303(19):1946-1953.

TOP

Hegel M, Arndt S. Escitalopram and problem-solving therapy for prevention of **poststroke depression**: a randomized controlled trial. JAMA. 2008 May 28;299(20):2391-400. In this study of nondepressed patients with recent stroke, the use of escitalopram or problem-solving therapy resulted in a significantly lower incidence of depression over 12 months of treatment compared with placebo, but problem-solving therapy did not achieve significant results over placebo using the intention-to-treat conservative method of analysis.
Hendron D et al. **Tricyclic antidepressant overdose** in a toddler treated with **intravenous lipid emulsion**. Pediatrics. 2011 Dec;128(6):e1628-32.
Herring MP, Puetz TW, O'Connor PJ, Dishman RK. Effect of **Exercise Training** on Depressive Symptoms Among Patients With a Chronic Illness: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2012 Jan 23;172(2):101-11.
Hickie Ian B, Rogers Naomi L. Novel **melatonin-based therapies**: (agomelatine) potential advances in the treatment of major depression. www.thelancet.com Published May 18, 2011 DOI:10.1016/S0140-6736(11)60095-0.
Hodgins David C, Stea Jonathan N, Grant Jon E. **Gambling disorders**. www.thelancet.com Published online May 19, 2011 DOI:10.1016/S0140-6736(10)62185-X
Hollander E et al. A Double-Blind Placebo-Controlled Trial of **Fluoxetine for Repetitive Behaviors and Global Severity in Adult Autism** Spectrum Disorders. Am J Psychiatry. 2011 Dec 2.
Honkola J, Hookana E, Malinen S, et al. Psychotropic medications (antipsychotics & antidepressants) and the **risk of sudden cardiac death** during an acute coronary event. Eur Heart J. 2012 Mar;33(6):745-51.
Howell EA, Balbierz A, Wang J, et al. Reducing **postpartum depressive symptoms** among black and latina mothers: a randomized controlled trial. Obstet Gynecol. 2012 May;119(5):942-9.
Hubbard R, Lewis S, et al. **Bupropion** and the risk of sudden death: a self-controlled case-series analysis using The Health Improvement Network. Thorax. 2005 Oct;60(10):848-50. Epub 2005 Jul 29.
Hubsher G, Haider M, Okun MS. **Amantadine**: The journey from **fighting flu to treating Parkinson** disease. Neurology. 2012 Apr 3;78(14):1096-9.
Hunkeler EM, et al. Long term outcomes from the **IMPACT** randomised trial for depressed elderly patients in primary care. BMJ. 2006 Feb 4;332(7536):259-63. Epub 2006 Jan 20.
El Husseini N, Goldstein LB, Peterson ED,et al.**Depression and Antidepressant Use After Stroke** and Transient Ischemic Attack. Stroke. 2012 Mar 29.
ICSI Institute for Clinical Systems Improvement. **Major depression in adults in primary care**. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 May.
Ingenhoven T, Lafay P, Rinne T, et al. Effectiveness of pharmacotherapy for **severe personality disorders**: meta-analyses of randomized controlled trials. J Clin Psychiatry 2010; 71:14-25.
Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and **poststroke depression**: a placebo-controlled trial of antidepressants. Am J Psychiatry. 2003 Oct;160(10):1823-9.
Jorge RE, Acion L, Moser D, et al. Escitalopram and enhancement of cognitive recovery **following stroke**. Arch Gen Psychiatry. 2010 Feb;67(2):187-96.
Johnson EM, et al. **Cardiovascular changes** associated with **venlafaxine** in the treatment of late-life depression. Am J Geriatr Psychiatry. 2006 Sep;14(9):796-802.
Kang Seung-Gul, Yoon Byung-Mun, Park Young-Min. **Mirtazapine-Induced Hepatocellular-Type Liver Injury** Articles Ahead of Print published on 1 June 2011, DOI 10.1345/aph.1Q078. Ann Pharmacother ;45:825-826.
Katila H, Mezhebovsky I, Mulroy A, et al. Randomized, Double-Blind Study of the Efficacy and Tolerability of **Extended Release Quetiapine** Fumarate (Quetiapine XR) Monotherapy in Elderly Patients With Major Depressive Disorder. Am J Geriatr Psychiatry. 2012 Jun 7.
Katon WJ, Lin EH, Von Korff M, et al. **Collaborative care for patients with depression** and chronic illnesses. N Engl J Med. 2010 Dec 30;363(27):2611-20.
Katz LY, Au W, Singal D, et al. **Suicide and suicide attempts in children and adolescents** in the child welfare system. CMAJ. 2011 Oct 17.
Keller MB, Trivedi MH, Thase ME, et al. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (**PREVENT**) Study: Outcomes from the **2-year** and combined maintenance phases. J Clin Psyc. 2007 Aug;68(8):1246-56. In this study, an additional 12 months of maintenance therapy with venlafaxine ER was effective in preventing recurrence of depression in pts who had been responders to venlafaxine ER after acute (10 weeks), continuation (6 months), and initial maintenance (12 months) therapy.
Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving **tamoxifen**: a population based cohort study BMJ 2010;340:c693, doi: 10.1136/bmj.c693 (8 Feb10).
Kendel Friederike; Gelbrich Gotz; Wirtz Markus; et al. Predictive Relationship Between Depression and Physical Functioning After **Coronary Surgery**. Arch Intern Med. 2010;170(19):1717-1721.
Kennedy SH, Andersen HF, Lam RW. Efficacy of **escitalopram** in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and **venlafaxine** XR: a meta-analysis. J Psychiatry Neurosci. 2006 Mar;31(2):122-31. Erratum in: J Psychiatry Neurosci. 2006 Jul;31(4):228.
Kennedy SH, et al. Sexual function during **bupropion** or paroxetine treatment of major depressive disorder. Can J Psychiatry. 2006 Mar;51(4):234-42.
Kennedy GJ, Marcus P. Use of antidepressants in **older patients** with co-morbid medical conditions: guidance from studies of depression in somatic illness. Drugs Aging. 2005;22(4):273-87.
Khoza S, Barner JC, Bohman TM, Rascati K, Lawson K, Wilson JP. Use of antidepressant agents and the **risk of type 2 diabetes**. Eur J Clin Pharmacol. 2011 Nov 26.
Kim H, et al. **Monoamine transporter gene polymorphisms** and antidepressant response in Koreans with late-life depression. JAMA. 2006 Oct 4;296(13):1609-18.
King Bryan H; Hollander Eric; et al.; for the **STAART** Psychopharmacology Network Lack of Efficacy of Citalopram in Children With Autism Spectrum Disorders and High Levels of Repetitive Behavior: **Citalopram** Ineffective in Children With Autism Arch Gen Psychiatry. 2009;66(6):583-590.
Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and **antidepressant benefits**: a meta-analysis of date submitted to the Food and Drug Administration. PLoS Med 2008;5:e45. (Limited or placebo like benefit)
Kisely S, Smith M, Lawrence D, Maaten S. **Mortality** in individuals who have had psychiatric treatment: Population-based study in Nova Scotia. Br J Psychiatry. 2005 Dec;187:552-558.
Kok RM, Aartsen M, Nolen WA, et al. The Course of Adverse Effects of Nortriptyline and Venlafaxine in **Elderly** Patients with Major Depression. J Am Geriatr Soc. 2009;57:3112-7. (both equally well tolerated)
Komossa K, Depping AM, Gaudchau A, et al. **Second-generation antipsychotics for major depressive** disorder and dysthymia. Cochrane Database Syst Rev. 2010 Dec 8;12:CD008121
Koren G, Nordeng H. **Antidepressant use during pregnancy**: the benefit-risk ratio. Am J Obstet Gynecol. 2012 Feb 21.
Kraus MR, et al. Therapy of interferon-induced depression in chronic **hepatitis C** with citalopram: a randomised, double-blind, placebo-controlled study. Gut. 2008 Apr;57(4):531-6. Epub 2007 Dec 13. The findings demonstrate clearly that citalopram treatment is highly effective in HCV patients on interferon therapy, when initiated after the onset of clinically relevant depressive symptoms. This suggests that a general SSRI prophylaxis is not necessary in these patients.
Kroenke Kurt; Bair Matthew J.; Damush Teresa M.; et al. Optimized Antidepressant Therapy and Pain Self-management in Primary Care Patients With Depression and **Musculoskeletal Pain**: A Randomized Controlled Trial. JAMA. 2009;301(20):2099-2110. Optimized antidepressant therapy followed by a pain selfmanagement program resulted in substantial improvement in depression as well as moderate reductions in pain severity and disability.
Kruithof Maartje K, Bruins Nynke A, van Roon Eric N. Coma After **Overdose with Duloxetine**. Articles Ahead of Print published on 1 January 2011, DOI 10.1345/aph.1P432. Ann Pharmacother ;45:e5.
Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet. 2011 Dec 19.
Lam RW, et al. The Can-SAD study: a randomized controlled trial of the effectiveness of **light therapy** and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry. 2006 May;163(5):805-12. (InfoPOEMs: Light therapy and fluoxetine (Prozac) are equally effective treatment options for patients with seasonal affective disorder (SAD). Patient preference and an individual assessment of risks and benefits should guide treatment selection. (LOE = 1b))
Lenze EJ, Rollman BL, Shear MK, et al. **Escitalopram for older adults** with **generalized anxiety** disorder: a randomized controlled trial. JAMA. 2009 Jan 21;301(3):295-303. Older adults $^{n=177}$ with GAD randomized to escitalopram 10-20mg od had a higher cumulative response rate for improvement vs placebo over 12 weeks; however, response rates were not significantly different using an intention-to-treat analysis. Further study is required to assess efficacy and safety over longer treatment durations.
Leon AC, Solomon DA, Li C, et al. Antidepressants and **risks of suicide and suicide attempts**: a 27-year observational study. J Clin Psychiatry. 2011;72:580-586.
Leucht S, Hierl S, Kissling W et al. Putting the efficacy of **psychiatric and general medicine medication into perspective**: review of meta-analyses. Br J Psychiatry. 2012 Feb;200:97-106.
Leverich GS, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and **bupropion** as adjuncts to mood stabilizers. Am J Psychiatry. 2006 Feb;163(2):232-9.
Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for **dysthymia**: a meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry. 2011 Apr;72(4):509-14.
Lewis G, Mulligan J, Wiles N, et al. **Polymorphism of the 5-HT transporter** and response to antidepressants: randomised controlled trial. Br J Psychiatry. 2011 Jun;198:464-71.
Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment **after FDA warnings**. Arch Gen Psychiatry. 2009 Jun;66(6):633-9.
Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. **Depression and Coronary Heart Disease**. Recommendations for Screening, Referral, and Treatment. A Science Advisory From the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation. 2008 Sep 29. [Epub ahead of print] **Patient Health Questionnaire** for Screening: http://www.phqscreeners.com/

TOP

Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM. Pharmacotherapy for **borderline personality disorder**: Cochrane systematic review of randomised trials. Br J Psychiatry 2010;196:4-12.
Linde K, Berner MM, Kriston L. **St John`s wort** for major depression. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD000448. The available evidence suggests that the hypericum extracts tested in the included trials a) are superior to placebo in patients with major depression; b) are similarly effective as standard antidepressants; c) and have fewer side effects than standard antidepressants. The association of country of origin and precision with effects sizes complicates the interpretation.
Lindsey WT. **Vilazodone** for the treatment of depression. Ann Pharmacother. 2011 Jul;45(7-8):946-53.
Linehan MM, et al. Two-Yr Randomized Controlled Trial & Follow-up of **Dialectical Behavior Therapy** vs Therapy by Experts for Suicidal Behaviors & Borderline Personality Disorder. Arch Gen Psyc. 2006 Jul;63(7):757-66.
Lisanby SH. **Electroconvulsive therapy** for depression. N Engl J Med. 2007 Nov 8;357(19):1939-45.
Little A., **Treatment-Resistant Depression**. Am Fam Physician. 2009;80(1):167-172.
Lucas M, Mirzaei F, Pan A, et al. **Coffee, caffeine**, and risk of depression among women. Arch Intern Med. 2011 Sep 26;171(17):1571-8.
Ludermir AB, Lewis G, Valongueiro SA, et al. **Violence against women** by their intimate partner during pregnancy and postnatal depression: a prospective cohort study. Lancet. 2010 Sep 11;376(9744):903-10.
Lustman PJ, et al. Sertraline for Prevention of Depression Recurrence in **Diabetes** Mellitus: A Randomized, Double-blind, Placebo-Controlled Trial. Arch Gen Psychiatry. 2006 May;63(5):521-9.
Ma J, et al. Association between antidepressant use and prescribing of **gastric acid suppressants**. Can J Psychiatry. 2006 Mar;51(3):178-84.
Makrides Maria; Gibson Robert A.;. McPhee Andrew J; et al.; and the DOMInO Investigative Team Effect of **DHA Supplementation** During Pregnancy on Maternal Depression and Neurodevelopment of Young Children: A Randomized Controlled Trial *JAMA*. 2010;304(15):1675-1683.
Mann JJ, Apter A, Bertolote J, et al. **Suicide prevention strategies**: a systematic review. JAMA. 2005 Oct 26;294(16):2064-74. CONCLUSIONS: Physician education in depression recognition and treatment and restricting access to lethal methods reduce suicide rates. Other interventions need more evidence of efficacy. Ascertaining which components of suicide prevention programs are effective in reducing rates of suicide and suicide attempt is essential in order to optimize use of limited resources.
Mann JJ. The **medical management of depression**. N Engl J Med. 2005 Oct 27;353(17):1819-34.
Marcy TR, Britton ML. Antidepressant-induced **sweating**.Ann Pharmacother. 2005 Apr;39(4):748-52. Epub 2005 Feb 22.
Mariappan P, Ballantyne Z, N'dow J, Alhasso A. Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004742.
MacMillan HL et al. Canadian Task Force on Preventive Health Care. Screening for depression in primary care: recommendation statement from the Canadian Task Force on Preventive Health Care.CMAJ.2005Jan 4;172(1):33-5.
Mahmoud RA, Pandina GJ, Turkoz I, et al. **Risperidone** for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med. 2007 Nov 6;147(9):593-602. n=274 6wks. Risperidone (up to 2mg/d) augmentation produced a statistically significant mean reduction in depression symptoms, substantially increased remission and response, and improved other patient- and clinician-rated measures.
Manea L, Gilbody S, McMillan D. **Optimal cut-off score** for diagnosing depression with the Patient Health Questionnaire (**PHQ-9**): a meta-analysis. CMAJ 2012;184:E191-6.
Mann R, Adamson J, Gilbody SM. Diagnostic accuracy of case-finding questions to **identify perinatal depression**. CMAJ. 2012 Apr 2.
Martinez Carlos, Assimes TL, Mines D, et al. Use of **venlafaxine** compared with other antidepressants and the risk of **sudden cardiac death or near death**: a nested case-control study. BMJ 2010;340:c249. (5 Feb 2010)
Mathew SJ, Shah A, Lapidus K, et al. **Ketamine** for treatment-resistant unipolar depression: current evidence. CNS Drugs. 2012 Mar 1;26(3):189-204.
Maurer, D et al. **Screening for Depression**. Am Fam Physician. 2012 Jan 15;85(2):139-144.
McGrath PJ, et al. **Predictors of relapse** in a prospective study of fluoxetine treatment of major depression. Am J Psychiatry. 2006 Sep;163(9):1542-8.
McGrath PJ, et al. Tranylcypromine Versus Venlafaxine Plus Mirtazapine Following Three Failed Antidepressant Medication Trials for Depression: A **STAR*D** Report. Am J Psychiatry. 2006 Sep;163(9):1531-41. Remission rates were modest for both the tranylcypromine group and the extended-release venlafaxine plus mirtazapine group, and the rates were not statistically different between groups. The lower side effect burden, lack of dietary restrictions, and ease of use of venlafaxine and mirtazapine suggest that this combination may be preferred over tranylcypromine for patients with highly treatment-resistant depression who have not benefited adequately from several prior treatments.
McLeod Melanie. An update on the pharmacotherapy of depression. Continuing Education Lesson. November 2011.
Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. **Exercise for depression**. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004366.
Medical Letter, **Duloxetine** for Diabetic Neuropathic pain. Vol 47 (Issue 1215/1216) Aug 15/29,2005. p.67-68.
Medical Letter. "Treatment Guidelines- Drugs for Psychiatric Disorders Vol 4 (Issue 46) June 2006.
Medical Letter. Treatment Guidelines. Drugs for Depression and Bipolar Disorder. May 2010.
Medical Letter, **L-Methylfolate** for Depression or Schizoprenia. April 2010.
Merry SN, Hetrick SE, Cox GR, et al. **Psychological and educational interventions for preventing depression** in children and adolescents. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD003380. DOI: 10.1002/14651858.CD003380.pub3. There is some evidence from this review that targeted and universal depression prevention programmes may prevent the onset of depressive disorders compared with no intervention.
Merry SN, Stasiak K, Shepherd M, et al. The effectiveness of **SPARX**, a computerised **self help intervention for adolescents** seeking help for depression: randomised controlled non-inferiority trial. BMJ. 2012 Apr 18
MHRA UK **Reboxetine**: benefit-risk balance reviewed. Sept 2011. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON128957
MHRA Dec/11 **Citalopram and escitalopram** are associated with dose-dependent **QT interval** prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval. ECG measurements should be considered for patients with cardiac disease, and electrolyte disturbances should be corrected before starting treatment. For citalopram, new restrictions on the maximum daily doses now apply: 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment. For escitalopram, the maximum daily dose for patients older than 65 years is now reduced to 10 mg/day; other doses remain unchanged.
Miller L et al. **Religiosity** (spirituality) and major depression in adults at high risk: A ten-year prospective study. Am J Psychiatry 2011 Aug 24
Mines D, Hill D, Yu H, Novelli L. Prevalence of risk factors for **suicide in patients prescribed venlafaxine, fluoxetine, and citalopram**. Pharmacoepidemiol Drug Saf. 2005 Jun;14(6):367-72.
Mitchell AJ, Vaze A, Rao S. Clinical **diagnosis of depression in primary care**: a meta-analysis. Lancet. 2009 Jul 27. [Epub ahead of print]
Mitchell PH, Veith RC, Becker KJ, et al. Brief **psychosocial-behavioral intervention** with antidepressant reduces poststroke depression significantly more than usual care with antidepressant: living well with stroke: randomized, controlled trial. Stroke. 2009 Sep;40(9):3073-8.
Mitchell Alex J, Chan Melissa, Bhatti Henna, et al. Prevalence of **depression, anxiety, and adjustment disorder in oncological**, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies, The Lancet Oncology, Volume 12, Issue 2, Feb 2011, Pages 160-174, ISSN 1470-2045, DOI: 10.1016/S1470-2045(11)70002-X.
Mohr DC, Ho J, Duffecy J, et al. Effect of **Telephone-Administered vs Face-to-face Cognitive Behavioral Therapy** on Adherence to Therapy and Depression Outcomes Among Primary Care Patients: A Randomized Trial Telephone vs In-Person Therapy for Depression. JAMA. 2012 Jun6;307(21):2278-85.
Moja P, Cusi C, Sterzi R, Canepari C. Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002919. CONCLUSIONS: Over 2 months of treatment, SSRIs are no more efficacious than placebo in patients with migraine. In patients with chronic TTH, SSRIs are less efficacious than tricyclic antidepressants. In comparison with SSRIs, the burden of adverse events in patients receiving tricyclics was greater. These results are based on short-term trials and may not generalise to longer-term treatment.
Mojtabai R, Olfson M. Proportion of **antidepressants prescribed without a psychiatric diagnosis is growing**. Health Aff (Millwood). 2011 Aug;30(8):1434-42.
Moncada LV. Management of **falls in older persons**: a prescription for prevention. Am Fam Physician. 2011 Dec 1;84(11):1267-76.
Montgomery SA, Baldwin DS, Blier P, et al. Which antidepressants have demonstrated superior efficacy? A review of the evidence. Int Clin Psychopharmacol. 2007 Nov;22(6):323-329. Only escitalopram was found to have definite superiority in the treatment of severe depression; probable superiority was identified for venlafaxine and possible superiority for milnacipran and clomipramine.
Moore M, Yuen HM, Dunn N, et al. Explaining the **rise in antidepressant prescribing**: a descriptive study using the general practice research database. BMJ. 2009 Oct 15;339:b3999. doi: 10.1136/bmj.b3999. (more long term users)

TOP

Moran P, Coff ey C, Romaniuk H, et al. The natural history of **self-harm from adolescence to young adulthood**: a population-based cohort study. Lancet 2011; published online Nov 17. DOI:10.1016/S0140-6736(11)61141-0.
Murdoch D, Keam SJ. **Escitalopram**: a review of its use in the management of major depressive disorder. Drugs. 2005;65(16):2379-404.
Musters C, McDonald E, Jones I. **Management of postnatal depression**. BMJ. 2008 Aug 8;337:a736. doi: 10.1136/bmj.a736.
Nahas Z, Marangell LB, Husain MM, et al. Two-Year Outcome of Vagus Nerve Stimulation (VNS) for Treatment of Major Depressive Episodes. J Clin Psychiatry. 2005 Sep;66(9):1097-1104.
Nahas Richard, Sheikh Osmaan. **Complementary and alternative medicine** for the treatment of major depressive disorder Can Fam Physician June 2011 57: 659-663. (**St John's wort & exercise**)
Navarro V, Gastó C, Torres X, et al. Continuation/maintenance treatment with nortriptyline (n=17) versus combined **nortriptyline and ECT** (n=16)in late-life psychotic depression: a two-year randomized study. Am J Geriatr Psychiatry. 2008 Jun;16(6):498-505. This study supports the judicious use of combined continuation/maintenance ECT and antidepressant treatment in elderly patients with psychotic unipolar depression who are ECT remitters.
Nelson JC, et al. **Mirtazapine** orally disintegrating tablets in depressed nursing home residents **85 years of age and older**. Int J Geriatr Psychiatry. 2006 Sep;21(9):898-901.
Nelson JC, Papakostas GI. Atypical **antipsychotic augmentation** in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry. 2009 Sep;166(9):980-91. Epub 2009 Aug 17.
Nelson JC, Devanand DP. A Systematic Review and Meta-Analysis of Placebo-Controlled Antidepressant Studies in People with **Depression and Dementia** J Am Geriatr Soc. 2011 Apr;59(4):577-85.
NICE: CG90 Depression in adults: quick reference guide Oct/2009 http://www.nice.org.uk/nicemedia/pdf/CG%2090%20QRG%20LR%20FINAL.pdf
NICE: CG91 National Collaborating Centre for Mental Health. Depression in adults with a chronic physical health problem. Treatment and management. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Oct. 54 p. (Clinical guideline; no. 91). http://guidance.nice.org.uk/CG91
NICE: Jan **2011**: **Generalised anxiety disorder** (GAD) and panic disorder (PD) (with or without agoraphobia) in adults. http://guidance.nice.org.uk/CG113/QuickRefGuide/pdf/English ; http://guidance.nice.org.uk/CG113
NICE: Pilling Stephen, Whittington Craig, Taylor Clare, et al. on behalf of the Guideline Development Group. Guidelines: Identification and **care pathways for common mental health disorders**: summary of NICE guidance. BMJ 2011;342:doi:10.1136/bmj.d2868 (Published 24 May 2011)
NICE: National Institute for Health and Clinical Excellence. Common mental health disorders: identification and **pathways to care**. (Clinical guideline CG123. 2011. http://guidance.nice.org.uk/CG123 .
NICE: National Institute for Health and Clinical Excellence. **Self-harm**: longer-term management. (Clinical guideline CG133.) 2011. http://guidance.nice.org.uk/CG133.
Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of **lithium and T(3)** augmentation following two failed medication treatments for depression: a **STAR*D** report. Am J Psychiatry. 2006 Sep;163(9):1519-30; quiz 1665. Remission rates with lithium (up to 900mg/d) and T(3) augmentation (up to 50ug/d) for participants who experienced unsatisfactory results with two prior medication treatments were modest and did not differ significantly. The lower side effect burden and ease of use of T(3) augmentation suggest that it has slight advantages over lithium augmentation for depressed patients who have experienced several failed medication trials.
Norris D , Clark M. **Evaluation and Treatment of the Suicidal** Patient Am Fam Physician. 2012 Mar 15;85(6):602-605.
Nunns D, Murphy R. Assessment and management of **vulval pain**. BMJ. 2012 Mar 28;344:e1723.
O'Brien Shaughn, Rapkin Andrea, Dennerstein Lorraine, et al. Diagnosis and management of **premenstrual disorders**. BMJ 2011;342:doi:10.1136/bmj.d2994 (Published 3 June 2011)
O`Connor EA, Whitlock EP, Beil TL, et al. **Screening for depression** in **adult patients** in primary care settings: a systematic evidence review. Ann Intern Med. 2009 Dec 1;151(11):793-803.
Ohayon MM, Mahowald MW, Dauvilliers Y, et al. Prevalence and comorbidity of **nocturnal wandering** in the US adult general population. Neurology.2012 May 15;78(20):1583-9. (association with SSRIs)
Oldham JM, Gabbard GO, Goin MK, et al. Practice guideline for the treatment of patients with **borderline personality disorder**. Am J Psychiatry 2001;158:Suppl:1-52.
Olfson M, Shaffer D, Marcus SC, Greenberg T. Relationship between antidepressant medication treatment and **suicide** in adolescents. Arch Gen Psychiatry. 2003 Oct;60(10):978-82.
Olfson M, Marcus SC, Tedeschi M, Wan GJ. **Continuity of antidepressant treatment** for adults with depression in the United States. Am J Psychiatry. 2006 Jan;163(1):101-8.
Omori IM, Watanabe N, Nakagawa A, et al. **Fluvoxamine** versus other anti-depressive agents for depression. Cochrane Database Syst Rev. 2010 Mar 17;3:CD006114.
O'reardon JP, et al. A randomized, placebo-controlled trial of sertraline in the treatment of **night eating syndrome**. Am J Psychiatry. 2006 May;163(5):893-8.
Owenby RK, Brown LT, Brown JN. Use of **Risperidone** as Augmentation Treatment for Major Depressive Disorder (January). Ann Pharmacother. 2010 Dec 28.
Owens C, Owen G, Belam J, Lloyd K, Rapport F, Donovan J, et al. Recognising and responding to **suicidal crisis** within the **family and social network**: qualitative study. BMJ 2011;343;d5801.
Pan An; Lucas Michel; Sun Qi; et al. **Bidirectional Association Between Depression and Type 2 Diabetes Mellitus** in Women. Arch Intern Med. 2010;170(21):1884-1891.
Pan A, Okereke OI, Sun Q, et al. Depression and **Incident Stroke** in Women. Stroke. 2011 Aug 11.
Pandya M, Pozuelo L, Malone D. **Electroconvulsive therapy** (ECT): what the internist needs to know. Cleve Clin J Med. 2007 Sep;74(9):679-85.
Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. **Depression and risk of stroke** morbidity and mortality: a meta-analysis and systematic review. JAMA. 2011 Sep 21;306(11):1241-9.
Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are antidepressant drugs that combine **serotonergic and noradrenergic mechanisms** of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry. 2007 Dec 1;62(11):1217-27. Epub 2007 Jun 22.
Papakostas GI. Managing partial response or nonresponse: **switching, augmentation, and combination** strategies for major depressive disorder. J Clin Psychiatry. 2009;70 Suppl 6:16-25. Review. PubMed PMID: 19922740.
Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: double-blind, randomized clinical trial. Am J Psychiatry. 2010 Aug;167(8):942-8. These preliminary results suggest that SAMe can be an effective, well-tolerated, and safe adjunctive treatment strategy for SRI nonresponders with major depressive disorder and warrant replication.
Parashar S, et al. Time course of depression and outcome of **myocardial infarction**. Arch Intern Med. 2006 Oct 9;166(18):2035-43.
Parmet S, Glass TJ, Glass RM. JAMA **patient page. Obsessive-compulsive disorder**. JAMA. 2004 Oct 27;292(16):2040.
Patatanian E, Toedter Williams N. Drug-Induced **Yawning**--A Review (October). Ann Pharmacother. 2011 Sep 20.
Paulden Mike, Palmer Stephen, Hewitt Catherine, et al. **Screening for postnatal** depression in primary care: cost effectiveness analysis. BMJ 2009;339:b5203, doi: 10.1136/bmj.b5203 (Published 22 Dec 2009)
Pedersen LH, Henriksen TB, Olsen J. **Fetal Exposure to Antidepressants** and Normal Milestone Development at 6 and 19 Months of Age. Pediatrics. 2010 Feb 22.
Pedersen MG, Mortensen PB, Norgaard-Pedersen B, Postolache TT. **Toxoplasma gondii Infection** and Self-directed Violence in MothersToxoplasma Gondii and Self-directed Violence. Arch Gen Psychiatry. 2012 Jul 2:1-8.
Pettinati HM, Oslin DW, Kampman KM, et al. A Double-Blind, Placebo-Controlled Trial Combining **Sertraline and Naltrexone** for Treating Co-Occurring **Depression and Alcohol** Dependence. Am J Psychiatry. 2010 Mar 15.
Pergadia ML, Glowinski AL, Wray NR, et al. A **3p26-3p25 Genetic Linkage** Finding for DSM-IV Major Depression in Heavy Smoking Families. Am J Psychiatry. 2011 May 15.
Perkins S, et al. Self-help and Guided **Self-help** for **Eating Disorders**. Cochrane Database Syst Rev. 2006 Jul 19;3:CD004191.
Perrin JS, Merz S, Bennett DM, et al. **Electroconvulsive therapy** reduces frontal cortical connectivity in severe depressive disorder. Proc Natl Acad Sci U S A. 2012 Mar 19.
Pharmacist's Letter May 2006: Pharmacotherapy of **Treatment-Resistant Depression**
PHQ-9 Patient Health Questionnaire: **Depression Screen** http://www.viha.ca/NR/rdonlyres/BCA23E92-223A-4A86-A07C-D45B37B5815E/8564/PHQ9PatientHealthQuestionnaireforDepression.pdf
Pizzi C, Rutjes AW, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-Analysis of Selective Serotonin Reuptake Inhibitors in Patients With Depression and **Coronary Heart Disease**. Am J Cardiol. 2011 Jan 20.
Portella MJ, de Diego-Adeliño J, Ballesteros J, et al. Can we really accelerate and enhance the selective serotonin reuptake inhibitor antidepressant effect? a randomized clinical trial and a meta-analysis of **pindolol** in nonresistant depression. J Clin Psychiatry. 2010 Oct 19
Posner K et al. The **columbia-suicide severity rating scale**: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec 1;168(12):1266-77.
Pratt LA, Brody DJ, Gu Q. **Antidepressant use in persons aged 12 and over**: United States, 2005–2008. NCHS data brief, no 76. Hyattsville, MD: National Center for Health Statistics. 2011. http://www.cdc.gov/nchs/data/databriefs/db76.pdf

TOP

Qaseem A, Snow V, Denberg TD, et al; Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using **second-generation antidepressants** to treat depressive disorders: a clinical practice guideline from the American College of Physicians (**ACP**). Ann Intern Med. 2008 Nov 18;149(10):725-33.
Rahimi-Ardabili B, et al. **Finasteride-induced depression** : A prospective study. BMC Clin Pharmacol. 2006 Oct 7;6(1):7 [Epub ahead of print]
Ramos É, St-André M, Bérard A. Association between antidepressant use during pregnancy and infants born **small for gestational age (Venlafaxine).** Can J Psychiatry. 2010 Oct;55(10):643-52.
Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. **Antidepressants for depression in physically ill** people. Cochrane Database Syst Rev. 2010 Mar 17;3:CD007503.
Reed SD, Guthrie KA, Joffe H, et al. **Sexual function in nondepressed women using escitalopram** for vasomotor symptoms: a randomized controlled trial. Obstet Gynecol. 2012 Mar;119(3):527-38.
Reid Steven, Barbui Corrado. **Long term treatment of depression** with selective serotonin reuptake inhibitors and newer antidepressants. BMJ 2010;340:c1468, doi: 10.1136/bmj.c1468 (26 March 2010)
Reynolds CF 3rd, Butters MA, Lopez O, et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of **donepezil** combined with antidepressant pharmacotherapy. Arch Gen Psychiatry. 2011 Jan;68(1):51-60. (no clear benefit)
Reynolds CF 3rd, et al. **Maintenance treatment** of major depression in **old age**. N Engl J Med. 2006 Mar 16;354(11):1130-8. CONCLUSIONS: Patients elderly 70 years of age or older with major depression who had a response to initial treatment with paroxetine and psychotherapy were less likely to have recurrent depression if they received two years of maintenance therapy with paroxetine. Monthly maintenance psychotherapy did not prevent recurrent depression. (InfoPOEMs: Prolonged treatment with paroxetine (Paxil) reduces the risk of recurrence of major depression in elderly patients. (LOE = 1b))
Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants (**paroxetine, venlafaxine**) in **Parkinson** disease. (**SAD-PD**) Neurology 2012;78:1229–1236.
Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the **risk of fracture**. Arch Intern Med. 2007 Jan 22;167(2):188-94. Daily SSRI use in adults 50 years and older remained associated with a 2-fold increased risk of clinical fragility fracture after adjustment for potential covariates. Depression and fragility fractures are common in this age group, and the elevated risk attributed to daily SSRI use may have important public health consequences.
Richards BL, Whittle SL, Buchbinder R. **Antidepressants** for **pain management** in **rheumatoid arthritis**. Cochrane Database Syst Rev. 2011 Nov 9;11:CD008920. There is currently insufficient evidence to support the routine prescription of antidepressants as analgesics in patients with RA as no reliable conclusions about their efficacy can be drawn from eight placebo RCTs.
Richardson, Laura P., Rockhill, Carol, Russo, Joan E., et al. Evaluation of the **PHQ-2** as a Brief Screen for Detecting Major Depression Among **Adolescents**. Pediatrics 2010 125: e1097-e1103.
Richardson LP, McCauley E, Grossman DC, et al. Evaluation of the Patient Health Questionnaire-9 **(PHQ-9)** Item for Detecting Major Depression Among **Adolescents**. Pediatrics. 2010 Nov 1.
Rickels K, Etemad B, Khalid-Khan S, et al. Time to relapse after 6 and **12 months' treatment** of **generalized anxiety disorder with venlafaxine** extended release. Arch Gen Psychiatry. 2010 Dec;67(12):1274-81.
Robinson RG, Jorge RE, Moser DJ, et al.; Vardenafil Study Site Investigators. Efficacy and tolerability of **vardenafil** in men with mild depression and erectile dysfunction: the depression-related improvement with vardenafil for erectile response study. Am J Psychiatry. 2006 Jan;163(1):79-87.
Rodda J, Walker Z, Carter J. Depression in **older adults**. BMJ. 2011 Sep 28;343:d5219. doi: 10.1136/bmj.d5219.
Rosenberg PB, Drye LT, Martin BK, et al. DIADS-2 Research Group. **Sertraline** for the treatment of **depression in Alzheimer disease**. Am J Geriatr Psychiatry. 2010 Feb;18(2):136-45. CONCLUSIONS: Sertraline not effective.
Rosenthal LJ, Goldner WS, O'Reardon JP. **T3 Augmentation** in Major Depressive Disorder: Safety Considerations. Am J Psychiatry 168:10, October 2011.
Rubio-Valera Maria, Serrano-Blanco Antoni, Magdalena-Belío Jesús, et al. Effectiveness of **Pharmacist Care in the Improvement of Adherence** to Antidepressants: A Systematic Review and Meta-Analysis. Articles Ahead of Print published on 1 January 2011, DOI 10.1345/aph.1P429. Ann Pharmacother ;45:39-48.
Rush AJ, et al. **STAR*D** Study. **Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs** (citalopram) for depression. n=727 N Engl J Med. 2006 Mar 23;354(12):1231-42. CONCLUSIONS: After unsuccessful treatment with an SSRI, approximately **one in four patients** had a **remission** of symptoms after switching to another antidepressant. Any one of the medications in the study provided a reasonable second-step choice for patients with depression. (InfoPOEMs: Bupropion SR (~283mg/d), sertraline(~136mg/d) & venlafaxine XR (~194mg/d) are equally effective at inducing remission or response in patients with persistent symptoms of depression despite initial treatment with citalopram (Celexa ~41mg/d). Most patients will not go into remission, though, and this study lacked a placebo control group. (LOE = 1b))
Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A **STAR*D** Report. Am J Psychiatry. 2006 Nov;163(11):1905-17. The QIDS-SR(16) remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively. The overall cumulative remission rate was 67%.
Rush AJ, Wisniewski SR, Warden D, Luther JF, Davis LL, Fava M, Nierenberg AA,
Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, Nierenberg AA. **STAR*D**: Revising Conventional Wisdom. CNS Drugs. 2009;23(8):627-47.
Rush AJ, Trivedi MH, Stewart JW, et al. **Combining Medications** to Enhance Depression Outcomes (CO-MED): Acute & Long-Term Outcomes of a Single-Blind Randomized Study. Am J Psychiatry. 2011 May 2. (Mono tx good)
Ryan D, Milis L, Misri N. Depression during **pregnancy**. Can Fam Physician. 2005 Aug;51:1087-93.
Robson WL. Clinical practice. Evaluation and management of **enuresis**. N Engl J Med. 2009 Apr 2;360(14):1429-36.
Rose Natalie; Koperski Sabrina; Golomb Beatrice A. Mood Food: **Chocolate** and Depressive Symptoms in a Cross-sectional Analysis. *Arch Intern Med*. 2010;170(8):699-703.
Runeson Bo, Tidemalm Dag, Dahlin Marie, et al. **Method of attempted suicide** as predictor of subsequent successful suicide: national long term cohort study. BMJ 2010;341:c3222, doi: 10.1136/bmj.c3222.
Saarto T, et al. Antidepressants for **neuropathic pain**. **Cochrane** Database Syst Rev. 2007 Oct 17;(4):CD005454.
Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following **electroconvulsive therapy**: a randomized controlled trial. JAMA. 2001 Mar 14;285(10):1299-307.
Sackeim HA, Dillingham EM, et al. Effect of **concomitant pharmacotherapy on electroconvulsive** therapy outcomes: short-term efficacy and adverse effects. Arch Gen Psychiatry. 2009 Jul;66(7):729-37. The efficacy of ECT is substantially increased by the addition of an antidepressant medication, but such medications may differ in whether they reduce or increase cognitive adverse effects. High-dose, right-sided, unilateral ECT is at least equivalent to moderate-dosage bilateral ECT in efficacy, but retains advantages with respect to cognitive adverse effects.
Saczynski, J.S., Beiser, A., Seshadri, S., et al. **Depressive symptoms** and risk of dementia: The Framingham Heart Study. Neurology 2010 75: 35-41.
Sayuk GS, Gott BM, Nix BD, Lustman PJ. **Improvement in sexual functioning** in patients with type 2 diabetes and depression treated with **bupropion**. Diabetes Care. 2011 Feb;34(2):332-4.
Schneeweiss S, Patrick AR, Solomon DH, et al. Comparative Safety of Antidepressant Agents for **Children and Adolescents** Regarding **Suicidal Acts**. Pediatrics. 2010 Apr 12.
Schneier FR, Neria Y, Pavlicova M, et al. **Combined Prolonged Exposure Therapy and Paroxetine** for **PTSD** Related to the World Trade Center Attack: A Randomized Controlled Trial. Am J Psychiatry. 2011 Sep 9.
Seccareccia D, Gebara N. **Pruritus in palliative care**: Getting up to scratch. Canadian Family Physician, 2011 Sep;57(9):1010-3. (consider use of **paroxetine, mirtazapine**)
Second generation Antidepressants: **Drug Class Review Sept 2006** Oregon Health & Science University http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf
Seitz DP, Adunuri N, Gill SS, et al. **Antidepressants for agitation and psychosis** in dementia. Cochrane Database Syst Rev. 2011 Feb 16;2:CD008191. Currently there are relatively few studies of antidepressants for the treatment of agitation and psychosis in dementia. The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies. Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics.
Serfaty MA, et al. Clinical effectiveness of individual **cognitive behavioral therapy** for depressed **older** people in primary care: a randomized controlled trial. Arch Gen Psychiatry. 2009 Dec;66(12):1332-40.
Serretti A, Chiesa A. **Treatment-emergent sexual dysfunction** related to antidepressants: a meta-analysis**.** J Clin Psychopharmacol. 2009 Jun;29(3):259-66.
Shah NR, Jones JB, Aperi J, Shemtov R, Karne A, Borenstein J. Selective Serotonin Reuptake Inhibitors for **Premenstrual Syndrome** and Premenstrual Dysphoric Disorder: A Meta-Analysis. Obstet Gynecol. 2008 May;111(5):1175-1182. Selective serotonin reuptake inhibitors were found to be effective in treating premenstrual symptoms, with continuous dosing regimens favored for effectiveness.
Shah AJ et al. Depression and history of attempted suicide as risk factors for **heart disease mortality** in young individuals. Arch Gen Psychiatry 2011 Nov; 68:1135.
Sharp RP, Welch EB. **Takotsubo cardiomyopathy** as a complication of **electroconvulsive therapy**. Ann Pharmacother. 2011 Dec;45(12):1559-65.
Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for **treatment-resistant depression**. CNS Drugs. 2010 Feb 1;24(2):131-61. doi: 10.2165/11530280-000000000-00000.
Sher L, Braquehais MD, Casas M. **Posttraumatic stress disorder, depression, and suicide in veterans**. Cleveland Clinic Journal of Medicine 2012; 79(2):92-97.

TOP

Shirayama T, et al. Usefulness of paroxetine in depressed men with paroxysmal **atrial fibrillation**. Am J Cardiol. 2006 Jun 15;97(12):1749-51. Epub 2006 Apr 21.
Shulman KI, Fischer HD, Herrmann N, et al. Current prescription patterns and safety profile of **irreversible monoamine oxidase inhibitors**: a population-based cohort study of older adults. J Clin Psychiatry. 2009 Oct 20.
Singh SP, Singh V, Kar N, Chan K. Efficacy of antidepressants in treating the **negative symptoms of chronic schizophrenia**: meta-analysis. Br J Psychiatry. 2010 Sep;197(3):174-9.
Skinner R, McFaull S. **Suicide among children and adolescents in Canada**: trends and sex differences, 1980-2008. CMAJ. 2012 Apr 2.
Smith GE, Rasmussen KG, Cullum CM, et al. for the CORE Investigators. A randomized controlled trial comparing the memory effects of continuation **electroconvulsive therapy**(ECT) versus continuation pharmacotherapy: results from the consortium for research in ECT (CORE) study. J Clin Psychiatry. 2010 Feb;71(2):185-193.
Smoller Jordan W.; Allison Matthew; Cochrane Barbara B.; J. et al. Antidepressant Use and Risk of Incident **Cardiovascular Morbidity and Mortality** Among Postmenopausal Women in the Women's Health Initiative Study. Arch Intern Med. 2009;169(22):2128-2139.
Sockalingam S, Abbey SE. Managing depression **during hepatitis C** treatment. Can J Psychiatry. 2009 Sep;54(9):614-25.
Soomro GM. **Deliberate self-harm** (and attempted suicide). Clin Evid (Online). 2008;2008.
Soomro G, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (**SSRIs**) versus placebo for obsessive compulsive disorder (OCD). **Cochrane** Database Syst Rev. 2008 Jan 23;(1):CD001765. SSRIs are more effective than placebo for OCD, at least in the short-term, although there are differences between the adverse effects of individual SSRI drugs.
Steiner M, Hirschberg AL, Bergeron R, et al. **Luteal phase** dosing with paroxetine controlled release (CR) in the treatment of premenstrual dysphoric disorder. Am J Obstet Gynecol. 2005 Aug;193(2):352-60.
Stearns V, Slack R, Greep N, et al. **Paroxetine** is an effective treatment **for hot flashes**: results from a prospective randomized clinical trial. J Clin Oncol. 2005 Oct 1;23(28):6919-30.
Sterke CS, Ziere G, van Beeck EF et al. Dose-response relationship between **Selective Serotonin Reuptake Inhibitors and Injurious Falls**: A study in Nursing Home Residents with Dementia. Br J Clin Pharmacol. 2012 Jan 18.
Stevens LM, Burke AE, Glass RM. JAMA **patient page. Posttraumatic stress disorder**. JAMA. 2007 Aug 1;298(5):588.
Stewart DE. Clinical practice. **Depression during Pregnancy**. N Engl J Med. 2011 Oct 27;365(17):1605-11.
Tack J, et al. A controlled crossover study of the selective serotonin reuptake inhibitor **citalopram** in **irritable bowel syndrome**. Gut. 2006 Aug;55(8):1095-103. Epub 2006 Jan 9. (InfoPOEMs: Citalopram in a dose of 20 mg daily for 3 weeks (perhaps increasing to 40 mg at that time) modestly improves symptoms in patients with irritable bowel syndrome (IBS). Paroxetine showed a similar benefit in a previous study, so this is likely a class effect of serotonin specific reuptake inhibitors (SSRIs). (LOE = 1b))
TADS Team. The Treatment for Adolescents With Depression Study (TADS): Long-term Effectiveness and Safety Outcomes. Arch Gen Psychiatry. 2007 Oct;64(10):1132-1143. In adolescents with moderate to severe depression, treatment with fluoxetine alone or in combination with **CBT** accelerates the response. Adding CBT to medication enhances the safety of medication. Taking benefits and harms into account, combined treatment appears superior to either monotherapy as a treatment for major depression in adolescents.
Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. **Early Onset** of Selective **Serotonin Reuptake Inhibitor** Antidepressant Action: Systematic Review and Meta-analysis. Arch Gen Psychiatry. 2006 Nov;63(11):1217-23.

Treatment with SSRIs is associated with symptomatic improvement in depression by the end of the first week of use, and the improvement continues at a decreasing rate for at least 6 weeks. (InfoPOEMs: Treatment of unipolar depression in adults with selective serotonin reuptake inhibitors (SSRIs) significantly improves symptoms in as quickly as 1 week. (LOE = 1a-))

Teichert M, Visser LE, Uitterlinden AG, et al. **Selective serotonin re-uptake inhibiting antidepressants** and the risk of overanticoagulation during acenocoumarol maintenance treatment. Br J Clin Pharmacol. 2011 Nov;72(5):798-805.
Tenback DE, et al. Evidence that **early extrapyramidal symptoms** predict later **tardive dyskinesia**: a prospective analysis of 10,000 patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) study. Am J Psychiatry. 2006 Aug;163(8):1438-40.
Tew JD Jr, et al. Impact of **Prior Treatment Exposure on Response** to Antidepressant Treatment in Late Life. Am J Geriatr Psychiatry. 2006 Nov;14(11):957-965.
Thapar Anita, Collishaw Stephan, Potter Robert, et al. **Managing and preventing depression in adolescents**. BMJ 2010;340:c209, doi: 10.1136/bmj.c209 (Published 22 January 2010)
Thapar A, Collishaw S, Pine DS, Thapar AK. **Depression in adolescence**. Lancet. 2012 Feb 1.
Thase ME, et al. A Double-blind Comparison Between **Bupropion** XL and **Venlafaxine** XR: **Sexual Functioning**, Antidepressant Efficacy, and Tolerability. J Clin Psychopharmacol. 2006 Oct;26(5):482-488. In conclusion, in this patient population (ie, relatively young, sexually active outpatients), bupropion XL was at least as effective as venlafaxine XR and had a significantly more favorable sexual side effect profile. N=348 12 week
Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry. 1997;58 Suppl 13:23-9.
Thase ME, Friedman ES, Biggs MM, et al. **Cognitive Therapy Versus Medication** in Augmentation and Switch Strategies as Second-Step Treatments: A **STAR*D** Report. Am J Psychiatry. 2007 May;164(5):739-752. After an unsatisfactory response to citalopram, patients who consented to random assignment to either cognitive therapy or alternative pharmacologic strategies had generally comparable outcomes. Pharmacologic augmentation was more rapidly effective than cognitive therapy augmentation of citalopram, whereas switching to cognitive therapy was better tolerated than switching to a different antidepressant.
Thase ME, Larsen KG, Kennedy SH. Assessing the `**true`** **effect of active antidepressant therapy** v. placebo in major depressive disorder: use of a mixture model. Br J Psychiatry. 2011 Dec;199(6):501-7.
Thase ME. Using **adjunctive treatments** when first-line antidepressants fail. J Clin Psychiatry. 2012 Jan;73(1):e01.
Thoma NC, McKay D, Gerber AJ et al. A quality-based review of randomized controlled trials of **cognitive-behavioral therapy** for depression: an assessment and metaregression. Am J Psychiatry. 2012 Jan;169(1):22-30.
Thombs BD, de Jonge P, Coyne JC, Whooley MA, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. JAMA. 2008 Nov 12;300(18):2161-71. Depression treatment with medication or cognitive behavioral therapy in patients with cardiovascular disease is associated with modest improvement in depressive symptoms but no improvement in cardiac outcomes. No clinical trials have assessed whether screening for depression improves depressive symptoms or cardiac outcomes in patients with cardiovascular disease.
Thombs BD, Arthurs E, El-Baalbaki G, et al. Risk of bias from inclusion of patients who already have diagnosis of or are undergoing treatment for depression in diagnostic accuracy studies of **screening tools for depression**: systematic review. BMJ. 2011 Aug 18;343:d4825.
Thombs BD, Coyne JC, Cuijpers P, et al. Rethinking recommendations for **screening for depression in primary care**. CMAJ. 2012 Mar 6;184(4):413-8.
Timonen M, Liukkonen T. **Management of depression in adults**. BMJ. 2008 Feb 23;336(7641):435-9.
Torpy JM, Burke AE, Golub RM. JAMA **patient page. Generalized Anxiety Disorder**. JAMA. 2011 Feb 2;305(5):522.
Treatment Guidelines from the Medical Letter. Pharmaceutical **Drug Overdose**. Sept 2006. (**TCAs**: sodium bicarbonate treatment)
Trivedi MH. **STAR*D** Selecting among **second-step antidepressant** medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry. 2008 Aug;65(8):870-80. Clinical, demographic, and treatment history were of little value in recommending 1 medication vs another as a second-step treatment for major depressive disorder. Participants most likely to remit in the second step had less Axis I psychiatric disorder comorbidity, less social disadvantage, and at least a response to citalopram in the first step.
Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in **STAR*D**: Implications for Clinical Practice. Am J Psychiatry. 2006 Jan;163(1):28-40. The mean exit citalopram dose was 41.8 mg/day. Remission rates were 28% (HAM-D) and 33% (QIDS-SR). The response rate was 47% (QIDS-SR) n=2,876.
Trivedi MH, et al. **STAR*D** Study Team. Medication **augmentation** after the **failure of SSRIs** for depression. n=565 N Engl J Med. 2006 Mar 23;354(12):1243-52. CONCLUSIONS: Augmentation of citalopram (40-60mg/d) with either sustained-release bupropion (~267mg/d) or buspirone (~41mg/d) appears to be useful in actual clinical settings. **Augmentation with sustained-release bupropion** does have certain advantages, including a greater reduction in the number and severity of symptoms and fewer side effects and adverse events. (InfoPOEMs: Buspirone and bupropion SR added to citalopram (Celexa) are similarly effective for patients with depression who do not initially respond to citalopram alone. Bupropion SR is somewhat better tolerated. The study was limited by the lack of a placebo control group. (LOE = 1b))
Tuccori M, Testi A, et al.Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during **pregnancy**: a review. Clin Ther. 2009 Jun;31(Pt 1):1426-53.

TOP

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. **Selective publication** of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008 Jan 17;358(3):252-60.

USPSTF: US Preventive Services Task Force. **Screening and treatment** for major depressive disorder in **children and adolescents**: recommendation statement. Pediatrics 2009 Apr;123(4):1223-8.
Screen adolescents (12-18 years of age) for major depressive disorder when systems are in place to ensure accurate diagnosis, psychotherapy (cognitive-behavioral or interpersonal), and follow-up (B recommendation). Evidence is insufficient to warrant a recommendation to screen children (7-11 years of age) for major depressive disorder (I statement).

USPSTF: U.S. Preventive Services Task Force. **Screening** for **Depression in Adults**: U.S. Preventive Services Task Force Recommendation Statement . Ann Intern Med December 1, 2009 151:784-792. The U.S. Preventive Services Task Force (USPSTF) recommends screening adults for depression when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up (grade B recommendation). It recommends against routinely screening adults for depression when staff-assisted depression care supports are not in place. There may be considerations that support screening for depression in an individual patient (grade C recommendation).

Urquhart D, et al. Antidepressants for non-specific **low back pain**. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001703. There is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic low-back pain.

Vahedi H, Merat S, et al. The effect of **fluoxetine** in patients with pain and constipation-predominant **irritable bowel syndrome**: a double-blind randomized-controlled study. Aliment Pharmacol Ther. 2005 Sep 1;22(5):381-5.

van Gorp F, Whyte IM, Isbister GK. Clinical and ECG effects of **escitalopram overdose**. Ann Emerg Med. 2009 Sep;54(3):404-8.

van Gorp F, Duffull S, Hackett LP, et al. Population pharmacokinetics and pharmacodynamics of **escitolapram in overdose** and the effect of activated charcoal. Br J Clin Pharmacol 2012; 73: 402–10.

Vignatelli L, D'Alessandro R, Candelise L. Antidepressant drugs for narcolepsy. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003724.

Viguera AC et al. Episodes of Mood Disorders in 2,252 **Pregnancies and Postpartum Periods**. Am J Psychiatry. 2011 Jul 28.

Wagena EJ, Knipschild PG, Huibers MJ, et al. Efficacy of bupropion & nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. Arch Intern Med. 2005 Oct 24;165(19):2286-92.
CONCLUSIONS: Bupropion SR treatment is an efficacious aid to smoking cessation in patients with COPD. Nortriptyline treatment seems to be a useful alternative.

Wagner KD, Jonas J, Findling RL, Ventura D, et al. A double-blind, randomized, placebo-controlled trial of **escitalopram** in the treatment of **pediatric** depression. J Am Acad Child Adolesc Psychiatry. 2006 Mar;45(3):280-8.

Walfisch Asnat, Sermer Corey, Matok Ilan, et al. **Screening for depressive symptoms (EPDS scale). Motherisk.** Can Fam Physician July 2011 57: 777-778

Walsh BT, et al. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. JAMA. 2006 Jun 14;295(22):2605-12. This study failed to demonstrate any benefit from fluoxetine in the treatment of patients with anorexia nervosa following weight restoration.

Watanabe N, Omori IM, Nakagawa A, et al. **Mirtazapine** versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2011 Dec 7;12:CD006528. Some statistically significant and possibly clinically meaningful differences between mirtazapine and other antidepressive agents were found for the acute-phase treatment of major depression. Mirtazapine is likely to have a faster onset of action than SSRIs during the acute-phase treatment. Dropouts occur similarly in participants treated with mirtazapine and those treated with other antidepressants, although the adverse event profile of mirtazapine is unique.

Warner CH, Bobo W, Warner C, Reid S, Rachal J. **Antidepressant discontinuation syndrome**. Am Fam Physician. 2006 Aug 1;74(3):449-56.

Weeke P, Jensen A, Folke F, et al. Antidepressant Use and **Risk of Out-of-Hospital Cardiac Arrest**: A Nationwide Case-Time-Control Study. Clin Pharmacol Ther. 2012 May 16. Weiner RD. **Retrograde amnesia with electroconvulsive therapy (ECT):** characteristics and implications. Arch Gen Psychiatry. 2000 Jun;57(6):591-2.

Weintraub D, Rosenberg PB, Drye LT, et al. **DIADS-2** Research Group. Sertraline for the treatment of depression in Alzheimer disease: week-24 outcomes. Am J Geriatr Psychiatry. 2010 Apr;18(4):332-40.

Weissman MM, et al; STAR*D-Child Team. Remissions in **maternal depression** and child psychopathology: a **STAR*D**-child report. JAMA. 2006 Mar 22;295(12):1389-98.

Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. **Offspring of depressed parents: 20 years later**. Am J Psychiatry. 2006 Jun;163(6):1001-8.

Weitzman M, Rosenthal DG, Liu YH. **Paternal depressive symptoms** and child behavioral or emotional problems in the United States. Pediatrics. 2011 Dec;128(6):1126-34.

Wernicke JF, et al. A randomized controlled trial of **duloxetine** in diabetic peripheral **neuropathic** pain. Neurology. 2006 Oct 24;67(8):1411-20.

Wiles NJ, Mulligan J, Peters TJ, et al. **Severity of depression and response to antidepressants**: **GENPOD** randomised controlled trial. Br J Psychiatry. 2012 Feb;200(2):130-6.

Whitley H, Lindsey W. **Sex-based** differences in drug activity. Am Fam Physician. 2009 Dec 1;80(11):1254-8.

Whooley MA. Depression and **cardiovascular disease**: healing the broken-hearted. JAMA. 2006 Jun 28;295(24):2874-81.

Whooley MA. Diagnosis and treatment of **depression in adults with comorbid medical conditions**: a 52-year-old man with depression. JAMA. 2012 May 2;307(17):1848-57.

Williams K, Wheeler DM, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for **autism spectrum disorders (ASD).** Cochrane Database Syst Rev. 2010 Aug 4;8:CD004677. There is no evidence of effect of SSRIs in children and emerging evidence of harm. There is limited evidence of the effectiveness of SSRIs in adults from small studies in which risk of bias is unclear.

Williams JR, Hirsch ES, Anderson K, et al. A comparison of **nine scales to detect depression in Parkinson disease**: Which scale to use? Neurology. 2012 Mar 27;78(13):998-1006. The GDS-30 may be the most efficient depression screening scale to use in PD because of its brevity, favorable psychometric properties, and lack of copyright protection. However, all scales studied, except for the UPDRS Depression, are valid screening tools when PD-specific cutoff scores are used.

Wijkstra J, Lijmer J, Balk F, Geddes J, Nolen W, Wijkstra J. Pharmacological treatment for **psychotic depression**. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004044.

Wimbiscus M, Kostenko O, Malone D. **MAO inhibitors**: Risks, benefits, and lore *Cleveland Clinic Journal of Medicine* 2010; 77(12):859-882; doi:10.3949/ccjm.77a.09103.

Woolcott John C.; Richardson Kathryn J.; Wiens Matthew O.; et al. Meta-analysis of the Impact of 9 Medication Classes on **Falls** in Elderly Persons. Arch Intern Med. 2009;169(21):1952-1960.

Wu Eric Q, Yu Andrew P, Lauzon Veronique, et al. Economic Impact of Therapeutic Substitution of a **Brand Selective Serotonin Reuptake Inhibitor with an Alternative Generic** Selective Serotonin Reuptake Inhibitor in Patients with Major Depressive Disorder. Articles Ahead of Print published on 1 April 2011, DOI 10.1345/aph.1P482. Ann Pharmacother ;45:441-451.

Xiong GL, et al. Prognosis of patients taking **selective serotonin reuptake** inhibitors before **coronary artery bypass grafting**. Am J Cardiol. 2006 Jul 1;98(1):42-7. Epub 2006 May 5.

Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association (**APA**) and the American College of Obstetricians and Gynecologists (**ACOG**). Gen Hosp Psychiatry. 2009 Sep-Oct;31(5):403-13.

Zarate CA Jr, et al. A randomized trial of an N-methyl-D-aspartate antagonist (**ketamine**) in treatment-resistant major depression. Arch Gen Psychiatry. 2006 Aug;63(8):856-64.

Zelefsky JR, Fine HF, Rubinstein VJ, Hsu IS, Finger PT. Escitalopram-induced uveal effusions and bilateral angle closure **glaucoma**. Am J Ophthalmol. 2006 Jun;141(6):1144-7.

Zimmermann P, Brückl T, Nocon A, et al. Interaction of **FKBP5 gene variants** and adverse life events in predicting depression onset: results from a 10-yr prospective community study. Am J Psychiatry 2011; 168:1107–1116.

TOP

nefazodone SERZONE	carbamazepine ⑨⑥ cisapride ⑥②$_{cv}$ lovastatin ⑥$_{(rhabdo)}$ MAOI's ③	sibutramine ③ simvastatin ⑥$_{(rhabdo)}$ sumatriptan ③	alprazolam ⑥ atorvastatin ⑥ cyclosporin ⑥	digoxin ⑥, fentanyl ⑧ fluvastatin ⑥ grapefruit juice ⑧ haloperidol ⑥	indinavir/ritonavir ⑧ L-tryptophan ③ midazolam ⑥ paroxetine ③	phenytoin ⑨⑥ **pimozide** ⑥ cv pravastatin ⑥ quinidine ⑥②, ritonavir ⑧	**sedatives** ① tacrolimus ⑥② triazolam ⑥

ANTIDEPRESSANT (AD) DRUG INTERACTIONS

Ref: **1**.Hansten & Horn-Drug Interactions'08. **2**.AHFS'08. **3**.Bezchlibnyk-Butler K. Serotonergic antidepressants:Drug response & drug interactions. Pharmacy Practice, Aug/98. **4**.CPS 2009. **5**.Micromedex 2010. **6**. Guidelines for Depressive Disorders. Cnd J Psyc Jun/01

7. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. Lancet Neurol. 2003 Aug;2(8):473-81. **CV**=cardiovascular **HTN**=hypertension

8. Palylyk-Colwell E. CYP450 genotyping for determining drug metabolizer status. Issues Emerg Health Technol. 2006 Mar;(81):1-4. (Roche AmpliChip does 2D6 & 2C19) **9**. Bezchlibnyk-Butler Clinical Handbook of Psychotropic Drugs, 18th Ed. 2009.

10. Aubert RE, Stanek EJ, Yao J, et al. Increased risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, May 30, 2009.

11. Kelly Catherine M, Juurlink David N, Gomes Tara, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving **tamoxifen**: a population based cohort study BMJ 2010;340:c693, doi: 10.1136/bmj.c693 (Published 8 February 2010).

12. Aung GL, O'Brien JG, Tien PG, et al. Increased Aripiprazole Concentrations in an HIV-Positive Male Concurrently Taking Duloxetine, Darunavir, and Ritonavir. Ahead of Print 1Nov2010, DOI 10.1345/aph.1P139. Ann Pharmacother ;44:1850-1854.

13. Health Canada Feb/11 Methylene blue injectable in combination with serotonin reuptake inhibitors - Association with serotonin toxicity Cases of serotonin toxicity have been reported and published in association with the use of methylene blue injectable in patients

exposed to drugs with serotonin reuptake inhibition properties.

TOP

ANTIPSYCHOTIC COMPARISON CHART

References

1. Allison DB et al. Antipsychotic Induced Weight Gain: A comprehensive Research Synthesis. Am J Psychiatry 1999;156(11):1686-96.
2. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry. 2001;62 Suppl 7:22-31.
3. Pharmacist Letter. Atypical Antipsychotics in Kids. January 2012.
4. Expert Consensus Guideline Series- Treatment of Schizophrenia 1999. J Clin Psychiatry 1999;60 (Suppl 11)
5. Switching Antipsychotics- Canadian Expert Consensus Panel July 2000
6. Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia, Nov 1998, Vol 43, Supp 2; Can J Psyc Vol 50 Suppl 1 Nov **2005**
   https://ww1.cpa-apc.org/Publications/Clinical_Guidelines/schizophrenia/november2005/cjp-cpg-suppl1-05_full_spread.pdf
7. Lehman AF, et al. APA: Practice guideline for the treatment of patients with schizophrenia, 2nd Ed. Am J Psychiatry. 2004 Feb;161(2 Supp):1-56.
   http://psychiatryonline.org/data/Books/prac/Schizophrenia2e_Inactivated_04-16-09.pdf

Additional References

AACAP-Practice parameter on the use of **psychotropic medication in children and adolescents**. J Am Acad Child Adolesc Psychiatry. 2009 Sep;48(9):961-73.

Addington DE, Labelle A, Kulkarni J, Johnson G, Loebel A, Mandel FS. A comparison of **ziprasidone and risperidone** in the long-term treatment of schizophrenia: a 44-week, double-blind, continuation study. Can J Psychiatry. 2009 Jan;54(1):46-54. Ziprasidone, 80 to 160 mg/day (n = 62), or risperidone, 6 to 10 mg/day (n = 77). Ziprasidone and risperidone demonstrated similar efficacy during long-term treatment of patients with schizophrenia or schizoaffective disorder. While more subjects on risperidone completed the extension study, ziprasidone was associated with fewer adverse effects on weight, EPS measures, and prolactin than risperidone.

Addington DE, Mohamed S, Rosenheck RA, et al. Impact of **second-generation antipsychotics and perphenazine** on depressive symptoms in a randomized trial of treatment for chronic schizophrenia.J Clin Psychiatry.2010Sep 21.

Ahuja TK, Cameron C, Yu C, et al. A systematic review of **combination and high-dose atypical antipsychotic** therapy in patients with schizophrenia Canadian Agency for Drugs and Technologies in Health. 2011 Dec;1:1-207.

Alexopoulos GS, Streim J, et al.; Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients. Using antipsychotic agents in older patients. J Clin Psychiatry. 2004;65 Suppl 2:5-99; discussion 100-102; quiz 103-4.

Alvarez-Jimenez M, et al. Non-pharmacological management of **antipsychotic-induced weight gain**: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry. 2008 Aug;193(2):101-7. Non-pharmacological weight-management interventions should be a priority, particularly during the early stages of antipsychotic treatment. Preventive approaches have the potential to be more effective, acceptable, cost-efficient and beneficial.

American Psychiatric Association Brochures: http://www.healthyminds.org/Functional-Library/brochures.aspx

Amminger GP, Schafer MR, Papageorgiou K, et al. Long-chain **omega-3 fatty acids** for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010 Feb;67(2):146-54.

Andrade Susan E, Lo Joan C, Roblin Douglas, et al. Antipsychotic Medication Use Among **Children and Risk of Diabetes Mellitus**. Pediatrics 2011; peds.2011-0855; ahead of print November 21, 2011.

Angstman K, Rasmussen NH. **Personality disorders**: review and clinical application in daily practice. Am Fam Physician. 2011 Dec 1;84(11):1253-60.

Anil Yagcioglu AE, et al. A double-blind controlled study of adjunctive treatment with **risperidone** in schizophrenic patients partially responsive to **clozapine**: efficacy and safety. J Clin Psychiatry. 2005 Jan;66(1):63-72.

Arango C, Rapado-Castro M, Reig S, et al. Progressive **brain changes in children and adolescents** with **first-episode psychosis**. Arch Gen Psychiatry. 2012 Jan;69(1):16-26.

Aripiprazole (Abilify) for schizophrenia. Med Lett Drugs Ther. 2003 Feb 17;45(1150):15-6.

Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. **Clozapine versus other atypical antipsychotics** for schizophrenia. Cochrane Database Syst Rev. 2010 Nov 10;11:CD006633. Clozapine may be a little more efficacious than zotepine and risperidone but further trials are required to confirm this finding. Clozapine differs more clearly in adverse effects from other second generation antipsychotics and the side-effect profile could be key in the selection of treatment depending on the clinical situation and a patient's preferences. Data on other important outcomes such as cognitive functioning, quality of life, death or service use are currently largely missing, making further large and well-designed trials necessary. It is also important to take into account that the large number of people leaving the studies early limits the validity and interpretation of our findings.

Athanasiou MC, Dettling M, Cascorbi I, et al. Candidate gene analysis identifies a polymorphism in **HLA-DBQ1** associated with **clozapine-induced agranulocytosis**. J Clin Psychiatry 2011; 72:458–463.

Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of **aggression and psychosis in Alzheimer's disease**. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003476.

Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszczak E, Yu LM, Jacoby R; for the DART-AD investigators. The dementia antipsychotic withdrawal trial (**DART-AD**): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009 Jan 8. [Epub ahead of print] There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients.

Ballard C, Gauthier S, Corbett A, et al. **Alzheimer's** disease. Lancet. 2011 Mar 19;377(9770):1019-31.

Ballard C, Corbett A. Management of **neuropsychiatric symptoms** in people with dementia. CNS Drugs. 2010 Sep 1;24(9):729-39. doi:10.2165/11319240-000000000-00000.

Banerjee S, Hellier J, Dewey M, et al. **Sertraline** (150mg/day) **or mirtazapine** (45mg/day) for depression in dementia (**HTA-SADD**): a randomised, multicentre, double-blind, **placebo**-controlled trial. Lancet 2011; July 18. (absence of benefit)

Baptista T, et al. Metformin for prevention of weight gain and insulin resistance with olanzapine: a double-blind placebo-controlled trial. Can J Psychiatry. 2006 Mar;51(3):192-6.

Barak Y, Plopski I, et al. **Escitalopram versus risperidone** for the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease: a randomized double-blind pilot study. Int Psychogeriatr. 2011 Apr 15:1-5.

Barnes TR, Paton C. Do **antidepressants improve negative symptoms in schizophrenia**? BMJ. 2011 Jun 10;342:d3371. doi: 10.1136/bmj.d3371.

Barnes TR, Drake MJ, Paton C. **Nocturnal enuresis** with antipsychotic medication. Br J Psychiatry. 2012 Jan;200:7-9. (esp. **clozapine**)

Barrowclough Christine, Haddock Gillian, Wykes Til, et al. **Integrated motivational interviewing and cognitive behavioural therapy** for people with psychosis and comorbid substance misuse: randomised controlled trial. BMJ 341:doi:10.1136/bmj.c6325 (Published 24 Nov 2010).

Bennett AC, Vila TM. The role of **ondansetron** in the treatment of schizophrenia. Ann Pharmacother. 2010 Jul-Aug;44(7-8):1301-6.

Bertelsen M, Jeppesen P, Petersen L, et al. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. Arch Gen Psychiatry. 2008 Jul;65(7):762-71. The intensive **early-intervention program** improved clinical outcome after 2 years, but the effects were not sustainable up to 5 years later. Secondary outcome measures showed differences in the proportion of patients living in supported housing and days in hospital at the 5-year follow-up in favor of the intensive early-intervention program.

Bhattacharjee J, El-Sayeh HG. **Aripiprazole** versus typical antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD006617.

Bhattacharyya S, Crippa JA, Allen P, et al. Induction of **psychosis by {delta}9-tetrahydrocannabinol** reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012 Jan;69(1):27-36.

Bird V, Premkumar P, Kendall T, et al. Early intervention services, **cognitive-behavioural therapy** and family intervention in early psychosis: systematic review. Br J Psychiatry. 2010 Nov;197:350-6.

Bird AM, Smith TL, Walton AE. Current treatment strategies for **clozapine-induced sialorrhea**. Ann Pharmacother. 2011 May;45(5):667-75.

Brauer R, Douglas I, Smeeth L. The association between **antipsychotic agents** and the risk of myocardial infarction: a systematic review. Br J Clin Pharmacol. 2011 Dec;72(6):871-8. doi: 10.1111/j.1365-2125.2011.04043.x.

Briesacher BA, Limcangco MR, Simoni-Wastila L, Doshi JA, Levens SR, Shea DG, Stuart B. The quality of antipsychotic drug prescribing in nursing homes. Arch Intern Med. 2005 Jun 13;165(11):1280-5.

Breitbart W, Alici Y. Agitation and **delirium** at the end of life: "We couldn't manage him". JAMA. 2008 Dec 24;300(24):2898-910, E1.

Brodaty H, Ames D, Snowdon J, et al. **Risperidone** for psychosis of Alzheimer's disease and mixed dementia: results of a double-blind, placebo-controlled trial. Int J Geriatr Psychiatry. 2005 Dec;20(12):1153-7.

TOP

Buchanan RW, et al. Schizophrenia Patient Outcomes Research Team (**PORT**): The 2009 Schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010; 36:71–93.
Chandran GJ, Mikler JR, Keegan DL. **Neuroleptic malignant syndrome**: case report and discussion. CMAJ. 2003 Sep 2;169(5):439-42.
Chang A, Krygier DS, Chatur N, Yoshida EM. **Clozapine-induced** fatal fulminant hepatic failure: A case report. Can J Gastroenterol. 2009 May;23(5):376-8.
Chen Yong; Briesacher Becky A.; Field Terry S.; et al. Unexplained Variation Across US **Nursing Homes** in Antipsychotic Prescribing Rates. Arch Intern Med. 2010;170(1):89-95.
Chen E. Y. H., Hui C. L. M., Lam M. M. L., et al. **Maintenance treatment with quetiapine** versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. BMJ 2010;341:c4024, doi: 10.1136/bmj.c4024
Chengappa KN, et al. A random-assignment, double-blind, clinical trial of od vs bid administration of quetiapine in patients with schizophrenia or schizoaffective disorder: a pilot study. Can J Psychiatry. 2003 Apr;48(3):187-94.
Choice of an antipsychotic. **Med Lett Drugs Ther. 2003 Dec** 22;45(1172):102-4.
Chrzanowski WK, et al. Effectiveness of long-term **aripiprazole** therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. Psychopharmacology (Berl). 2006 Dec;189(2):259-66. Epub 2006 Oct 21. Aripiprazole showed similar efficacy to olanzapine for long-term treatment of acutely psychotic and chronic, stable schizophrenia patients, with a lower liability for weight gain or increased lipid levels.
Cipriani A, Boso M, Barbui C. **Clozapine combined** with different antipsychotic drugs for treatment resistant schizophrenia. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006324.
Citrome LL, Jaffe AB. Relationship of atypical antipsychotics with development of **diabetes** mellitus. Ann Pharmacother. 2003 Dec;37(12):1849-57.
Citrome L. Comparison of intramuscular **ziprasidone, olanzapine, or aripiprazole for agitation**: a quantitative review of efficacy and safety. J Clin Psychiatry. 2007 Dec;68(12):1876-85. Although the lowest NNT, & hence strongest therapeutic effect, was seen for the studies of ziprasidone and olanzapine as opposed to aripiprazole, head-to-head controlled studies directly comparing these 3 agents are needed.
Comer JS, Mojtabai R, Olfson M: **National trends in the antipsychotic treatment** of psychiatric outpatients with **anxiety** disorders. Am J Psychiatry 2011; 168:1057–1065.
Consensus Development Conference on Antipsychotic Drugs and Obesity and **Diabetes**; Diabetes Care.**2004**; 27: 596-558.
Correll CU, Leucht S, Kane JM. Lower risk for **tardive dyskinesia** associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry. 2004 Mar;161(3):414-25. CONCLUSIONS: Results from 11 long-term studies support the idea that second-generation antipsychotics have a reduced risk for tardive dyskinesia, compared to first-generation antipsychotics, although the doses of haloperidol used in the comparator studies were relatively high. More carefully designed studies, ideally lasting beyond 1 year and comparing the effects of different second-generation antipsychotics in patients who have never taken first-generation antipsychotics, are needed to estimate the true risk. It would not appear premature for clinicians to consider these findings in making long-term treatment decisions.
Correll Christoph U.; Manu Peter; Olshanskiy Vladimir; et al. **Cardiometabolic Risk of Second-Generation** Antipsychotic Medications During First-Time Use in **Children and Adolescents**. *JAMA*. 2009;302(16):1765-1773.
Crabtree Brian L., Montgomery John, **Iloperidone** for the Management of Adults with Schizophrenia, Clinical Therapeutics, Volume 33, Issue 3, March 2011, Pages 330-345.
Crawford MJ, Killaspy H, Barnes TRE, Barrett B, Byford S, Clayton K, et al. **Group art therapy** as an adjunctive treatment for people with schizophrenia: multicentre pragmatic randomised trial (**Matisse**). BMJ 2012;344:e846.
Csernansky JG, Mahmoud R, Brenner R; Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med. 2002 Jan 3;346(1):16-22.
Daniel DG. Antipsychotic treatment of psychosis and agitation in the elderly. J Clin Psychiatry 2000; 61(suppl 14):49-52.
Davidson M, Galderisi S, et al. **Cognitive Effects** of Antipsychotic Drugs in First-Episode Schizophrenia and Schizophreniform Disorder: A Randomized, Open-Label Clinical Trial (EUFEST). Am J Psychiatry. 2009 Apr 15. Treatment with antipsychotic medication is associated with moderate improvement in the cognitive test performance of patients who have schizophreniform disorder or who are in their first episode of schizophrenia. The magnitude of improvement does not differ between treatment with haloperidol and treatment with second-generation antipsychotics. Moreover, cognitive improvement is weakly related to symptom change.
Davis JM, Chen N, Glick ID. A **meta-analysis** of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003 Jun;60(6):553-64.
Deberdt WG, Dysken MW, Rappaport SA, Feldman PD, et al.. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry. 2005 Aug;13(8):722-30. CONCLUSIONS: Patients' neuropsychiatric functioning improved with olanzapine, risperidone, and placebo treatment. There was a substantial response in the placebo group, and no significant differences emerged among treatments.
De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999;53:946-55.
Devanand DP, Pelton GH, Cunqueiro K, Sackeim HA, Marder K. A 6-month, randomized, double-blind, placebo-controlled pilot **discontinuation trial following response to haloperidol** treatment of psychosis and agitation In Alzheimer's disease. Int J Geriatr Psychiatry. 2011 Sep;26(9):937-43.
Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of **quetiapine in critically ill patients with delirium**: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010; 38:419-27.
Dewey RB Jr, O'Suilleabhain PE. Treatment of drug-induced psychosis with quetiapine and clozapine in Parkinson's disease. Neurology 2000;55:1753-4.
Doody RS, Stevens JC, ET AL. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1154-66.
Dore DD, Trivedi AN, Mor V, Friedman JH, et al. Atypical antipsychotic use and risk of **fracture in persons with Parkinsonism**. Mov Disord. 2009 Jul 30. [Epub ahead of print] Use of an AA was associated with a higher rate of fracture in persons with parkinsonism.
Dorsey E. Ray; Rabbani Atonu; Gallagher Sarah A.; et al. Impact of **FDA Black Box** Advisory on Antipsychotic Medication Use. Arch Intern Med. 2010;170(1):96-103.
dosReis Susan, Yoon Yesel, Rubin David M., et al. Antipsychotic Treatment **Among Youth in Foster Care**. Pediatrics 2011; peds.2010-2970; published ahead of print November 21, 2011, doi:10.1542/peds.2010-2970.
Dossenbach M, Arango-Davila C, Silva Ibarra H, et al. Response and Relapse in Patients With Schizophrenia Treated With Olanzapine, Risperidone, Quetiapine, or Haloperidol: 12-Month Follow-Up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) Study. J Clin Psychiatry. 2005 Aug;66(8):1021-1030.
Dossenbach M, et al. Effects of atypical and typical antipsychotic treatments on **sexual function** in patients with schizophrenia: 12-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. Eur Psychiatry. 2006 Mar 9; [Epub ahead of print]
Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ. 2008 Aug 28;337:a1227. doi: 10.1136/bmj.a1227. **All antipsychotics are associated with an increased risk of stroke**, and the risk might be higher in patients receiving atypical antipsychotics than those receiving typical antipsychotics. People with dementia seem to be at a higher risk of an associated stroke than people without dementia and use of antipsychotics should, when possible, be avoided in these patients.
Duggan L, Fenton M, Dardennes RM, El-Dosoky A, Indran S. **Olanzapine** for schizophrenia. Cochrane Database Syst Rev. 2003;(1):CD001359.
Einarson A, Boskovic R. Use and safety of antipsychotic drugs during **pregnancy**. J Psychiatr Pract. 2009 May;15(3):183-92.
El-Sayeh HG, Morganti C. **Aripiprazole** for schizophrenia. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD004578.
El-Sayeh HG, et al. **Aripiprazole** for schizophrenia. Systematic review. Br J Psychiatry. 2006 Aug;189:102-8.
Essali A, Al-Haj Haasan N, Li C, Rathbone J. **Clozapine versus typical neuroleptic** medication for schizophrenia. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000059. Clozapine may be more effective in reducing symptoms of schizophrenia, producing clinically meaningful improvements and postponing relapse, than typical antipsychotic drugs - but data are weak and prone to bias. Participants were more satisfied with clozapine treatment than with typical neuroleptic treatment. The clinical effect of clozapine, however, is, at least in the short term, not reflected in measures of global functioning such as ability to leave the hospital and maintain an occupation. The short-term benefits of clozapine have to be weighed against the risk of adverse effects. Within the context of trials, the potentially dangerous white blood cell decline seems to be more frequent in children and adolescents and in the elderly than in young adults or people of middle-age.The existing trials have largely neglected to assess the views of participants and their families on clozapine. More community-based long-term randomised trials are needed to evaluate the efficacy of clozapine on global and social functioning as trials in special groups such as people with learning disabilities.
Essock, Susan M., Schooler, Nina R., Stroup, T. Scott, et al. The Schizophrenia Trials Network, Effectiveness of **Switching From Antipsychotic Polypharmacy to Monotherapy**. Am J Psychiatry 2011 168: 702-708.
Fardet L et al. Suicidal behavior and severe **neuropsychiatric disorders following glucocorticoid** therapy in primary care. Am J Psychiatry 2012 May 1; 169:491.
Faulkner G, Cohn TA. Pharmacologic and nonpharmacologic strategies for **weight gain** and metabolic disturbance in patients treated with antipsychotic medications. Can J Psychiatry. 2006 Jul;51(8):502-11. Review. Erratum in:

TOP

Can J Psychiatry. 2006 Aug;51(9):620. Although difficult, the prevention of weight gain and the promotion of weight loss are possible for individuals treated with antipsychotic medications. Further research, including diabetes prevention studies, is required. We suggest a pathway for the management of weight gain and emerging metabolic disturbance.

Fazel S, Gulati G, Linsell L, Geddes JR, Grann M, 2009 Schizophrenia and **Violence**: Systematic Review and Meta-Analysis. PLoS Med 6(8): e1000120. doi:10.1371/journal.pmed.1000120 However, most of the excess risk appears to be mediated by substance abuse comorbidity.

FDA Sep/11 notified healthcare professionals and patients that serious allergic reactions have been reported with the use of **Saphris (asenapine maleate).**

Fernandez HH, Friedman JH, Jacques C, Rosenfeld M. Quetiapine for the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord 1999; 14:484-7.

Fernandez HH, Trieschmann ME, Burke MA, Jacques C, Friedman JH. Long-term outcome of quetiapine use for psychosis among parkinsonian patients. Mov Disord. 2003 May;18(5):510-4.

Fernandez H, Trieschmann M, Friedman J. Treatment of **psychosis in Parkinson's** disease : safety considerations. Drug Saf. 2003;26(9):643-59.

Findling RL, Robb A, Nyilas M, et al. A multiple-center, randomized, double-blind, placebo-controlled study of oral **aripiprazole** for treatment of adolescents with schizophrenia. Am J Psychiatry. 2008 Nov;165(11):1432-41. Epub 2008 Sep 2. Both 10- and 30-mg/day doses of aripiprazole were superior to placebo in the acute treatment of adolescents with schizophrenia. Aripiprazole was generally well tolerated.

Flood C, et al. **Joint crisis plans** for people with psychosis: economic evaluation of a randomised controlled trial. BMJ. 2006 Oct 7;333(7571):729. Epub 2006 Aug 16.

Foley Debra L.; Morley Katherine I.. Systematic Review of Early **Cardiometabolic Outcomes** of the First Treated Episode of Psychosis. *Arch Gen Psychiatry*. 2011;0(2011):archgenpsychiatry.2011.2.

Ford RL, Sallam A, Towler HM. Intraoperative **floppy iris syndrome associated with risperidone** intake. Eur J Ophthalmol. 2010 Sep 7. pii: 5B197916-3344-4098-A76D-04BC44510903.

Fortinguerra, Filomena, Clavenna, Antonio, Bonati, Maurizio. Psychotropic Drug Use During **Breastfeeding**: A Review of the Evidence. Pediatrics 2009 124: e547-e556.

Frampton JE. **Olanzapine Long-Acting Injection**: A Review of its Use in the Treatment of Schizophrenia. Drugs. 2010 Dec 3;70(17):2289-2313.

Freedman, R. **Schizophrenia**. N Engl J Med **2003** 349: 1738-1749.

Freudenreich O, Henderson DC, Macklin EA, Evins AE, Fan X, Cather C, Walsh JP, Goff DC. **Modafinil** for clozapine-treated schizophrenia patients: a double-blind, placebo-controlled pilot trial. J Clin Psychiatry. 2009 Aug 11.

Friedman JH. Atypical Antipsychotics in the Treatment of Drug Induced Psychosis in Parkinson's Disease. Movement Disorders 2000;15(2):201-211.

Fusar-Poli P, Bonoldi I, Yung AR, et al. **Predicting Psychosis**: Meta-analysis of Transition Outcomes in Individuals at High Clinical Risk. Arch Gen Psychiatry. 2012 Mar;69(3):220-9.

Gaebel W, Riesbeck M, Wölwer W, Klimke A, et al.; German Study Group on First-Episode Schizophrenia. Maintenance treatment with risperidone or low-dose haloperidol (both target 2-4mg/d) in first-episode schizophrenia: 1-year results of a randomized controlled trial within the German research network on schizophrenia. J Clin Psychiatry. 2007 Nov;68(11):1763-74. Against the background of an overall favorable outcome, the hypothesized difference between risperidone and low-dose haloperidol regarding relapse prevention could not be supported for this sample of patients with first-episode schizophrenia.

Gao K, Muzina D, Gajwani P, Calabrese JR. Efficacy of **typical and atypical antipsychotics** for primary and comorbid **anxiety** symptoms or disorders: a review. J Clin Psychiatry. 2006 Sep;67(9):1327-40. Except for trifluoperazine, there is no large, well-designed study of antipsychotics in the treatment of primary or comorbid anxiety symptoms or disorders. The efficacy of these agents in various anxiety conditions needs to be further investigated with large, well-designed comparison studies.

Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a **critical overview**. **CMAJ**. **2005** Jun 21;172(13):1703-11.

Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: **systematic overview** and meta-regression analysis. BMJ. 2000 Dec 2;321(7273):1371-6.

Gentile S. Long-term treatment with atypical antipsychotics and the risk of **weight gain** : a literature analysis. Drug Saf. 2006;29(4):303-19.

Gentile S. Infant safety with **antipsychotic therapy in breast-feeding**: a systematic review. J Clin Psychiatry. 2008 Apr;69(4):666-73.

Gharabawi GM, et al.An assessment of emergent **tardive dyskinesia** and existing dyskinesia in patients receiving long-acting, injectable risperidone: results from a long-term study. Schizophr Res. 2005 Sep 15;77(2-3):129-39. Five of 530 subjects without dyskinesia at baseline (0.94%) over 50week open label trial met the predefined criteria for emergent persistent TD during therapy.

Gill Sudeep S, Rochon Paula A, Herrmann Nathan, et al. Atypical antipsychotic drugs & risk of ischaemic **stroke**: population based retrospective cohort study BMJ, doi:10.1136/bmj.38330.470486.8F (published 24 January 2005)

Gopalakrishnan R, et al. **Sildenafil** in the treatment of antipsychotic-induced erectile dysfunction: a randomized, double-blind, placebo-controlled, flexible-dose, two-way crossover trial. Am J Psychiatry. 2006 Mar;163(3):494-9.

Goetz CG, Blasucci LM, Leurgans S, Pappert EJ. Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. Neurology 2000;55:789-94.

Gold JM, Waltz JA, Matveeva TM, et al. Negative symptoms and the failure to represent the **expected reward value of actions**: behavioral and computational modeling evidence. Arch Gen Psychiatry. 2012 Feb;69(2):129-38

Goodwin GM, Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating **bipolar disorder**: revised second edition—recommendations from the British Association for Psychopharmacology. J Psychopharmacol [Internet]. June 2009 [cited 2011 Feb 18]; 23(4):346-388. Available from: http://www.bap.org.uk/pdfs/Bipolar_guidelines.pdf

Gorczynski P, Faulkner G. **Exercise therapy** for schizophrenia. Cochrane Database Syst Rev. 2010 May 12;5:CD004412. Results of this Cochrane review are similar to existing reviews that have examined the health benefits of exercise in this population.

Graham KA, Gu H, Lieberman JA, et al. Double-blind, placebo-controlled investigation of **amantadine** for weight loss in subjects who gained weight with **olanzapine**. Am J Psychiatry. 2005 Sep;162(9):1744-6. n=21

Grant PM, Huh GA, Perivoliotis D, et al. Randomized trial to evaluate the efficacy of **cognitive therapy** for low-functioning patients with schizophrenia [online October 3, 2011]. Arch Gen Psychiatry. 2012;69 (2):121-127.

Gray R, et al. **Adherence therapy** for people with schizophrenia: European multicentre randomised controlled trial. Br J Psychiatry. 2006 Dec;189:508-514. This effectiveness trial provides evidence for the lack of effect of adherence therapy in people with schizophrenia with recent clinical instability, treated in ordinary clinical settings.

Green MF, Marder SR, Glynn SM, McGurk SR, Wirshing WC, Wirshing DA, et al. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biol Psychiatry. 2002 Jun 15;51(12):972-8.

Gunderson John G., **Borderline Personality Disorder**. N Engl J Med 2011; 364:2037-2042.

Guo JJ, et al. Risk of **diabetes mellitus** associated with **atypical antipsychotic** use among patients with bipolar disorder: A retrospective, population-based, case-control study. J Clin Psychiatry. 2006 Jul;67(7):1055-61. Compared to patients receiving conventional antipsychotics, the risk of diabetes was greatest among patients taking clozapine (hazard ratio [HR] = 7.0, 95% confidence interval [CI] = 1.7 to 28.9), risperidone (HR = 3.4, 95% CI = 2.8 to 4.2), olanzapine (HR = 3.2, 95% CI = 2.7 to 3.8), and quetiapine (HR = 1.8, 95% CI =1.4 to 2.4), with controlling covariates of age; sex; duration of follow-up; use of lithium, anticonvulsants, antidepressants, or concomitant drugs; and psychiatric and medical comorbidities.

Guo X, et al. Effect of Antipsychotic Medication Alone vs Combined With **Psychosocial Intervention** on Outcomes of Early-Stage Schizophrenia: A Randomized, 1-Year Study. Arch Gen Psychiatry. 2010 Sep;67(9):895-904.

Gurvich T, Cunningham JA. Appropriate use of psychotropic drugs in nursing homes. Am Fam Physician 2000;61:1437-46.

Haddad P. **Weight** change with atypical antipsychotics in the treatment of schizophrenia. J Psychopharmacol. 2005 Nov;19(6 Suppl):16-27.

Hägg S, Bate A, Stahl M, Spigset O. Associations between **venous thromboembolism** and antipsychotics. A study of the WHO database of adverse drug reactions. Drug Saf. 2008;31(8):685-94.

Haslemo T, et al. The effect of variable **cigarette** consumption on the interaction with **clozapine** and **olanzapine**. Eur J Clin Pharmacol. 2006 Nov 7; [Epub ahead of print] A daily consumption of 7-12 cigarettes is probably sufficient for maximum induction of clozapine and olanzapine metabolism. A 50% lower starting dose of both drugs in non-smokers seems rational to avoid side effects.

Haupt DW, et al. Prevalence and predictors of **lipid and glucose monitoring** in commercially insured patients treated with second-generation antipsychotic agents. Am J Psychiatry. 2009 Mar;166(3):345-53. Epub 2009 Jan 15.

Health Canada Mar/11 **Salvia divinorum** (S. divinorum) is a species of sage belonging to the mint family. Some street names for S. divinorum include: Sally D, Lady Sally, Maria pastora, ska Maria pastora, ska pastora, diviner's sage, magic mint, puff, incense special, and salvia. Canadians are cautioned against the use of products containing S. divinorum and/or salvinorin A because these products are known to cause hallucinations and little is known about the long-term effects of these substances on the brain and body.

Health Canada June/11 Antipsychotic drugs: Labelling update regarding the risk of abnormal **muscle movements and withdrawal symptoms in newborns** exposed during pregnancy.

Henderson DC, Copeland PM, Daley TB, et al. A double-blind, placebo-controlled trial of sibutramine for olanzapine-associated weight gain. Am J Psychiatry. 2005 May;162(5):954-62. (n=37 112weeks)

Hennen J, Baldessarini RJ. **Suicidal risk during treatment with clozapine**: a meta-analysis. Schizophr Res. 2005 Mar 1;73(2-3):139-45.

Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation

TOP

antipsychotics. Am J Psychiatry. 2006 Feb;163(2):185-94.
Ho J, Panagiotopoulos C, McCrindle B, Grisaru S, Pringsheim T; **CAMESA** guideline group. Management recommendations for **metabolic complications** associated with second generation antipsychotic use in **children and youth**. J Can Acad Child Adolesc Psychiatry. 2011 Aug;20(3):234-41.
Hoang U, Stewart R, Goldacre MJ. **Mortality after hospital discharge** for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006. BMJ 2011;343:d5422.
Honer WG, et al. Clozapine and Risperidone Enhancement (CARE) Study Group. Clozapine alone versus **clozapine and risperidone** with refractory schizophrenia. N Engl J Med. 2006 Feb 2;354(5):472-82. CONCLUSIONS: In this short-term study, the addition of risperidone to clozapine did not improve symptoms in patients with severe schizophrenia.
Hong LE, Thaker GK, McMahon RP, et al. Effects of moderate-dose treatment with **varenicline** on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 2011;68:1195-206.
Honkaniemi J, et al. **Haloperidol** in the **acute treatment of migraine**: a randomized, double-blind, placebo-controlled study. Headache. 2006 May;46(5):781-7.
Hosalli P, Davis JM. **Depot risperidone** for schizophrenia. Cochrane Database Syst Rev. 2003;(4):CD004161.
Hough DW, Natarajan J, Vandebosch A, et al. Evaluation of the effect of **paliperidone** extended release and **quetiapine** on corrected QT intervals: a randomized, double-blind, placebo-controlled study. Int Clin Psychopharmacol. 2010 Sep 28.
Howes OD, Kambeitz J, Kim E, et al. The Nature of **Dopamine Dysfunction** in Schizophrenia and What This Means for Treatment: Meta-analysis of Imaging Studies. Arch Gen Psychiatry. 2012 Apr 2.
Hoy SM, Scott LJ, Keating GM. **Intramuscular paliperidone palmitate**. CNS Drugs. 2010 Mar 1;24(3):227-44.
Huf G, Coutinho ES, Adams CE; TREC Collaborative Group. **Rapid tranquillisation** in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine. BMJ. 2007 Oct 22; [Epub ahead of print] **Haloperidol plus promethazine** is a better option than haloperidol alone in terms of speed of onset of action & safety. Enough data are now available to change guidelines that continue to recommend treatments that leave people exposed to longer periods of aggression than necessary and patients vulnerable to distressing and unsafe adverse effects.
Hugenholtz GW, et al. **Haloperidol Dose When Used as Active Comparator** in Randomized Controlled Trials With Atypical Antipsychotics in Schizophrenia: Comparison With Officially Recommended Doses. J Clin Psychiatry. 2006 Jun;67(6):897-903. Compared with recommended doses for severely ill patients in both the United Kingdom and United States (range, 6-15 mg daily), in 17 studies (35%) the mean actual used dose was above the upper dose border for severely ill patients (15 mg daily).
Huybrechts KF, Rothman KJ, Silliman RA., et al. **Risk of death and hospital admission** for major medical events after initiation of psychotropic medications in older adults admitted to nursing homes. CMAJ 2011 0: cmaj.101406
Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, et al. Differential risk of **death in older residents in nursing homes prescribed specific antipsychotic drugs**: population based cohort study. BMJ 2012;344:e977.
Ingenhoven T, Lafay P, Rinne T, et al. Effectiveness of pharmacotherapy for **severe personality disorders**: meta-analyses of randomized controlled trials. J Clin Psychiatry 2010; 71:14-25.
Jayaram MB, Hosalli P, Stroup S. **Risperidone versus olanzapine** for schizophrenia. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD005237.
Jeste DV, Rockwell E, Harris MJ, Lohr JB, Lacro J. Conventional vs. newer antipsychotics in elderly patients. Am J Geriatr Psychiatry 1999;7:70-6.
Joffe G, Takala P, Tchoukhine E, et al.. **Orlistat** in Clozapine- or Olanzapine-Treated Patients With Overweight or Obesity: A 16-Week Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Psychiatry. 2008 Mar 11;:e1-e6 [Epub ahead of print] Without a hypocaloric diet, the effect of orlistat in overweight/obese clozapine-or olanzapine-treated patients is modest and may only be seen in men.
Johnson KC, Laprairie JL, Brennan PA, et al. **Prenatal Antipsychotic Exposure and Neuromotor Performance** During Infancy. Arch Gen Psychiatry. 2012 Apr 2.
Jones PB, et al. Randomized controlled trial of the effect on **Quality of Life of second- vs first-generation antipsychotic** drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006 Oct;63(10):1079-87. In people with schizophrenia whose medication is changed for clinical reasons, there is no disadvantage across 1 year in terms of quality of life, symptoms, or associated costs of care in using FGAs rather than nonclozapine SGAs. Neither inadequate power nor patterns of drug discontinuation accounted for the result.
Josiassen RC, et al. **Clozapine augmented with risperidone** in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2005 Jan;162(1):130-6.
Joy CB, Mumby-Croft R, Joy LA. **Polyunsaturated fatty acid supplementation** for schizophrenia. Cochrane Database Syst Rev. 2006 Jul 19;3:CD001257.
Juncos JL. Management of psychotic aspects of Parkinson's Disease. J Clin Psychiatry 1999;60 (suppl 8); 42-53.
Kales HC , Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C , Cunningham F, Schneider LS, Blow FC: Risk of **mortality among individual antipsychotics** in patients with **dementia**. Am J Psychiatry 2011; 168:71–79.
Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. **Haloperidol** prophylaxis for elderly hip-surgery patients at risk for **delirium**: a randomized placebo-controlled study. J Am Geriatr Soc. 2005 Oct;53(10):1658-66. (InfoPOEMs: Low-dose haloperidol was no more effective than placebo in preventing delirium in elderly patients undergoing hip surgery. However, when delirium occurred, it was milder and shorter in patients receiving haloperidol. Furthermore, haloperidol shortened the hospital length of stay among patients who became delirious. (LOE = 1b-))
Kamble P, Chen H, Sherer JT, et al. Use of antipsychotics among elderly nursing home residents with dementia in US: an analysis of National Survey Data. Drugs Aging.2009;26(6):483-92.doi:10.2165/00002512-200926060-00005.
Kane JM, Detke HC, Naber D, et al. **Olanzapine Long-Acting Injection**: A 24-Week, Randomized, Double-Blind Trial of Maintenance Treatment in Patients With Schizophrenia. Am J Psychiatry. . [Epub ahead of print]
Katz IR, Jeste DV, et al.. Comparison of risperidone & placebo for psychosis & behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry 1999;60:107-15.
Keefe RS, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on **neurocognition** in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry. 2004 Jun;161(6):985-95.
Keefe RS, Bilder RM, Davis SM, Harvey PD, et al. **Neurocognitive Effects of Antipsychotic** Medications in Patients With Chronic Schizophrenia in the **CATIE** Trial. Arch Gen Psychiatry. 2007 Jun;64(6):633-47. After 2 months of antipsychotic treatment, all groups had a small but significant improvement in neurocognition. There were no differences between any pair of agents, including the typical drug perphenazine.
Kelly DL, Conley RR. A randomized double-blind 12-week study of quetiapine, risperidone or fluphenazine on **sexual functioning** in people with schizophrenia. Psychoneuroendocrinology. 2005 Sep 27; [Epub ahead of print]
Kahn RS, Fleischhacker WW, Boter H, et al. EUFEST study group. Effectiveness of antipsychotic drugs in **first-episode schizophrenia** and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008 Mar 29;371(9618):1085-97. This pragmatic trial suggests that clinically meaningful antipsychotic treatment of first-episode of schizophrenia is achievable, for at least 1 year. However, we cannot conclude that second-generation drugs are more efficacious than is haloperidol, since discontinuation rates are not necessarily consistent with symptomatic improvement.
Kennedy J, Deberdt W, Siegal A, et al. **Olanzapine does not enhance cognition** in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. Int J Geriatr Psychiatry. 2005 Nov;20(11):1020-7.
Kessing LV, Thomsen AF, Mogensen UB, Andersen PK. Treatment with antipsychotics and the **risk of diabetes** in clinical practice. Br J Psychiatry. 2010 Oct;197(4):266-71.
Kindermann SS, Dolder CR, Bailey A, Katz IR, Jeste DV. Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. Drugs Aging. 2002;19(4):257-76.
Kinon BJ, et al. Randomized, Double-blind 6-Month Comparison of **Olanzapine and Quetiapine** in Patients With Schizophrenia or Schizoaffective Disorder With Prominent Negative Symptoms and Poor Functioning. J Clin Psychopharmacol. 2006 Oct;26(5):453-461.
Kinon BJ, Ahl J, Stauffer VL, Hill AL, Buckley PF. Dose response and atypical antipsychotics in schizophrenia. CNS Drugs. 2004;18(9):597-616.
Kisely S, Smith M, Lawrence D, Maaten S. **Mortality** in individuals who have had psychiatric treatment: Population-based study in Nova Scotia. Br J Psychiatry. 2005 Dec;187:552-558.
Knapp P, Chait A, Pappadopulos E, et al. Treatment of **Maladaptive Aggression in Youth**: CERT Guidelines I. Engagement, Assessment, and Management. Pediatrics. 2012 May 28.
Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic Drug Use and Risk of **Pneumonia** in Elderly People. J Am Geriatr Soc. 2008 Feb 7; [Epub ahead of print] Use of antipsychotics in elderly people is associated with greater risk of pneumonia. This risk is highest shortly after the initiation of treatment, with the greatest increase in risk found for atypical antipsychotics.
Komossa K, Rummel-Kluge C, Hunger H, et al. **Ziprasidone** versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006627. Ziprasidone may be a slightly less efficacious antipsychotic drug than amisulpride, olanzapine and risperidone. Its main advantage is the low propensity to induce weight gain and associated adverse effects.
Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, et al. **Quetiapine** versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006625.

TOP

Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, El-Sayeh HG, Kissling W, Leucht S. **Aripiprazole** versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006569.

Komossa K, Depping AM, Gaudchau A, et al. **Second-generation antipsychotics for major depressive** disorder and dysthymia. Cochrane Database Syst Rev. 2010 Dec 8;12:CD008121

Komossa K, Depping AM, Meyer M, et al. **Second-generation antipsychotics** for **obsessive compulsive disorder**. Cochrane Database Syst Rev. 2010 Dec 8;12:CD008141. The available data of the effects of olanzapine in OCD are too limited to draw any conclusions. There is some evidence that adding quetiapine or risperidone to antidepressants increases efficacy, but this must be weighed against less tolerability and limited data.

Komossa K, Rummel-Kluge C, Schwarz S, et al. **Risperidone** versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2011 Jan 19;1:CD006626. Risperidone seems to produce somewhat more extrapyramidal side effects and clearly more prolactin increase than most other SGAs. It may also differ from other compounds in efficacy and in the occurrence of other adverse effects such as weight gain, metabolic problems, cardiac effects, sedation and seizures. Nevertheless, the large proportion of participants leaving studies early and incomplete reporting of outcomes makes it difficult to draw firm conclusions.

Kontaxakis VP, et al. **Risperidone augmentation** of clozapine : A critical review. Eur Arch Psychiatry Clin Neurosci. 2006 Aug 8; [Epub ahead of print]

Köpke S, Mühlhauser I, Gerlach A, et al. Effect of a guideline-based **multicomponent intervention on use of physical restraints** in nursing homes: a randomized controlled trial. JAMA. 2012 May 23;307(20):2177-84.

Krakowski MI, et al. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry. 2006 Jun;63(6):622-9. Clozapine shows greater efficacy than olanzapine and olanzapine greater efficacy than haloperidol in reducing aggressive behavior. This antiaggressive effect appears to be separate from the antipsychotic and sedative action of these medications.

Kryzhanovskaya LA, et al. Comparison of Long-Term (At Least 24 Weeks) **Weight Gain** and Metabolic Changes Between **Adolescents and Adults Treated with Olanzapine**. J Child Adolesc Psychopharmacol. 2012 Feb 28.

Kurlan R. Clinical practice. **Tourette's Syndrome**. N Engl J Med. 2010 Dec 9;363(24):2332-8.

Krystal JH et al. Adjunctive **risperidone** treatment for antidepressant-resistant symptoms of chronic military service–related PTSD: randomized trial. JAMA 2011 Aug 3. (ineffective)

Lambert BL, et al. **Diabetes risk** associated with use of **olanzapine**, **quetiapine**, and **risperidone** in veterans health administration patients with schizophrenia. Am J Epidemiol. 2006 Oct 1;164(7):672-81. Epub 2006 Aug 30. With patients initiating haloperidol use designated the reference group, diabetes risk was increased equally with new use of olanzapine (hazard ratio (HR) = 1.64, 95% confidence interval (CI): 1.22, 2.19), risperidone (HR = 1.60, 95% CI: 1.19, 2.14), or quetiapine (HR = 1.67, 95% CI: 1.01, 2.76).

Lamberti JS, Olson D, Crilly JF, Olivares T, Williams GC, Tu X, Tang W, Wiener K, Dvorin S, Dietz MB. Prevalence of the metabolic syndrome among patients receiving **clozapine**. Am J Psychiatry. 2006 Jul;163(7):1273-6.

Lerner V, Miodownik C, Kaptsan A, et al. **Vitamin B6 treatment for tardive dyskinesia**: a randomized, double-blind, placebo-controlled, crossover study. J Clin Psychiatry. 2007 Nov;68(11):1648-54. Vitamin B(6) 1200mg/d appears to be effective in reducing symptoms of TD. The specific mechanisms by which vitamin B(6) attenuates symptoms of TD are not clear.

Lee PE, Sykora K, Gill SS, Mamdani M et al. Antipsychotic medications & drug-induced **movement disorders** other than parkinsonism: a population-based cohort study in older adults. J Am Geriatr Soc. 2005 Aug;53(8):1374-9.

Leopold NA. Risperidone Treatment of Drug Related Psychosis in Patients with Parkinsomism. Movement Disorders 2000;15(1):301-304.

Leslie DL, Rosenheck RA. Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. Am J Psychiatry. 2004 Sep;161(9):1709-11.

Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and **meta-analysis**. Lancet. 2003 May 10;361(9369):1581-9.

Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. **Second-generation versus first-generation** antipsychotic drugs for schizophrenia: a meta-analysis.Lancet. 2009 Jan 3;373(9657):31-41. Epub 2008 Dec 6. Second-generation antipsychotic drugs differ in many properties and are not a homogeneous class. This meta-analysis provides data for individualised treatment based on efficacy, side-effects, and cost.

Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Lobos CA, Schwarz S, Davis JM. A Meta-Analysis of Head-to-Head **Comparisons of Second-Generation** Antipsychotics in the Treatment of Schizophrenia. Am J Psychiatry. 2008 Nov 17. [Epub ahead of print] The findings suggest that some second-generation antipsychotics may be somewhat more efficacious than others, but the limitations of meta-analysis must be considered. In tailoring drug treatment to the individual patient, small efficacy superiorities must be weighed against large differences in side effects and cost.

Leucht S, Hierl S, Kissling W et al. Putting the efficacy of **psychiatric and general medicine medication into perspective**: review of meta-analyses. Br J Psychiatry. 2012 Feb;200:97-106.

Leucht S, Tardy M, Komossa K, et al. **Antipsychotic drugs versus placebo for relapse prevention in schizophrenia**: a systematic review and meta-analysis. Lancet 2012; published online May 3.

Leung Jonathan G, Breden Ericka L. **Tetrabenazine for the Treatment of Tardive Dyskinesia.** Articles Ahead of Print published on 1 April 2011, DOI 10.1345/aph.1P312. Ann Pharmacother ;45:525-531.

Leung JG, Puri NV, Jacobson MJ. Immediate-release **oxybutynin for the treatment of clozapine-induced sialorrhea**. Ann Pharmacother. 2011 Sep;45(9):e45.

Li C, Xia J, Wang J. **Risperidone** dose for schizophrenia. Cochrane Database Syst Rev. 2009;(4).

Lichtenstein P, Yip BH, Bjork C, et al. **Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study.** Lancet. 2009 Jan **17;373(9659):234-239.** Similar to molecular genetic studies, we showed evidence that schizophrenia and bipolar disorder partly share a common genetic cause. These results challenge the current nosological dichotomy between schizophrenia and bipolar disorder, and are consistent with a reappraisal of these disorders as distinct diagnostic entities.

Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM. Pharmacotherapy for **borderline personality disorder**: Cochrane systematic review of randomised trials. Br J Psychiatry 2010;196:4-12.

Lieberman JA, Stroup TS, McEvoy JP, et al.; Clinical Antipsychotic Trials of Intervention Effectiveness (**CATIE**) Investigators. Effectiveness of **antipsychotic drugs in patients with chronic schizophrenia**. N Engl J Med. 2005 Sep 22;353(12):1209-23. Epub 2005 Sep 19. & see also Pharmacist Letter Nov/05. CONCLUSIONS: The majority of patients in each group discontinued their assigned treatment owing to inefficacy or intolerable side effects or for other reasons. **Olanzapine** was the most effective in terms of the rates of discontinuation, and the efficacy of the conventional antipsychotic agent **perphenazine appeared similar to that of quetiapine, risperidone, and ziprasidone**. **Olanzapine** was associated with greater weight gain and increases in measures of glucose and lipid metabolism. (n=1493 over 18 months; average age 40yrs; not studied was aripiprazole & clozapine) (InfoPOEMs: There are few differences among newer antipsychotics & few differences between newer agents and perphenazine, an older agent. Olanzapine seems to offer somewhat greater effectiveness, but is less well tolerated & can produce adverse changes to physiologic end points. All the newer antipsychotics are also much more expensive, which is a concern for this vulnerable group of patients. Based on its similar efficacy and better-than-expected tolerability, perphenazine at a dose of up to 20 mg per day should remain a treatment option for psychosis. (LOE = 1b))

Liperoti R, Pedone C, Lapane KL, et al. **Venous Thromboembolism** Among Elderly Patients Treated With **Atypical** and Conventional Antipsychotic Agents. Arch Intern Med. 2005 Dec 12;165(22):2677-2682.

Lipscombe LL, Levesque L, Gruneir A, et al. **Antipsychotic drugs and hyperglycemia** in older patients with diabetes. Arch Intern Med. 2009 Jul 27;169(14):1282-9.

Luft B, Taylor D. A review of **atypical antipsychotic** drugs **versus conventional** medication in schizophrenia. Expert Opin Pharmacother. 2006 Sep;7(13):1739-48.

Luna B, Feinglos MN. Drug-induced hyperglycemia. JAMA 2001;286:1945-8.

Mackin P, Thomas SH. **Atypical antipsychotic drugs**. BMJ. 2011 Mar 4;342:d1126. doi: 10.1136/bmj.d1126.

Maher AR et al. Efficacy and comparative effectiveness of **atypical antipsychotic medications for off-label uses in adults**. JAMA 2011 Sep 28; 306:1359.

Marcantonio Edward R. In the Clinic: **Delirium**. Ann Intern Med June 7, 2011 154:ITC6-1; doi:10.1059/0003-4819-154-11-201106070-01006.

Marcus SC, Olfson M. **National trends in the treatment for depression from 1998 to 2007**. Arch Gen Psychiatry. 2010 Dec;67(12):1265-73.

Margolese HC, Chouinard G, Kolivakis TT, et al. **Tardive dyskinesia** in the era of typical and atypical antipsychotics. Part 1: **pathophysiology and mechanisms** of induction. Can J Psychiatry. 2005 Aug;50(9):541-7. & Margolese HC, et al. Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 2: **Incidence and management** strategies in patients with schizophrenia. Can J Psychiatry. 2005 Oct;50(11):703-14. (Bergman J, Dwolatzky T, Brettholz I, Lerner V. Beneficial effect of donepezil in the treatment of elderly patients with tardive movement disorders. J Clin Psychiatry. 2005 Jan;66(1):107-10.)

Marshall M, Rathbone J. **Early intervention for psychosis**. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD004718. DOI: 10.1002/14651858.CD004718.pub3. There is emerging, but as yet inconclusive evidence, to suggest that people in the prodrome of psychosis can be helped by some interventions.

Marshall M, Crowther R, Sledge WH, et al. **Day hospital versus admission** for acute psychiatric disorders. Cochrane Database Syst Rev. 2011 Dec 7;12:CD004026. Caring for people in acute day hospitals is as effective as inpatient care in treating acutely ill psychiatric patients. However, further data are still needed on the cost effectiveness of day hospitals.

McCrone P, Craig TK, Power P, et al. **Cost-effectiveness of an early intervention** service for people with psychosis. Br J Psychiatry. 2010 May;196(5):377-82.

McCue RE, et al. Comparative effectiveness of **second-generation antipsychotics and haloperidol** in acute schizophrenia. Br J Psychiatry. 2006 Nov;189:433-40. Haloperidol, olanzapine and risperidone are superior to aripiprazole, quetiapine and ziprasidone for the acute treatment of psychosis in hospitalised patients with schizophrenia, schizoaffective disorder or schizophreniform disorder.

McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RS, Davis CE, (Catie trial). Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did **not respond to prior atypical antipsychotic** treatment. Am J Psychiatry. 2006 Apr;163(4):600-10. For these patients with schizophrenia who prospectively failed to improve with an atypical antipsychotic, clozapine was more effective than switching to another newer atypical antipsychotic. Safety monitoring is necessary to detect and manage clozapine's serious side effects.

McGlashan TH, et al. Randomized, double-blind trial of olanzapine versus placebo in patients **prodromally symptomatic for psychosis**. Am J Psychiatry. 2006 May;163(5):790-9.

TOP

McKenna K, Koren G, Tetelbaum M, et al. **Pregnancy** Outcome of Women Using **Atypical Antipsychotic Drugs (n=151)**: A Prospective Comparative Study. J Clin Psychiatry. 2005 Apr;66(4):444-449.
McPheeters ML, Warren Z, Sathe N, et al. A systematic review of medical treatments for children with **autism spectrum disorders**. Pediatrics. 2011 May;127(5):e1312-21.
Medical Letter "Treatment Guidelines- Drugs for Psychiatric Disorders August 2010 {Vol 4 (Issue 46) June 2006.}
Medical Letter. Treatment Guidelines. Drugs for Depression and Bipolar Disorder. May 2010.
Medical Letter. **Iloperidone** –another Second-Generation Antipsychotic. Feb 22, 2010.
Medical Letter. **Asenapine** (Saphris) for Schizophrenia and Bipolar Disorder. Feb 2010.
Medical Letter. **Lurasidone** (Latuda) for Schizophrenia. Feb 21, 2011.
Melmed S, Casanueva FF, Hoffman AR, et al. **Diagnosis and treatment of hyperprolactinemia**: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88.
Meltzer HY, Alphs L, Green AI, et al.; International **Suicide** Prevention Trial Study Group. **Clozapine** treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry. 2003 Jan;60(1):82-91. Erratum in: Arch Gen Psychiatry.2003 Jul;60(7):735.
Meltzer, Herbert Y., Cucchiaro, Josephine, Silva, Robert, et al. **Lurasidone** in the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study. Am J Psychiatry 2011 168: 957-967
Miller del D, Caroff SN, Davis SM, et a; Clinical Antipsychotic Trials of Intervention Effectiveness (**CATIE**) Investigators. Extrapyramidal side-effects of antipsychotics in a randomised trial. Br J Psychiatry. 2008 Oct;193(4):279-88. The incidence of **treatment-emergent EPS and change in EPS ratings** indicated that there are no significant differences between second-generation antipsychotics and perphenazine or between second-generation antipsychotics in people with schizophrenia.
Moncada LV. Management of **falls in older persons**: a prescription for prevention. Am Fam Physician. 2011 Dec 1;84(11):1267-76.
Morrison AP, French P, Stewart SL, et al. **Early detection and intervention** evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ. 2012 Apr 5;344:e2233.
Motsinger CD, Perron GA, Lacy TJ. Use of atypical antipsychotic drugs in patients with **dementia**. Am Fam Physician. 2003 Jun 1;67(11):2335-40.
Muench J, Hamer AM. **Adverse effects of antipsychotic medications**. Am Fam Physician. 2010 Mar 1;81(5):617-22.
Mukundan A, Faulkner G, Cohn T, Remington G. **Antipsychotic switching** for people with schizophrenia who have neuroleptic-induced **weight or metabolic problems**. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD006629. DOI: 10.1002/14651858.CD006629.pub2. Evidence from this review suggests that switching antipsychotic medication to one with lesser potential for causing weight gain or metabolic problems could be an effective way to manage these side effects, but the data were weak due to the limited number of trials in this area and small sample sizes. Poor reporting of data also hindered using some trials and outcomes. There was no difference in mental state, global state and other treatment related adverse events between switching to another medication and continuing on the previous one. When the three switching strategies were compared none of them had an advantage over the others in their effects on the primary outcomes considered in this review. Better designed trials with adequate power would provide more convincing evidence for using medication switching as an intervention strategy.
Munk-Olsen T, Laursen TM, Pedersen CB, Lidegaard O, Mortensen PB. **Induced First-Trimester Abortion** and Risk of Mental Disorder. N Engl J Med. 2011 Jan 27;364(4):332-339.
Munk-Olsen T, Laursen TM, Meltzer-Brody S et al. **Psychiatric disorders with postpartum onset**: possible early manifestations of bipolar affective disorders. Arch Gen Psychiatry. 2012 Apr;69(4):428-34.
Musselman ME, Browning LA, Parker D Jr, Saely S. **Neuroleptic malignant syndrome** associated with the use of **prochlorperazine** in a patient with a recent history of antipsychotic-induced neuroleptic malignant syndrome. Ann Pharmacother. 2011 Nov;45(11):e61.
Nakagawa S, et al. Antipsychotics and risk of first-time hospitalization for **myocardial infarction**: a population-based case-control study. J Intern Med. 2006 Nov;260(5):451-8.
Nelson JC, Papakostas GI. Atypical **antipsychotic augmentation** in major **depressive** disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry. 2009 Sep;166(9):980-91. Epub 2009 Aug 17.
Newcomer JW, Campos JA, Marcus RN, et al. A multicenter, randomized, double-blind study of the effects of **aripiprazole in overweight** subjects with schizophrenia or schizoaffective disorder **switched from olanzapine**. J Clin Psychiatry 2008; 69:1046–1056
Newham JJ, Thomas SH, MacRitchie K, et al. **Birth weight of infants after maternal exposure** to typical and atypical antipsychotics: prospective comparison study. Br J Psychiatry. 2008 May;192(5):333-7.
NICE: National Collaborating Centre for Mental Health. **Antenatal and postnatal mental health**: clinical management and service guidance [Internet]. London: National Institute for Health and Clinical Excellence; 2007 Feb [reissued 2007 Apr; cited 2011 Feb 18]. (NICE clinical guideline 45). Available from: http://www.nice.org.uk/nicemedia/pdf/CG045NICEGuidelineCorrected.pdf *See: Antipsychotics, pp.21-2*
NICE: National Collaborating Centre for Mental Health. Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (**NICE**); 2009 Mar. 41 p. (NICE clinical guideline; no. 82). http://guidance.nice.org.uk/CG82
NICE: Clinical Guideline 120. Mar 2011. **Psychosis with coexisting substance misuse**. http://www.nice.org.uk/nicemedia/live/13414/53691/53691.pdf Guick Guide http://www.nice.org.uk/nicemedia/live/13414/53731/53731.pdf
NICE: Pilling Stephen, Whittington Craig, Taylor Clare, et al. on behalf of the Guideline Development Group. Guidelines: Identification and care pathways for common mental health disorders: summary of NICE guidance. BMJ 2011;342:doi:10.1136/bmj.d2868 (Published 24 May 2011)
NICE: National Institute for Health and Clinical Excellence. Common mental health disorders: identification and pathways to care. (Clinical guideline CG123. 2011. http://guidance.nice.org.uk/CG123 .
Nielsen SF, Hjorthøj CR, Erlangsen A, Nordentoft M. Psychiatric disorders and mortality among people in **homeless shelters** in Denmark: a nationwide register-based cohort study. Lancet 2011; published online June 14.
Nisbet AC. **Intramuscular gluteal injections** in the increasingly obese population: retrospective study. BMJ. 2006 Mar 18;332(7542):637-8. Epub 2006 Mar 8.
Nosarti C, Reichenberg A, Murray RM, et al. **Preterm Birth and Psychiatric Disorders** in Young Adult LifePreterm Birth and Psychiatric Disorders. Arch Gen Psychiatry. 2012 Jun1:610-617.
Nussbaum AM, Stroup TS. Oral **paliperidone** for schizophrenia. Cochrane Database Syst Rev. 2008;(2).
Oldham JM, Gabbard GO, Goin MK, et al. Practice **guideline for the treatment of patients with borderline personality disorder**. Am J Psychiatry 2001;158:Suppl:1-52.
Owen, Randall, Sikich, Linmarie, Marcus, Ronald N., et al. **Aripiprazole** in the Treatment of Irritability in Children and Adolescents With **Autistic** Disorder. Pediatrics 2009 124: 1533-1540.
Owenby RK, Brown LT, Brown JN. Use of **Risperidone** as Augmentation Treatment for Major Depressive Disorder (January). Ann Pharmacother. 2010 Dec 28.
Pariente A, Fourrier-Réglat A, Ducruet T, et al. Antipsychotic use and **myocardial infarction** in older patients with treated **dementia** [published online Mar 26, 2012]. Arch Intern Med doi:10.1001/archinternmed.2012.28.
Parker C et al. **Antipsychotic drugs and risk of venous thromboembolism**: nested case-control study. BMJ 2010; 341: c4245
Patel JJ, Lisi PA, Lathara Z, Lipchik RJ. **Clozapine-Induced Peripheral and Pleural Fluid Eosinophilia** (February). Ann Pharmacother. 2012 Jan 24.
Patton SW, Misri S, Corral MR, Perry KF, Kuan AJ. Antipsychotic medication during **pregnancy and lactation** in women with schizophrenia: evaluating the risk. Can J Psychiatry. 2002 Dec;47(10):959-65.
Peluso MJ, Lewis SW, Barnes TR, Jones PB. **Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs**. Br J Psychiatry. 2012 May;200:387-92.
Pharmacist's Letter: Drug Treatment for Behavioral Symptoms Associated with **Autism**. Dec/06.
Pharmacist's Letter. **Quetiapine (Seroquel) abuse**. Oct 2007.
Pharoah F, Mari J, Rathbone J, Wong W. **Family intervention** for schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD000088. DOI: 10.1002/14651858.CD000088.pub2. Family intervention may reduce the number of relapse events and hospitalisations and would therefore be of interest to people with schizophrenia, clinicians and policy makers.
Picchioni MM, Murray RM. **Schizophrenia**. BMJ. 2007 Jul 14;335(7610):91-5.
Pollack TM, McCoy C, Stead W. Clinically significant adverse events from a drug interaction between **quetiapine** and **atazanavir-ritonavir** in two patients. Pharmacotherapy. 2009 Nov;29(11):1386-91.
Premkumar TS, Pick J. **Lamotrigine** for schizophrenia. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005962.
Pringsheim T, Lam D, Ching H, Patten S. **Metabolic** and **neurological complications** of second-generation antipsychotic use in **children**: a systematic review and meta-analysis of randomized controlled trials.

TOP

Drug Saf. 2011 Aug 1;34(8):651-68.
Pringsheim T, Lam D, Patten SB. The **pharmacoepidemiology** of antipsychotic medications for Canadian **children and adolescents**: 2005-2009. J Child Adolesc Psychopharmacol. 2011 Dec;21(6):537-43.
Pringsheim T, Lam D, Tano DS, Patten SB. The **pharmacoepidemiology** of antipsychotics for **adults** with schizophrenia in Canada, 2005 to 2009. Can J Psychiatry. 2011 Oct;56(10):630-4.
Pringsheim T, Panagiotopoulos C, Davidson J, Ho J; **CAMESA** guideline group. Evidence-based recommendations for **monitoring** safety of second generation antipsychotics in **children and youth**. J Can Acad Child Adolesc Psychiatry. 2011 Aug;20(3):218-33.
Pringsheim T, Doja A, Belanger S et al. Treatment recommendations for **extrapyramidal** side effects associated with second-generation antipsychotic use in **children and youth**. Paediatr Child Health 2011;16(9):590-598.
Raivio MM, Laurila JV, Strandberg TE, et al. **Neither atypical nor conventional antipsychotics increase mortality** or hospital admissions among elderly patients with dementia: a two-year prospective study. Am J Geriatr Psychiatry. 2007 May;15(5):416-24.
Rapaport MH, et al. Effects of **Risperidone Augmentation** in Patients with Treatment-Resistant Depression: Results of Open-Label Treatment Followed by Double-Blind Continuation. Neuropsychopharmacology. 2006 Jun 7
Rattehalli RD, Jayaram MB, Smith M. **Risperidone** versus placebo for schizophrenia. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006918.
Raveendran NS, Tharyan P, Alexander J, Adams CE; TREC-India II Collaborative Group. **Rapid tranquillisation** in psychiatric emergency settings in India: pragmatic randomised controlled trial of intramuscular olanzapine versus Intramuscular haloperidol plus promethazine. BMJ. 2007 Oct 22; [Epub ahead of print] Intramuscular olanzapine & intramuscular **haloperidol plus promethazine** were effective at rapidly tranquillising or sedating agitated or violent patients with mental illness but the combination resulted in fewer additional medical interventions within four hours of intervention.
Ray WA, Chung CP, Murray KT et al. Atypical antipsychotic drugs and the risk of **sudden cardiac death**. New Engl J Med 2009; 360: 225-235. Both typical & atypical antipsychotics increase risk of sudden cardiac death. The absolute risk of sudden cardiac death in pts taking these drugs is 1.8 per 100 persons taking the drugs for 10yrs, which is approx. twice as high as for patients in the general population. Newer drugs are not safer than older drugs with respect to cardiovascular outcomes, & thioridazine, clozapine, & risperidone in high doses appear to be slightly more risky. (LOE = 2b)
Remington G, Seeman P, Feingold A, Mann S, Shammi C, Kapur S. "**Extended**" antipsychotic **dosing** in the maintenance treatment of schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry. 2010 Sep 7.
Riedel M, et al. **Quetiapine** has equivalent efficacy & **superior tolerability to risperidone** in schizophrenia with predominantly negative symptoms. Eur Arch Psychiatry Clin Neurosci. 2005 Dec;255(6):432-7. Epub 2005 Nov 4.
Robottom BJ, Factor SA, Weiner WJ. Movement disorders emergencies part 2: **hyperkinetic disorders** (chorea, tics, ballism, myoclonus, dystonia). Arch Neurol. 2011 Jun;68(6):719-24.
Rochon PA, Stukel TA, Sykora K, Gill S, Garfinkel S, et al. **Atypical antipsychotics and parkinsonism**. Arch Intern Med. 2005 Sep 12;165(16):1882-8. CONCLUSIONS: The risk of development of parkinsonism associated with the use of high-dose atypical antipsychotics was similar to that associated with the use of typical antipsychotics. Caution should be used when prescribing atypical antipsychotic therapy at high doses.
Rosenheck, Robert; Perlick, Deborah et al. Effectiveness and Cost of **Olanzapine and Haloperidol** in the Treatment of Schizophrenia: A Randomized Controlled Trial. JAMA. 2003;290:2693-2702.
Rosenheck RA., Krystal JH., Lew R, et al. for the CSP555 Research Group. **Long-Acting Risperidone** and Oral Antipsychotics in Unstable Schizophrenia. N Engl J Med 2011; 364:842-851. (No Benefit, More SE With Injectable Risperidone)
Rubio G, et al. **Long-acting injectable risperidone** compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. Can J Psychiatry. 2006 Jul;51(8):531-9.
Rummel-Kluge C, Komossa K, Schwarz S, et al. **Second-Generation Antipsychotic** Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons. Schizophr Bull. 2010 May 31.
Sacchetti E, Turrina C, Valsecchi P. **Cerebrovascular accidents in elderly people treated with antipsychotic** drugs: a systematic review. Drug Saf. 2010 Apr 1;33(4):273-88. doi: 10.2165/11319120-000000000-00000.
Sanford M, Keating GM. **Quetiapine**: a review of its use in the management of **bipolar depression**. CNS Drugs. 2012 May 1;26(5):435-60.
Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ. 2007 Feb 27;176(5):627-32. Among elderly patients, the risk of death associated with conventional antipsychotic medications is comparable to and possibly greater than the risk of death associated with atypical antipsychotic medications. Until further evidence is available, physicians should consider all antipsychotic medications to be equally risky in elderly patients.
Schneider LS, Tariot PN, Dagerman KS, et al. **CATIE-AD** Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med. 2006 Oct 12;355(15):1525-38. (n=421 36weeks risperidone 1mg/d, olanzapine 5.5mg/d, & quetiapine 56.5mg/d) Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) (P=0.52). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) (P=0.002). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, & 5% of patients who received placebo discontinued their assigned treatment owing to intolerability (P=0.009). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo (P=0.22). (InfoPOEMs: Atypical antipsychotics are minimally, if at all, effective for patients with Alzheimer's disease (AD), and they have significant adverse effects. They should not be routinely used for the treatment of psychosis, agitation, or aggression in these patients. (LOE = 1b))
Schooler N, Rabinowitz J, et al. **Risperidone and haloperidol in first-episode** psychosis: a long-term randomized trial. Am J Psychiatry. 2005 May;162(5):947-53.
Scotto Rosato N, Correll CU, Pappadopulos E, et al; on behalf of the Treatment of **Maladaptive Aggressive in Youth** Steering Committee. Treatment of Maladaptive Aggression in Youth: CERT Guidelines II. Treatments and Ongoing Management. Pediatrics. 2012 Jun;129(6):e1577-e1586.
Second generation antipsychotics- **Aripiprazole** revisited. The Medical Letter Oct 10,2005.
Seida JC, Schouten JR, Boylan K, et al. **Antipsychotics for children and young adults**: a comparative effectiveness review.Pediatrics. 2012 Mar;129(3):e771-84.
Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of **diabetes** mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry. 2002 Apr;159(4):561-6.
Shaw P, et al. **Childhood-onset schizophrenia**: a double-blind, randomized clozapine-olanzapine comparison. Arch Gen Psychiatry. 2006 Jul;63(7):721-30.
Sheldon Tony. Study of **rivastigmine for delirium** in intensive care is stopped after **deaths.** BMJ 2010;340:c2895, doi: 10.1136/bmj.c2895 (Published 28 May 2010)
Sikich L, Frazier JA, McClellan J, et al. Double-Blind Comparison of First- and Second-Generation Antipsychotics in Early-Onset Schizophrenia and Schizo-affective Disorder: Findings From the Treatment of Early-Onset Schizophrenia Spectrum Disorders (**TEOSS**) Study. Am J Psychiatry. 2008 Sep 15. [Epub ahead of print] n=119. Olanzapine (2.5-20 mg/day), risperidone (0.5-6 mg/day), or molindone (10-140 mg/day, plus 1 mg/day of benztropine) for 8 weeks. Risperidone and olanzapine did not demonstrate superior efficacy over molindone for treating early-onset schizophrenia and schizoaffective disorder. Adverse effects were frequent but differed among medications. The results question the nearly exclusive use of second-generation antipsychotics to treat early-onset schizophrenia and schizoaffective disorder. The safety findings related to weight gain and metabolic problems raise important public health concerns, given the widespread use of second-generation antipsychotics in youth for nonpsychotic disorders.
Singh SP, Singh V, Kar N, Chan K. Efficacy of **antidepressants in treating the negative symptoms** of chronic schizophrenia: meta-analysis. Br J Psychiatry. 2010 Sep;197(3):174-9.
Singh J, Kour K, Jayaram MB. **Acetylcholinesterase inhibitors for schizophrenia**. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD007967. DOI: 10.1002/14651858.CD007967.pub2. The results seem to favour the use of acetylcholinesterase inhibitors in combination with antipsychotics on a few domains of mental state and cognition, but because of the various limitations in the studies as mentioned in the main text, the evidence is weak.
Stahl SM. Essential psychopharmacology: neuroscientific basis and practical application. 2d ed. New York, N.Y.: Cambridge University Press, 2000.
Stip E et al. **Ziprasidone** for psychotic disorders: a meta-analysis and systematic review of the relationship between pharmacokinetics, pharmacodynamics, and clinical profile. Clin Ther. 2011 Dec;33(12):1853-67.
Stoffers J, Vollm BA, Rucker G, et al. Pharmacological interventions for **borderline personality disorder**. Cochrane Database Syst Rev. 2010 Jun 16;6:CD005653.
Straus SM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the **risk of sudden cardiac death**. Arch Intern Med. 2004 Jun 28;164(12):1293-7. Erratum in: Arch Intern Med. 2004 Sep 27;164(17):1839. The risk of sudden cardiac death was highest among those using butyrophenone antipsychotics, those with a defined daily dose equivalent of more than 0.5 and short-term (</=90 days) users.
St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, Zheng X, Gu N, Feng G, Sham P, He L. Rates of adult schizophrenia following prenatal exposure to the Chinese **famine** of 1959-1961. JAMA. 2005 Aug 3;294(5):557-62.
Street J, Mitan S, Tamura R, et al. Olanzapine in the treatment of psychosis and behavioral disturbances associated with Alzheimer's disease. Eur J Neurology 1998;5:S39.
Strom BL, Eng SM, Faich G, Reynolds RF, et al. Comparative Mortality Associated With **Ziprasidone and Olanzapine** in Real-World Use Among 18,154 Patients With Schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). Am J Psychiatry. 2010 Nov 1.
Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of **olanzapine**, quetiapine, **risperidone**, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic (from the **Catie** trial). Am J Psychiatry. 2006 Apr;163(4):611-22.

TOP

Stroup, T. Scott, McEvoy, Joseph P., Ring, Kimberly D., et al. the Schizophrenia Trials Network, A Randomized Trial Examining the Effectiveness of Switching **From Olanzapine, Quetiapine, or Risperidone to Aripiprazole** to Reduce Metabolic Risk: Comparison of Antipsychotics for Metabolic Problems (**CAMP**). Am J Psychiatry 2011 168: 947-956
Subotnik, Kenneth L., Nuechterlein, Keith H., Ventura, Joseph, et al. **Risperidone Nonadherence** and Return of Positive Symptoms in the Early Course of Schizophrenia. Am J Psychiatry 2011 0: appi.ajp.2010.09010087.
Suh GH, Shah A. Effect of **antipsychotics on mortality** in elderly patients with dementia: a 1-year prospective study in a nursing home. Int Psychogeriatr. 2005 Sep;17(3):429-41.
Sultzer DL, Davis SM, et al. **CATIE-AD**. Clinical **symptom responses** to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes CATIE-AD effectiveness trial. Am J Psychiatry. 2008 Jul;165(7):844-54.
Swanson JW, et al. Facilitated psychiatric **advance directives**: a randomized trial of an intervention to foster advance treatment planning among persons with severe mental illness. Am J Psychiatry. 2006 Nov;163(11):1943-51.
Szarfman A, et al. Atypical antipsychotics and **pituitary tumors**: a pharmacovigilance study. Pharmacotherapy. 2006 Jun;26(6):748-58.
Targum SD, Abbott JL. Efficacy of quetiapine in Parkinson's patients with psychosis. *J Clin Psychopharmacol* 2000; 20(1): 54-60.
Tariot PN, Ryan JM, Porsteinsson AP, Loy R, Schneider LS. Pharmacologic therapy for behavioral symptoms of Alzheimer's disease. Clin Geriatr Med 2001;17:359-76.
Tariot PN, Salzman C, Yeung PP, Pultz J, Rak IW. Long-term use of quetiapine in elderly patients with psychotic disorders. Clin Ther 2000;22:1068-84.
Tchoukhine E, Takala P, et al. **Orlistat** in clozapine- or olanzapine-treated patients with overweight or obesity: a 16-week open-label extension phase and both phases of a randomized controlled trial. J Clin Psychiatry. 2010 Aug 24.
Tenback DE, van Harten PN, van Os J. Non-therapeutic risk factors for onset of **tardive dyskinesia** in schizophrenia: A meta-analysis. Mov Disord. 2009 Jul 30. [Epub ahead of print] However, the fact that early EPS predicts onset of TD has important clinical and research implications.
The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. The Lancet 1999;353:2041-2042.
The Parkinson Study Group. Low dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *NEJM* 1999;340(10):757-63.
Thornicroft G, et al.; INDIGO Study Group. Global pattern of **experienced and anticipated discrimination** against people with schizophrenia: a cross-sectional survey. Lancet. 2009 Jan 31;373(9661):408-15. Epub 2009 Jan 21.
Tiihonen J, Halonen P, Wahlbeck K, et a. Topiramate Add-On in Treatment-Resistant Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J Clin Psychiatry. 2005 Aug;66(8):1012-1015.
Tiihonen J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ. 2006 Jul 6; [Epub ahead of print] The effectiveness of first and second generation antipsychotics varies greatly in the community. Patients treated with perphenazine depot, clozapine, or olanzapine have a substantially lower risk of rehospitalisation or discontinuation (for any reason) of their initial treatment than do patients treated with haloperidol. Excess mortality is seen mostly in patients not using antipsychotic drugs.
Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (**FIN11 study**). Lancet. 2009 Jul 10. [Epub ahead of print] Long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use. Second-generation drugs are a highly heterogeneous group, and clozapine seems to be associated with a substantially lower mortality than any other antipsychotics. Restrictions on the use of clozapine should be reassessed.
Tiihonen J, Haukka J, Taylor M, et al. A Nationwide Cohort Study of Oral and **Depot Antipsychotics After First Hospitalization** for Schizophrenia. Am J Psychiatry. 2011 Mar 1.
Tiihonen J, Suokas JT, Suvisaari JM, et al. **Polypharmacy with antipsychotics, antidepressants, or benzodiazepines** and mortality in schizophrenia. Arch Gen Psychiatry. 2012 May;69(5):476-83.
Trifirò Gianluca, Gambassi Giovanni, Sen Elif F., et al. Association of **Community-Acquired Pneumonia** With **Antipsychotic** Drug Use in Elderly Patients: A Nested Case–Control Study.*Ann Intern Med* April 6, 2010.
Treatment Guidelines: Drugs for Psychiatric Disorders. **The Medical Letter**: July, **2003**; p. 69-76. (**Medical Letter "Treatment Guidelines- Drugs for Psychiatric Disorders** Vol 4 (Issue 46) June **2006**.)
Tsai AC, Rosenlicht NZ, Jureidini JN, et al. **Aripiprazole** in the maintenance treatment of bipolar disorder: a **critical review** of the evidence and its dissemination into the scientific literature. PLoS Med 2011;8:e1000434.
Turkington D, et al. Outcomes of an effectiveness trial of **cognitive-behavioural intervention** by mental health nurses in schizophrenia. Br J Psychiatry. 2006 Jul;189:36-40.
Turner EH, Knoepflmacher D, Shapley L. **Publication Bias in Antipsychotic Trials**: An Analysis of Efficacy Comparing the Published Literature to the US Food and Drug Administration Database. PLoS Med. 2012 Mar;9(3):e1001189.
Tyrer P, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with **intellectual disability**: a randomised controlled trial. Lancet. 2008 Jan 5;371(9606):57-63. Antipsychotic drugs should no longer be regarded as an acceptable routine treatment for aggressive challenging behaviour in people with intellectual disability.
Ularntinon S, Tzuang D, Dahl G, Shaw RJ. Concurrent treatment of **steroid-related** mood and psychotic symptoms with risperidone. Pediatrics. 2010 May;125(5):e1241-5. Epub 2010 Apr 12.
Vigen CL, Mack WJ, Keefe RS, et al. **Cognitive Effects of Atypical Antipsychotic** Medications in Patients With Alzheimer's Disease: Outcomes From **CATIE-AD**. Am J Psychiatry. 2011 May 15.
Wang CY, Xiang YT, Cai ZJ, et al. For the **Risperidone Maintenance** Treatment in Schizophrenia (**RMTS**) investigators. Risperidone Maintenance Treatment in Schizophrenia: A Randomized, Controlled Trial. Am J Psychiatry. 2010 Mar 15. (initial optimal therapeutic dose continued for 4 weeks ~4.2mg/d, followed by a 50% dose reduction that was maintained until the end of the study), or a 26-week group (initial optimal therapeutic dose continued for 26 weeks, followed by a 50% dose reduction until the end of the study).
Wang S et al. Age, Antipsychotics, and the **Risk of Ischemic Stroke** in the Veterans Health Administration. Stroke. 2011 Oct 27.
Ward RK, Zamorski MA. Benefits and risks of psychiatric medications during **pregnancy**. Am Fam Physician. 2002 Aug 15;66(4):629-36.
Watkins ME, Newport DJ. Psychosis in **pregnancy**. Obstet Gynecol. 2009 Jun;113(6):1349-53.
Weiner WJ. Quetiapine for L-dopa induced psychosis in PD. Neurology 2000;54: 1538.
Werbeloff N, Drukker M, Dohrenwend BP, et al. **Self-reported Attenuated Psychotic Symptoms as Forerunners** of Severe Mental Disorders Later in Life. Arch Gen Psychiatry. 2012 Jan 2.
Whitley H, Lindsey W. **Sex-based** differences in drug activity. Am Fam Physician. 2009 Dec 1;80(11):1254-8.
Woods SW, Saksa JR, Baker CB, Cohen SJ, Tek C. Effects of levetiracetam (0.5-3g/d) on **tardive dyskinesia**: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2008 Apr;69(4):546-54. (n=50 12+12 weeks) **Levetiracetam appeared effective for TD** in this study. The mechanisms of its therapeutic effect are unclear but may involve reducing neuronal hypersynchrony in basal ganglia.
Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry. 2003 Jun;64(6):663-7.
Woods SW, Morgenstern H, Saksa JR, et al. Incidence of **tardive dyskinesia** with atypical versus conventional antipsychotic medications: a prospective cohort study. J Clin Psychiatry. 2010 Feb 9.
Wolters EC. Dopamimetic psychosis in Parkinson's disease patients-diagnosis and treatment. Neurology 1999: 52 (Suppl 3): S10-13.
Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. CMAJ. 2002 Nov 26;167(11):1269-70.
Wu RR, Zhao JP, Jin H, et al. Lifestyle intervention and **metformin for treatment of antipsychotic-induced** weight gain: a randomized controlled trial. JAMA. 2008 Jan 9;299(2):185-93.Lifestyle intervention and metformin alone and in combination demonstrated efficacy for antipsychotic-induced weight gain. Lifestyle intervention plus metformin showed the best effect on weight loss. Metformin alone was more effective in weight loss and improving insulin sensitivity than lifestyle intervention alone.
Wykes T, Huddy V, Cellard C, et al. A meta-analysis of **cognitive remediation** for schizophrenia: methodology and effect sizes. Am J Psychiatry. 2011 May;168(5):472-85.
Yatham LN et al. Canadian Network for Mood and Anxiety Treatments (**CANMAT**) guidelines for the management of patients with **bipolar** disorder: update **2006**. Bipolar Disorders 2006:8: 1-19
Zhong KX, et al. Comparison of **quetiapine and risperidone** in the treatment of schizophrenia: A randomized, double-blind, flexible-dose, 8-week study. J Clin Psychiatry. 2006 Jul;67(7):1093-103.
Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA. **Quetiapine to treat agitation in dementia**: a randomized, double-blind, placebo-controlled study. Curr Alzheimer Res. 2007 Feb;4(1):81-93.(~200mg/day effective)

June 2005 Health Canada & April 2005 FDA Issues Public Health Advisory for **Antipsychotic Drugs used for Treatment of Behavioral Disorders in Elderly Patients**
http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_63_e.html (Singh S, Wooltorton E. Increased mortality among elderly patients with dementia using atypical antipsychotics. CMAJ. 2005 Aug 2;173(3):252.) (Medical Letter August 1,2005 -Atypical antipsychotics in the Elderly FDA n=5106 17 RCTs mortality rate of 4.5% with atypical antipsychotic therapy vs 2.6% with placebo, most deaths were due to cardiovascular & infectious causes such as pneumonia.) Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: **meta-analysis** of randomized placebo-controlled trials. JAMA. 2005 Oct 19;294(15):1934-43. (InfoPOEMs: The use of atypical antipsychotic drugs for even short periods (less than 8 to 12 weeks) is associated with a significantly increased risk of death. Antipsychotic drugs should be used only in individual situations of an identifiable risk of harm and when alternate therapies have failed. (LOE = 1a)) {15 trials (9 unpublished) of atypical antipsychotics vs placebo for ~10-12weeks

TOP

n=5110; 3.5 vs 2.3% death rate}(Wang PS et al. **Risk of Death** in Elderly Users of Conventional vs Atypical Antipsychotic Medications. N Engl J Med 2005;353:2335-41. Conclusion: If confirmed, these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should no be used to replace atypical agents discontinued in response to the FDA warning. (InfoPOEMs: It seems reasonable to conclude that conventional and atypical antipsychotic agents are both associated with an increased risk of death in elderly patients. The limitations of this study do not allow us to confidently conclude that older agents are less safe than newer agents, though. (LOE = 2b)) (Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N, Gurwitz JH, Rochon PA. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007 Jun 5;146(11):775-86. Atypical antipsychotic use is associated with an increased risk for death compared with nonuse among older adults with dementia. The risk for death may be greater with conventional antipsychotics than with atypical antipsychotics.)

Rochon PA, Normand SL, et al. Antipsychotic therapy and short-term **serious events** in older adults with dementia. Arch Intern Med. 2008 May 26;168(10):1090-6. Relative to those who received no antipsychotic therapy, community-dwelling older adults newly dispensed an atypical antipsychotic therapy were 3.2 times more likely (95% confidence interval, 2.77-3.68) and those who received conventional antipsychotic therapy were 3.8 times more likely (95% confidence interval, 3.31-4.39) to develop any serious event during the 30 days of follow-up. The pattern of serious events was similar but less pronounced among older adults living in a nursing home. Serious events, as indicated by a hospital admission or death, are frequent following the short-term use of antipsychotic drugs in older adults with dementia. Antipsychotic drugs should be used with caution even when short-term therapy is being prescribed.

FDA Conventional Antipsychotic Warning June/08 http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm

Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ. 2008 Aug 28;337:a1227. doi: 10.1136/bmj.a1227. **All antipsychotics are associated with an increased risk of stroke**, and the risk might be higher in patients receiving atypical antipsychotics than those receiving typical antipsychotics. People with dementia seem to be at a higher risk of an associated stroke than people without dementia & use of antipsychotics should, when possible, be avoided in these patients.

Ray WA, Chung CP, Murray KT et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. New Engl J Med 2009; 360: 225-235.

Clinical Handbook of Psychotropic Drugs 18th Edition, Bezchlibnyk-Butler K, Jeffries J. 2009
Drugs in Pregnancy & Lactation 9th edition 2011
Drug Information Handbook Lexi 17th edition 2008-2009
Therapeutic Choices 5th edition 2007
Geriatric Dosage Handbook 6th Edition
Pharmacotherapy Handbook 2nd edition (Wells,Dipiro et al.)
Micromedex 2008

TOP

SEDATIVE COMPARISON CHART

References:

Anthierens, Sibyl, Pasteels, Inge, Habraken, H, et al. Barriers to nonpharmacologic treatments for **stress, anxiety, and insomnia**: Family physicians' attitudes toward benzodiazepine prescribing. Can Fam Physician 2010 56: e398-406.

Archbold KH, Vasquez MM, Goodwin J et al. Effects of **Sleep Patterns** and Obesity on Increases in **Blood Pressure** in a 5-Year Period: Report from the Tucson Children's Assessment of Sleep Apnea Study. J Pediatr. 2012 Jan 25.

Aurora RN, Zak RS, Auerbach SH, et al. Standards of Practice Committee, American Academy of Sleep Medicine. Best practice guide for the treatment of **nightmare disorder in adults**. J Clin Sleep Med 2010 Aug 15;6(4):389-401. (prazosin, ? clonidine etc)

Aurora RN, Zak RS, Maganti RK, et al. Standards of Practice Committee, American Academy of Sleep Medicine. Best practice guide for the treatment of **REM sleep behavior disorder** (RBD). J Clin Sleep Med 2010 Feb15;6(1):85-95.

Baillargeon L, et al. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. CMAJ. 2003 Nov 11;169(10):1015-1020. (Benzodiazepines: How they work & how to withdraw "aka The Ashton Manual" protocol http://www.benzo.org.uk/manual/index.htm)

Barbera J, Shaprio C. Benefit-risk assessment of zaleplon in the treatment of insomnia. Drug Saf. 2005;28(4):301-18.

Beck CA, Williams JV, Wang JL, et al. **Psychotropic medication use in Canada**. Can J Psychiatry. 2005 Sep;50(10):605-13. RESULTS: Overall psychotropic drug utilization was 7.2%. Utilization was higher for women and with increasing age. With any lifetime CIDI-diagnosed disorder assessed in the CCHS 1.2, utilization was 19.3%, whereas without such disorders, it was 4.1%. Selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants for those with a past-year major depressive episode (17.8%), followed by venlafaxine (7.4%). Among people aged 15 to 19 years, antidepressant use was 1.8% overall and 11.7% among those with past-year depression; SSRIs made up the majority of use. **Sedative-hypnotics** were used by 3.1% overall, increasing with age to 11.1% over 75 years.

Bélanger L, **Mortality Hazard** Associated With Anxiolytic and Hypnotic Drug Use in the National Population Health Survey. Can J Psychiatry. 2010;55(9):558–567.

Benedict C et al. **Acute sleep deprivation** enhances the brain's response to hedonic food stimuli: An fMRI study. J Clin Endocrinol Metab 2012 Jan 18.

Bloom HG, Ahmed I, Alessi CA, et al. **Evidence-based recommendations for the assessment and management of sleep disorders in older persons.** J Am Geriatr Soc. 2009;57:761–89.

Bruni O, Novelli L. **Sleep disorders in children** [Internet]. BMJ Clinical Evidence. 10; 2009 [cited 2011 Mar 07]. Available from: http://clinicalevidence.bmj.com/ceweb/conditions/chd/2304/2304-get.pdf

Buscemi N, et al. Melatonin for treatment of sleep disorders. Evidence Report/Technology Assessment No. 108. AHRQ Publication No. 05-E002-1. Rockville MD: Agency for Healthcare Research and Quality. November 2004.

Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous **melatonin** for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ. 2006 Feb 18;332(7538):385-93. CONCLUSIONS: There is no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder. There is evidence that melatonin is safe with short term use.

Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for **chronic insomnia** in adults: a **meta-analysis of RCTs**. J Gen Intern Med [Internet]. 2007 Sep;22(9):1335-50.

Buysse Daniel J.; Germain Anne; Moul Douglas E.; et al. Efficacy of Brief **Behavioral Treatment** for Chronic Insomnia in Older Adults. Arch Intern Med. 2011;0(2011):archinternmed.2010.535.

CADTH: HTIS – Report Feb08: Safety of Zopiclone or Trazodone for insomnia in adults (upon request from htis@cadth.ca).

Carter PJ, Taylor BJ, Williams SM, Taylor RW. Longitudinal analysis of **sleep in relation to BMI and body fat in children**: the **FLAME** study. BMJ 2011;342:d2712.

CDC: Effect of **Short Sleep Duration on Daily Activities** --- Uni ted States, 2005—2008 Weekly March 4, 2011 / 60(08);239-242 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6008a3.htm?s_cid=mm6008a3_x

Calhoun DA, Harding SM. **Sleep and hypertension**. Chest. 2010 Aug;138(2):434-43.

Campos FL, et al. Melatonin improves sleep in asthma: a randomized, double-blind, placebo-controlled study. (Melatonin improves sleep quality in women with asthma, but not in a clinically meaningful way). (LOE = 2b) Am J Respir Crit Care Med 2004; 170:947-51.

Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I et al. Cardiovascular mortality in **women with obstructive sleep apnea** with or without continuous positive airway pressure treatment: a cohort study. Ann Intern Med. 2012 Jan 17;156(2):115-22.

Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. **Sleep duration predicts cardiovascular outcomes**: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011; online 7 February.

Carlsten A, et al. Are sedatives and hypnotics associated with increased **suicide risk** of suicide in the elderly? BMC Geriatr. 2009 Jun 4;9:20. Sedatives and hypnotics were both associated with increased risk for suicide after adjustment for appropriate indications

Carter MD, Juurlink DN. **Melatonin**. CMAJ. 2012 Apr 16.

Clinical Handbook of Psychotropic Drugs 18th edition 2009 (Bezchlibnyk-Butler,Jeffries)

Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D, Turner RB. Sleep habits and susceptibility to the **common cold**. Arch Intern Med. 2009 Jan 12;169(1):62-7.

Costa LR et al. Post-Discharge Adverse Events following Pediatric Sedation with High Doses of Oral Medication. J Pediatr. 2011 Nov 30. (chloral hydrate, midazolam)

Covinsky KE, Pierluissi E, Johnston CB. **Hospitalization-associated disability**: "she was probably able to ambulate, but I'm not sure." JAMA. 2011;306(16):1782-1793.

Drug Information Lexi Handbook 17th edition 2008-2009

Drugs in Pregnancy & Lactation 9th edition 2011

Earley CJ. Clinical practice. Restless legs syndrome. N Engl J Med. 2003 May 22;348(21):2103-9. Review.

Eddy M, Walbroehl GS. Insomnia. Am Fam Physician 1999;59:1911-1916.

Ensrud KE, et al. for the Study of Osteoporotic Fractures Research Group. Use of selective **serotonin reuptake inhibitors** and **sleep** disturbances in community-dwelling older women. J Am Geriatr Soc. 2006 Oct;54(10):1508-15.

Epstein LJ, Kristo D, Strollo PJ Jr, et al. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of **obstructive sleep apnea** in adults. J Clin Sleep Med 2009 Jun 15;5(3):263-76.

Eszopiclone (Lunesta) a New Hypnotic. Med Letter 2005;47:17-19.

Falloon Karen, Arroll Bruce, Elley C Raina, et al. The **assessment and management of insomnia in primary care**. BMJ 2011;342:doi:10.1136/bmj.d2899 (Published 27 May 2011)

Faruqui F, Khubchandani J, Price JH, Bolyard D, Reddy R. **Sleep Disorders in Children: A National Assessment of Primary Care Pediatrician Practices and Perceptions**. Pediatrics. 2011 Aug 28.

FDA Sedative warning Mar/07 The U.S. Food and Drug Administration (FDA) has requested that all manufacturers of sedative-hypnotic drug products, a class of drugs used to induce and/or maintain sleep, strengthen their product labeling to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving. Sleep driving is defined as driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event. http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html

Ferber SG, Als H, McAnulty G. **Melatonin** and Mental Capacities in Newborn Infants. J Pediatr 2011;159:99-103.

Fortinguerra, Filomena, Clavenna, Antonio, Bonati, Maurizio. Psychotropic Drug Use During **Breastfeeding**: A Review of the Evidence. Pediatrics 2009 124: e547-e556.

Fung MM, Peters K, Redline S, et al. for the Osteoporotic Fractures in Men Research Group. Decreased Slow Wave Sleep Increases **Risk of Developing Hypertension** in Elderly Men. Hypertension. 2011 Aug 29.

Garrison Michelle M., Liekweg Kimberly, Christakis DA. **Media Use** and Child Sleep: The Impact of Content, Timing, and Environment. Pediatrics 2011; peds.2010-3304; published June 27, 2011, doi:10.1542/peds.2010-3304.

Geriatric Dosage Handbook 7th Edition 2002

Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: **meta-analysis** of risks and benefits. BMJ. 2005 Nov 11; [Epub ahead of print] CONCLUSIONS: Improvements in sleep with sedative use are statistically

TOP

significant, but the magnitude of effect is small. The increased risk of adverse events is statistically significant and potentially clinically relevant in older people at risk of falls and cognitive impairment. In people over 60, the benefits of these drugs may not justify the increased risk, particularly if the patient has additional risk factors for cognitive or psychomotor adverse events.

Gregory AM, Van der Ende J, et al. Parent-reported sleep problems during development and self-reported anxiety/depression, attention problems, & aggressive **behavior later in life**. Arch Pediatr Adolesc Med. 2008 Apr;162(4):330-5.

Giannotti F, Cortesi F. An open-label study of controlled release melatonin in treatment of sleep disorders in children with autism. J Autism Dev Disord 2006;36:741-52

Handbook of Clinical Drug Data 10th edition 2002

Harris J et al. A randomized controlled trial of **intensive sleep retraining (ISR):** A brief conditioning treatment for chronic insomnia. Sleep 2012 Jan 1; 35:49.

Harsora P, Kessmann J. **Nonpharmacologic management** of chronic insomnia. Am Fam Physician. 2009 Jan 15;79(2):125-30.

Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well Dietary Supplement** because a sample analyzed by Health Canada has been found to contain **estazolam**,

Health Canada Dec/06 is advising consumers not to use a product called **Eden Herbal Formulations Sleep Ease Dietary Supplement**, because it was found to contain an undeclared drug estazolam http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_127_e.html

Health Canada April/07is advising consumers not to use a product called **Eden Herbal Formulations Serenity Pills II** because it contains the undeclared drug **estazolam**.

Health Canada Dec/11 **Sublinox** is the first formulation of **zolpidem** in Canada. Internationally, it has been reported in association with **complex sleep behaviours**.

Health Canada May/12 **[Chung Lien Kulin Brand] Anshen Bunai Pian.** Hong Kong Department of Health warned that this traditional Chinese health product, used for insomnia, contains excessive levels of the heavy metal mercury.

Herxheimer A, Petrie KJ. **Melatonin** for the prevention and treatment of jet lag. Cochrane Database Syst Rev. 2002;(2):CD001520.

Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000 Jan 25;162(2):225-33.

Holbrook AM. **Treating insomnia**. BMJ. 2004 Nov 20;329(7476):1198-9.

Holbrook AM, Crowther R, Lotter A, Cheng C, King D. The diagnosis and management of insomnia in clinical practice: a practical evidence-based approach. CMAJ. 2000 Jan 25;162(2):216-20.

Horne Rosemary S. C., Yang Joel S. C., Walter Lisa M., et al. **Elevated Blood Pressure During Sleep** and Wake in Children With Sleep-Disordered Breathing. Pediatrics 2011; 128:1 e85-e92; doi:10.1542/peds.2010-3431

Hypnotic Drugs, Medical Letter Aug7/2000

Johnson MW, Suess PE, Griffiths RR. **Ramelteon**: a novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psychiatry. 2006 Oct;63(10):1149-57.

Jones GM, Murphy CV, Gerlach AT, et al. High-Dose **Dexmedetomidine** for Sedation in the Intensive Care Unit: An Evaluation of Clinical Efficacy and Safety. 1 June 2011, DOI 10.1345/aph.1P726. Ann Pharmacother ;45:740-747.

Kain ZN, MacLaren JE, Herrmann L, et al. **Preoperative melatonin** and its effects on induction and emergence in children undergoing anesthesia and surgery. Anesthesiology. 2009 Jul;111(1):44-9. Midazolam is more effective than melatonin in reducing children's anxiety at induction of anesthesia. Melatonin showed a direct dose-dependent effect on emergence delirium.

Kandil TS, Mousa AA, El-Gendy AA, Abbas AM. The potential therapeutic effect of **melatonin** in **Gastro-Esophageal Reflux Disease**. BMC Gastroenterol. 2010 Jan 18;10:7.

King CR, Knutson KL, Rathouz PJ, Sidney S, Liu K, Lauderdale DS. Short sleep duration and incident **coronary artery** calcification. JAMA. 2008 Dec 24;300(24):2859-66. Longer measured sleep is associated with lower calcification incidence independent of examined potential mediators and confounders.

Knutson Kristen L.; Cauter Eve Van; et al. **Association Between Sleep and Blood Pressure in Midlife: The CARDIA Sleep Study.** *Arch Intern Med*. 2009;169(11):1055-1061.

Kolla BP, Auger RR**. Jet lag and shift work** sleep disorders: How to help reset the internal clock. Cleve Clin J Med. 2011 Oct;78(10):675-84.

Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S; for the Osteoporotic Fractures in Men (MrOS) Study Group. Association of Incident Cardiovascular Disease With **Periodic Limb Movements During Sleep** in Older Men: Outcomes of Sleep Disorders in Older Men (**MrOS**) Study. Circulation. 2011 Sep 13;124(11):1223-1231.

Kotagal S, Pianosi P. Sleep disorders in **children and adolescents**. BMJ. 2006 Apr 8;332(7545):828-32.

Kripke DF, Langer RD, Kline LE. Hypnotics' association with **mortality or cancer**: a matched cohort study. BMJ Open. 2012 Feb 27;2(1):e000850.

Kupfer DJ, Reynolds CF. Management of insomnia NEJM 1997;336:341-346.

Larson AM, Ryther RC, Jennesson M, et al. Impact of **pediatric epilepsy on sleep** patterns and behaviors in children and parents. Epilepsia. 2012 May 17.

Laugsand LE, Vatten LJ, Platou C, Janszky I. **Insomnia** and the **Risk of Acute Myocardial Infarction**: A Population Study. Circulation. 2011 Oct 24.

Leproult Rachel, Cauter Eve Van. Effect of 1 Week of **Sleep Restriction on Testosterone Levels** in Young Healthy Men. JAMA. 2011;305(21):2173-2174.doi:10.1001/jama.2011.710.

Lettieri CJ, Shah AA, Holley AB, et al. for the CPAP ASAP (**CPAP** Promotion and Prognosis—The Army Sleep Apnea Program) Trial. Effects of a Short Course of Eszopiclone on Continuous Positive Airway Pressure Adherence: A Randomized Trial. Ann Intern Med. 2009 Nov 17;151(10):696-702.

McLarnon ME, Monaghan TL, Stewart SH, Barrett SP. Drug **misuse and diversion** in adults prescribed anxiolytics and sedatives. Pharmacotherapy. 2011;31: 262-272.

Meltzer LJ, Mindell JA, Owens JA, Byars KC. Use of sleep medications in hospitalized **pediatric** patients. Pediatrics. 2007 Jun;119(6):1047-55. Approximately 3% to 6% of children are treated pharmacologically with a broad array of sleep medications in hospital settings. Prescription practices vary by hospital, medical service, child age, and diagnosis. The results from this study indicate that medications are being prescribed for sleep in hospitalized children, especially in children with psychiatric diagnoses.

Micromedex 2011

Mindell JA, et al. Pharmacologic management of insomnia in **children and adolescents**: consensus statement. Pediatrics. 2006 Jun;117(6):e1223-32.

Moncada LV. Management of **falls in older persons**: a prescription for prevention. Am Fam Physician. 2011 Dec 1;84(11):1267-76.

Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the clinical evaluation and treatment of **circadian rhythm sleep disorders**. An American Academy of Sleep Medicine report. Sleep. 2007 Nov 1;30(11):1445-59.

Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T, et al. Practice parameters for the **psychological and behavioral treatment of insomnia**: an update. An **American academy of sleep medicine** report. Sleep 2006;29:1415-9.

Morin CM, Colecchi C, Stone J, Sood R, Brink D. **Behavioral** and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA. 1999 Mar 17;281(11):991-9.

Morin CM, Vallières A, Guay B, et al. **Cognitive behavioral therapy**, singly and combined with medication, for persistent insomnia: a randomized controlled trial. JAMA. 2009 May 20;301(19):2005-15. In patients with persistent insomnia, the addition of medication to CBT produced added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT.

Morin CM, Bélanger L, LeBlanc M, Ivers H, Savard J, Espie CA, Mérette C, Baillargeon L, Grégoire JP. The **natural history of insomnia**: a population-based 3-year longitudinal study. Arch Intern Med. 2009 Mar 9;169(5):447-53.

Morin Charles M, Benca Ruth. **Chronic insomnia**. Lancet Online Jan 20, 2012. DOI:10.1016/S0140-6736(11)60750-2.

Nedeltcheva Arlet V, Kilkus Jennifer M., Imperial J, et al. Insufficient Sleep **Undermines Dietary Efforts to Reduce Adiposity**. Ann Intern Med October 5, 2010 153:435-441; doi:10.1059/0003-4819-153-7-201010050-00006.

Neubauer DN. **Sleep problems in the elderly**. Am Fam Physician. 1999 May 1;59(9):2551-8, 2559-60.

Neutel CI, Patten SB. Sleep medication use in **Canadian seniors**. Can J Clin Pharmacol. 2009 Fall;16(3):e443-52. Epub 2009 Nov 16.

NICE April 2004: Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. http://www.nice.org.uk/pdf/TA077fullguidance.pdf

Nixon, Gillian M, Thompson, John M D, Han, et al. **Falling asleep: the determinants of sleep latency.** Arch Dis Child 2009 0: adc.2009.157453

TOP

Nurok Michael, Czeisler Charles A., Lehmann Lisa Soleymani. **Sleep Deprivation, Elective Surgical Procedures**, and Informed Consent. N Engl J Med 2010; 363:2577-2579.
Patel D, Goldman-Levine JD. **Doxepin (silenor)** for insomnia. Am Fam Physician. 2011 Aug 15;84(4):453-4.
Pharmacotherapy Handbook 2nd edition (Wells,Dipiro et al.)
Ross KR et al. Sleep-Disordered Breathing is Associated with **Asthma Severity** in Children. J Pediatr. 2011 Nov 30.
Powell S, Kubba H, O'Brien C, Tremlett M. **Paediatric obstructive sleep apnoea**. BMJ. 2010 Apr 14;340:c1918. doi: 10.1136/bmj.c1918.
Punjabi NM, Caffo BS, Goodwin JL, et al. **Sleep-disordered breathing** and **mortality**: a prospective cohort study. PLoS Med 2009; 6:e1000132.
Quach J, Hiscock H, Ukoumunne OC, Wake M. A brief **sleep intervention** improves outcomes in the school entry year: a randomized controlled trial. Pediatrics. 2011 Oct;128(4):692-701.
Rajaratnam SM, Barger LK, Lockley SW, et al. Sleep disorders, health, and **safety in police officers**. JAMA. 2011;306(23):2567-2578.
Ramakrishnan K, Scheid DC. Treatment options for **insomnia**. Am Fam Physician. 2007 Aug 15;76(4):517-26.
Ramelteon (Rozerem) for Insomnia. The Medical Letter. Nov 7,2005. p 89-91. (see also Pharmacist's Letter Nov 2006)
Rondanelli M, Opizzi A, Monteferrario F, et al. The effect of **melatonin, magnesium, and zinc** on primary insomnia in long-term care facility residents in Italy: a double-blind, placebo-controlled clinical trial. J Am Geriatr Soc. 2011 Jan;59(1):82-90. doi: 10.1111/j.1532-5415.2010.03232.x.
Sabanayagam C; Shankar A. **Sleep duration** and **cardiovascular disease**: Results from the National Health Interview Survey. Sleep 2010; 33:1037-1042.
Sack, Robert L. **Jet Lag**. N Engl J Med 2010 362: 440-447.
Schapira AH. Restless legs syndrome: an update on treatment options. Drugs. 2004;64(2):149-58.
Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. **Clinical guideline** for the evaluation and management of **chronic insomnia** in adults. J Clin Sleep Med 2008 Oct 15;4(5):487-504.
Sharma SK et al. **CPAP** for the metabolic syndrome in patients with **obstructive sleep apnea**. N Engl J Med. 2011 Dec 15;365(24):2277-86.
Silber M. **Chronic Insomnia.** NEJM **2005**;353:803-10.
Sivertsen B, et al. **Cognitive behavioral therapy vs zopiclone** for treatment of chronic primary insomnia in older adults: a randomized controlled trial. JAMA. 2006 Jun 28;295(24):2851-8. These results suggest that interventions based on CBT are superior to zopiclone treatment both in short- and long-term management of insomnia in older adults. (InfoPOEMs: Cognitive behavioral therapy (CBT), consisting of one 50-minute session per week for 6 weeks, is significantly more effective than zopiclone (Imovane) in the treatment of chronic insomnia in older adults. It is uncertain whether less intensive counseling offered directly by primary care clinicians is similarly effective. (LOE = 1b))
Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, et al. Comparative meta-analysis of **pharmacotherapy and behavior therapy** for persistent insomnia. Am J Psychiatry 2002;159:5-11.
Song GH, Leng PH, et al. **Melatonin** improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances:a randomised, double blind, placebo controlled study. Gut. 2005 Oct;54(10):1402-7. Epub 2005 May 24.
Spruyt K, Molfese DL, Gozal D. **Sleep Duration, Sleep Regularity, Body Weight, and Metabolic** Homeostasis in School-aged Children. Pediatrics. 2011 Jan 24.
Stacey T, Thompson JMD, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LME. Association between maternal **sleep position and risk of late stillbirth**: a case-control study. *BMJ* 2011;342:d3403.
Stone KC, LaGasse LL, Lester BM, et al. **Sleep problems in children** with prenatal substance exposure (**nicotine**) : the Maternal Lifestyle study. Arch Pediatr Adolesc Med. 2010 May;164(5):452-6.
Strøm T, Martinussen T, Toft P. A protocol of **no sedation for critically ill patients** receiving mechanical ventilation: a randomised trial. Lancet. 2010 Feb 6;375(9713):475-80.
Substance Abuse and Mental Health Services Administration **SAMHSA**, Center for Behavioral Health Quality and Statistics. (Nov 3, 2011). The DAWN Report: **Drug-Related Emergency Department Visits Attributed to Intentional Poisoning**. Rockville, MD. http://oas.samhsa.gov/2k11/DAWN040/WEB_DAWN_040.htm
Tamblyn R, Abrahamowicz M, du Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. J Am Geriatr Soc. 2005 Feb;53(2):233-41. CONCLUSION: The risk of injury varied by benzodiazepine, independent of half-life, as did the risk associated with increasing dosage for individual products. Higher doses of oxazepam, flurazepam, and chlordiazepoxide are associated with the greatest risk of injury in the elderly.
TASK FORCE ON **SUDDEN INFANT DEATH SYNDROME. SIDS** and Other Sleep-Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment. Pediatrics. 2011 Oct 17.
Taveras EM, Rifas-Shiman SL, Oken E, Gunderson EP, Gillman MW. Short sleep duration in infancy and risk of **childhood overweight**. Arch Pediatr Adolesc Med. 2008 Apr;162(4):305-11. Daily sleep duration of less than 12 hours during infancy appears to be a risk factor for overweight and adiposity in preschool-aged children.
Thase, ME. Depression, Sleep, and Antidepressants. J Clin Psychiatry 1998;59(suppl 4):55-65.
The Search for Sleep, Pharmacy Practice Oct/2000 p45-51.
Therapeutic Choices 5th edition 2007
Treatments for Insomnia, Pharmacist's Letter. Sept. **2005**.
Treatment of Insomnia. Treatment Guidelines, Med Lett. **2006** Feb;4(42):5-10. Updated Mar 2009. **Updated July 2012.**
Touma C, Pannain S. Does lack of sleep **cause diabetes**? Cleve Clin J Med. 2011 Aug;78(8):549-58.
Venkateshiah SB, Collop NA. Sleep and **sleep disorders in the hospital**. Chest. 2012 May;141(5):1337-45.
Vinson, Daniel C., Manning, Brian K., Galliher, James M., et al. **Alcohol and Sleep Problems** in Primary Care Patients: A Report from the AAFP National Research Network. Ann Fam Med 2010 8: 484-492.
Wagner J, Wagner ML, Hening. Beyond Benzodiazepines: Alternative Pharmacologic Agents for the Treatment of Insomnia. Ann Pharmacother 1998;32:680-91.
Wei JL, Bond J, Mayo MS, et al. Improved behavior and sleep after **adenotonsillectomy** in children with sleep-disordered breathing: long-term follow-up. Arch Otolaryngol Head Neck Surg. 2009 Jul;135(7):642-6.
Wiegand MH. **Antidepressants** for the treatment of insomnia : a suitable approach? Drugs. 2008;68(17):2411-7. In general, drugs lacking strong cholinergic activity should be preferred. Drugs blocking serotonin 5-HT(2A) or 5-HT(2C) receptors should be preferred over those whose sedative property is caused by histamine receptor blockade only. The dose should be as low as possible (e.g. as an initial dose: doxepin 25 mg, mirtazapine 15 mg, trazodone 50 mg, trimipramine 25 mg).Regarding the lack of substantial data allowing for evidence-based recommendations, we are facing a clear need for well designed, long-term, comparative studies to further define the role of antidepressants versus other agents in the management of insomnia.
Wilson SJ, Nutt DJ, Alford C, et al. **British Association for Psychopharmacology consensus statement** on evidence-based treatment of **insomnia, parasomnias and circadian rhythm** disorders. J Psychopharmacol. 2010 Sep 2.
Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 2. **Management of sleep disorders in older people**. CMAJ. 2007 May 8;176(10):1449-54.
Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 1. Sleep disorders commonly found in older people. CMAJ. 2007 Apr 24;176(9):1299-304.
Woolcott John C.; Richardson Kathryn J.; Wiens Matthew O.; et al. Meta-analysis of the Impact of 9 Medication Classes on **Falls** in Elderly Persons. Arch Intern Med. 2009;169(21):1952-1960.
Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild **cognitive impairment** and dementia in older women. JAMA. 2011; 306(6):613-619.
Zammit G. Comparative tolerability of **newer agents for insomnia**. Drug Saf. 2009;32(9):735-48. doi: 10.2165/11312920-000000000-00000. PubMed PMID: 19670914.
Zolpidem (Ambien CR) For Insomnia. Med Letter Dec 2005;47:97-98.

TOP

Web Sites:
National Heart Lung and Blood Institute http://www.nhlbi.nih.gov/health/dci/Diseases/inso/inso_whatis.html
American Academy of Sleep Medicine www.sleepeducation.com

TOP

ASTHMA & COPD PHARMACOTHERAPY: Comparison Chart

[1] Global Initiative for Chronic Obstructive Lung Disease (**GOLD**). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); **2010**. http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf
Fabbri LM, Hurd SS; GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: **2009 update**. http://www.goldcopd.com
Rabe KF, Hurd S, Anzueto A, Barnes PJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: **GOLD** Executive Summary. Am J Respir Crit Care Med. 2007 Sep 15;176(6):532-55. Epub **2007** May 16.

[2] American Thoracic Society Guidelines 2004 http://www.thoracic.org/copd
Qaseem A, Wilt TJ, Weinberger SE, et al. American College of Physicians (**ACP**); American College of Chest Physicians (**ACCP**); American Thoracic Society (**ATS**); European Respiratory Society (**ERS**). Diagnosis and management of **stable chronic obstructive pulmonary disease**: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. **2011** Aug 2;155(3):179-91.

[3] Nice Guidelines 2004 http://www.nice.org.uk/pdf/CG012_niceguideline.pdf
NICE: National Institute for Health and Clinical Excellence. Chronic obstructive pulmonary disease (update). (Clinical guideline 101.) **2010**. http://guidance.nice.org.uk/CG101.

[4] Micromedex 2010; Drugs in Pregnancy and Lactation, 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Baltimore, MD: 2011.; Hansten & Horn-Drug Interactions 2008.

[5] Boulet LP et al. Canadian **Asthma Consensus Report 1999**. CMAJ 1999; 161 (11 Suppl) & Boulet LP, et al.. What is new since the last (1999) Canadian Asthma Consensus Guidelines? Can Respir J. **2001** Mar-Apr;8 Suppl A:5A-27A & Lemiere C, Bai T, Balter M, et al. **Adult Asthma Consensus Guidelines Update 2003**. Can Respir J. 2004 May-Jun;11(Suppl A):9A-18A & Becker A, et al.; Asthma Guidelines Working Group of the Canadian Network For Asthma Care. Summary of recommendations from the Canadian Asthma Consensus guidelines, 2003. CMAJ. **2005** Sep 13;173(6 Suppl):S3-11. http://www.pulsus.com/Respir/11_SA/supp_A.pdf (See also: The Global Initiative for Asthma (GINA) **2007 update** http://www.ginasthma.com)
Respiratory Review Panel. Respiratory (Asthma and COPD) Guidelines for Family Practice. Toronto: MUMS Guidelines Clearinghouse; **2007**.
National Asthma Education & Prevention Program (NAEPP) Expert Panel Report 3 available at www.nhlbi.nih.gov/guidelines/asthma **2007**.
Laugheed MD, Lemiere C, Dell S, Ducharme F, FitzGerald JM, Leigh R, et al. **Canadian Thoracic Society (CTS)** Asthma Management Continuum – **2010 Consensus** Summary for children six years of age and over , and adults. Can Respir J 2010;17:15-24.
Lougheed MD, Lemiere C, Ducharme FM, et al; Canadian Thoracic Society Asthma Clinical Assembly. **Canadian Thoracic Society 2012** guideline update: diagnosis and management of asthma in preschoolers, children and adults. Can Respir J 2012;19(2):127-64.

[6] Anon. **Drugs for Asthma**. The Medical Letter. March 6, 2000: Vol. 42: issue 1073. & **Dec 2008**.

[7] Walters EH, Walters J. Inhaled **short acting beta2-agonist** use in chronic asthma: regular versus as needed treatment (Cochrane Review). Cochrane Database Syst Rev. 2003;(2):CD001285.

[8] Simon RA. Clinical implications of combination therapy on the future of asthma management. Allergy Asthma Proc. 2003 Mar-Apr;24(2):91-3.

[9] Williams SG, Schmidt DK, Redd SC, Storms W; National Asthma Education and Prevention Program. Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program. MMWR Recomm Rep. 2003 Mar 28;52(RR-6):1-8.

[10] **Treatment Guidelines**: Drugs for **Asthma**. **The Medical Letter**: Vol 3 (Issue 33) May 2005 (previously October, 2002; (2) pp. 7-12). **Drugs for Asthma**. Dec 2008. **Feb 2012.**

[11] Sin DD, Man J, Sharpe H, Gan WQ, Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. JAMA. 2004 Jul 21;292(3):367-76.

[12] Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. Lancet. 2000 Apr 22;355(9213):1399-403. (Hubbard R, Tattersfield A, Smith C, West J, Smeeth L, Fletcher A. Use of inhaled corticosteroids and the risk of fracture. Chest. 2006 Oct;130(4):1082-8.)
Loke YK et al. **Risk of fractures** with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax 2011

[13] Health Canada Endorsed Important Safety Information on FLUTICASONE PROPIONATE (FLONASE/ FLOVENT/ ADVAIR) and RITONAVIR (NORVIR/KALETRA) Jan 22, 2004 & Bolland MJ, Bagg W, Thomas MG, et al. **Cushing's** syndrome due to interaction between inhaled corticosteroids (budesonide) and itraconazole. Ann Pharmacother. 2004 Jan;38(1):46-9.
Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med. 2008 May 3. [Epub ahead of print] The combination of ritonavir and fluticasone should be avoided. Budesonide, beclomethasone, triamcinolone and flunisolide appear to be safer options.

[14] Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA. 2003 Nov 5;290(17):2301-12.

[15] Calverley PM, Boonsawat W, Cseke Z, Zhong N, et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J. 2003 Dec;22(6):912-9.

[16] Health Canada Sep,2005 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/serevent_2_hpc-cps_e.pdf , Aug, 2003 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/serevent_hpc-cps_e.pdf; GlaxoSmithKline Clinical trial registry SLGA5011: http://ctr.gsk.co.uk/Summary/salmeterol/studylist.asp
SMART - the Salmeterol Multi-Center Asthma Research Trial n=26,355; Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006 Jan;129(1):15-26. Erratum in: Chest. 2006 May;129(5):1393.
(Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-Analysis (19 trials n=33,826): Effect of Long-Acting {beta}-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths (Smart Trial info: 13 in LABA vs 3 in placebo groups NNH=1300 over 28 weeks). Ann Intern Med. 2006 Jun 5; [Epub ahead of print] Editorial: The Arg/Arg genotype may be reason LABAs less effective in some esp. African Americans. Use good doses of ICS first & if a LABA unresponsive pt the use of anticholinergics may be helpful.)
Rodrigo GJ, Nannini LJ, Rodríguez-Roisin R. Safety of Long-Acting {beta}-Agonists in Stable COPD: A Systematic Review. Chest. 2008 May;133(5):1079-87. This review supports the beneficial effects of the use of LABAs in patients with stable moderate-to-severe COPD, and did not confirm previous data about an increased risk for respiratory deaths. Also, our analysis suggests the superiority of tiotropium over LABAs for the treatment of stable COPD patients.

[17] Calverley PM, Walker P. Chronic obstructive pulmonary disease. Lancet. 2003 Sep 27;362(9389):1053-61.

[18] O'Donnell DE., Aaron S, Bourbeau J. et al. **Canadian Thoracic Society** recommendations for management of chronic obstructive pulmonary disease - **2003**. Can Respir J. May/June 2003;10 (Suppl A): 11A-33A & State of the Art Compendium: CTSociety recommendations for the management of chronic obstructive pulmonary disease. Can Respir July/August **2004**; 11(Suppl B):7
(**Updated 2007** http://www.copdguidelines.ca/pdf/07CODP%20guidelines.pdf)

TOP

Respiratory Review Panel RRP. Respiratory (Asthma and COPD) Guidelines for Family Practice. Toronto: MUMS Guidelines Clearinghouse; **2007**. (Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. Ann Intern Med. 2007 Nov 6;147(9):639-53. Long-acting inhaled therapies, supplemental oxygen, and pulmonary rehabilitation are beneficial in adults who have bothersome respiratory symptoms, especially dyspnea, and FEV1 less than 60% predicted.)
Qaseem A, Snow V, Shekelle P, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2007 Nov 6;147(9):633-8.
O'Donnell DE, Hernandez P, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease- 2008 update -highlights for **primary care**. Can Respir J. 2008 Jan-Feb;15 Suppl A:1A-8A.
Marciniuk DD, Brooks D, Butcher S, et al. Canadian Thoracic Society COPD Committee Expert Working Group. Optimizing **pulmonary rehabilitation** in chronic obstructive pulmonary disease--practical issues: a Canadian Thoracic Society Clinical Practice Guideline. Can Respir J. 2010 Jul-Aug;17(4):159-68.
Marciniuk DD, Goodridge D, Hernandez P, et al; **Canadian Thoracic Society (CTS)** COPD Committee Dyspnea Expert Working Group. Managing **dyspnea** in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guide. Can Respir J 2011;18(2). http://www.respiratoryguidelines.ca/sites/all/files/2011_CTS_guideline_COPD_dyspnea.pdf
Qaseem A, Wilt TJ, Weinberger SE, et al. American College of Physicians (**ACP**); American College of Chest Physicians (**ACCP**); American Thoracic Society (**ATS**); European Respiratory Society (**ERS**). Diagnosis and management of **stable chronic obstructive pulmonary disease**: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. **2011** Aug 2;155(3):179-91.

[19] Sutherland ER, Cherniack RM. **Management** of chronic obstructive pulmonary disease. N Engl J Med. **2004** Jun 24;350(26):2689-97. (Rodrigo GJ, Nannini LJ. **Tiotropium** for the treatment of stable chronic obstructive pulmonary disease: A systematic review with meta-analysis. Pulm Pharmacol Ther. 2006 Mar 2; [Epub ahead of print])
Vogelmeier C, Hederer B, Glaab T, et al. **Tiotropium versus salmeterol** for the prevention of exacerbations of COPD. **POET-COPD**. N Engl J Med 2011;364:1093-103.

[20] Ducharme FM. Inhaled **glucocorticoids versus leukotriene** receptor antagonists as single agent asthma treatment: systematic review of current evidence. BMJ. 2003 Mar 22;326(7390):621.
[21] Ram F, Cates C, **Long-acting beta2-agonists vs anti-leukotrienes** as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD003137.
Castro-Rodriguez JA, Rodrigo GJ. The role of **inhaled corticosteroids and montelukast** in children with mild-moderate asthma: results of a systematic review with meta-analysis. Arch Dis Child. 2010 May;95(5):365-70.
[22] Bisgaard H, Zielen S, Garcia-Garcia ML, et al. **Montelukast** reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005; 171:315-22.
(In this manufacturer-sponsored study, montelukast reduced the annual frequency of exacerbations by 0.7 in children with mild intermittent asthma triggered by upper respiratory infections. Hospitalization rates were unaffected. One would need to treat 9 of these children for 1 year to prevent 1 exacerbation. (LOE = 2b-) InfoPOEMs)
[23] Silverman RA, Nowak RM, Korenblat PE, et al. **Zafirlukast** treatment for acute asthma. Chest 2004; 126:1480-89.
[24] Barr RG, Rowe BH, Camargo CA Jr. **Methylxanthines** for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. BMJ. 2003 Sep 20;327(7416):643.
[25] Ram FS, et al. Efficacy of **theophylline** in people with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Med. 2005 Feb;99(2):135-44.
VA/DoD Department of Veterans Affairs and Department of Defense. COPD Guideline 2007 . At www.healthquality.va.gov/Chronic_Obstructive_Pulmonary_Disease_COPD.asp on 27 Nov 2010.

Additional references:
Aalbers R et al. **Adjustable** maintenance dosing with budesonide/formoterol vs fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin. 2004;20(2):225-40.
Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'donnell D, McIvor A, Sharma S, Bishop G, Anthony J, Cowie R, Field S, Hirsch A, Hernandez P, Rivington R, Road J, Hoffstein V, Hodder R, Marciniuk D, McCormack D, Fox G, Cox G, Prins HB, Ford G, Bleskie D, Doucette S, Mayers I, Chapman K, Zamel N, Fitzgerald M. **Tiotropium in Combination** with Placebo, Salmeterol, or Fluticasone-Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease: A Randomized Trial. Ann Intern Med. 2007 Feb 19; [Epub ahead of print] Addition of fluticasone-salmeterol to tiotropium therapy did not statistically influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD. The addition of fluticasone-salmeterol (Advair) to a regimen that includes tiotropium (Spiriva) reduces hospitalizations and improves quality of life symptom scores, but does not decrease the frequency of chronic obstructive pulmonary disease (COPD) exacerbations. The addition of salmeterol (Serevent) to tiotropium has no effect on hospitalizations and no clinically significant effect on other quality of life measures. (LOE = 1b)
Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D; Canadian Respiratory Clinical Research Consortium. **Overdiagnosis of asthma** in obese and nonobese adults. CMAJ. 2008 Nov 18;179(11):1121-31.
Abramson MJ, Puy RM, Weiner JM. **Injection allergen immunotherapy** for asthma. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD001186. Immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity. One trial found that the size of the benefit is possibly comparable to inhaled steroids. The possibility of local or systemic adverse effects (such as anaphylaxis) must be considered.
Abramson MJ, Schattner RL, Sulaiman ND, et al. Do **spirometry** and regular follow-up improve health outcomes in general practice patients with asthma or COPD? A cluster randomized controlled trial. Med J Aust. 2010 Jul 19;193(2):104-9.
Adachi M, Taniguchi H, Tohda Y, et al. The Efficacy and Tolerability of **Intravenous Montelukast** in Acute Asthma Exacerbations in Japanese Patients. J Asthma. 2012 Jun 28.
Adams NP, Bestall JC, Jones PW, et al. Inhaled **fluticasone at different doses** for chronic asthma in adults and children. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003534.
Adams NP, Jones PW. The dose-response characteristics of inhaled corticosteroids when used to treat asthma: An **overview of Cochrane systematic reviews**. Respir Med. 2006 Aug;100(8):1297-306. Epub 2006 Jun 23. The key findings are that all inhaled corticosteroids demonstrate a dose-response relationship for efficacy measures, but most of the benefit in mild-to-moderate severity disease is gained in the low-to-moderate dose range of each drug. In this group, high doses of fluticasone lead to small improvements in measures of control at the expense of a steep increase in the incidence of oral side-effects. In patients with severe disease who are dependent on oral steroids, there may be appreciable benefit in reducing oral steroids from very high compared with high doses of fluticasone.
Adams NP, Bestall JC, Jones P, et al. Fluticasone at different doses for chronic asthma in adults and children. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD003534. We have not found evidence of a pronounced dose response in FEV1 with increasing doses of fluticasone. The number of studies contributing to our primary outcomes was low. At dose ratios of 1:2, there are statistically significant differences in favour of the higher dose in morning peak flow across the low dose range. The clinical impact of these differences is open to interpretation. Patients with moderate disease achieve similar levels of asthma control on medium doses of fluticasone (400 to 500 microg/day) as they do on high doses (800 to 1000 microg/day). More work in severe asthma would help to confirm that doses of FP above 500 microg/day confer greater benefit in this subgroup than doses of around 200 microg/day. In oral corticosteroid-dependent asthmatics, reductions in prednisolone requirement may be gained with FP 2000 microg/day.
Afonso AS, Verhamme KM, Stricker BH, et al. Inhaled anticholinergic drugs and risk of **acute urinary retention**. BJU Int. 2010 Sep 29. doi: 10.1111/j.1464-410X.2010.

TOP

Agrawal SK, Singh M, Mathew JL, Malhi P. Efficacy of an individualized written **home-management plan** in the control of moderate persistent asthma: A randomized, controlled trial. Acta Paediatr. 2005 Dec;94(12):1742-6.

Aggarwal P, et al. Comparison of nebulised **magnesium** sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. Emerg Med J. 2006 May;23(5):358-62.

Agarwal R, Aggarwal AN, Gupta D, Jindal SK. **Inhaled corticosteroids** vs. placebo for preventing COPD exacerbations:a systematic review and meta-regression of randomized controlled trials. Chest. 2009 Sep 25.

Ahmedzai S et al. Managing passengers with stable respiratory disease planning **air travel**: British Thoracic Society recommendations. Thorax 2011; 66: i1ei30

Akuete K, Oh SS, Thyne S, et al. Ethnic Variability in **Persistent Asthma After In Utero Tobacco Exposure**. Pediatrics. 2011 Aug 22.

Alair Bronchial Thermoplasty System is a catheter-based device that delivers radiofrequency energy to the airways through the nose or mouth. The energy warms the airway linings and prevents the muscle from contracting. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm209909.htm

Albert RK, Connett J, Bailey WC, et al. **Azithromycin** for prevention of exacerbations of COPD. N Engl J Med 2011;365: 689-98.

Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of **anti-pneumococcal vaccination** in patients with COPD. Thorax. 2005 Oct 14; [Epub ahead of print]

Alía I, de la Cal MA, Esteban A, et al. Efficacy of **corticosteroid therapy** in patients with an acute exacerbation of **chronic obstructive pulmonary disease** receiving **ventilatory support**. Arch Intern Med. 2011;171(21):1939-1946.

Alvaro RE et al. CO(2) Inhalation as a Treatment for **Apnea of Prematurity**: A Randomized Double-Blind Controlled Trial. (**theophylline**) J Pediatr. 2011 Sep 8.

American Lung Association Asthma Clinical Research Centers; Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, Wise RA. Randomized comparison of strategies for **reducing treatment in mild persistent** asthma. N Engl J Med. 2007 May 17;356(20):2027-39. We randomly assigned 500 patients that was well controlled by inhaled fluticasone (100 microg twice daily) to receive continued fluticasone (100 microg twice daily) (169 patients), montelukast (5 or 10 mg each night) (166 patients), or fluticasone (100 microg) plus salmeterol (50 microg) each night (165 patients) for 16 weeks. Patients with asthma that is well controlled with the use of twice-daily inhaled fluticasone can be switched to once-daily fluticasone plus salmeterol without increased rates of treatment failure. A switch to montelukast results in an increased rate of treatment failure and decreased asthma control; however, patients taking montelukast remained free of symptoms on 78.7% of treatment days. . InfoPoems (At first glance the results seem to favor fluticasone plus salmeterol over montelukast for step-down therapy in patients with mild persistent asthma. However, a closer at look at the benefit of the former (based largely on disease-oriented end points) and its potential harms (more respiratory infections) makes montelukast look like an excellent alternative, particularly given the concerns regarding long-term use of long-acting beta-agonists and corticosteroids. (LOE = 1b))

American Lung Association Asthma Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. Am J Respir Crit Care Med. 2007 Feb 1;175(3):235-42. Epub 2006 Sep 22. Neither montelukast nor low-dose theophylline lowered the EPAC rate of poor asthma control in patients with poorly controlled asthma despite improved lung function. For patients not using inhaled corticosteroids, low-dose theophylline improved asthma symptom control more than montelukast or placebo, and provides a safe and low-cost alternative asthma treatment.

Anderson HR, Ayres JG, Sturdy PM, et al. Bronchodilator treatment and **deaths** from asthma: case-control study. BMJ. 2005 Jan 15;330(7483):117. Epub 2004 Dec 23.

Anthonisen NR, et al.; Lung Health Study Research Group. The effects of a **smoking cessation** intervention on 14.5-year **mortality**: a randomized clinical trial. Ann Intern Med. 2005 Feb 15;142(4):233-9.

Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. **Antibiotic therapy in exacerbation** of chronic obstructive pulmonary disease. Ann Intern Med 1987;106(2):196-204.

Appleton S, et al. **Long-acting beta2**-agonists for poorly reversible chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006 Jul 19;3:CD001104.

Arrington-Sanders R, et al. **Ritonavir-fluticasone** interaction causing Cushing syndrome in HIV-infected children and adolescents. Pediatr Infect Dis J. 2006 Nov;25(11):1044-8.

Austin MA et al. Effect of high flow **oxygen on mortality in chronic obstructive pulmonary disease** patients in prehospital setting: Randomised controlled trial. BMJ 2010 Oct 18; 341:c5462.

Bacharier LB, et al. Long-term effect of budesonide on **hypothalamic-pituitary-adrenal axis** function in children with mild to moderate asthma. Pediatrics.2004 Jun;113(6):1693-9.

Bafadhel M, Clark TW, Reid C, et al. **Procalcitonin and C-reactive protein** in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. Chest. 2011 Jun;139(6):1410-8.

Bakkeheim E, Mowinckel P, Carlsen KH, Håland G, Carlsen KC. Paracetamol (**acetaminophen**) in early infancy: the risk of childhood allergy and asthma. Acta Paediatr. 2011 Jan;100(1):90-6. doi: 10.1111/j.1651-2227.2010.01942.x.

Balter, Meyer S, Bell, Alan D, Kaplan, Alan G, Kim, Harold, McIvor, Andrew. **Management of asthma in adults**. CMAJ 2009 0: cmaj.080007

Barr RG, Bourbeau J, Camargo CA, Ram FS. **Tiotropium** for stable chronic obstructive pulmonary disease: A meta-analysis. Thorax. 2006 Oct;61(10):854-62. Epub 2006 Jul 14. Tiotropium reduced COPD exacerbations and related hospitalisations, improved quality of life and symptoms, and may have slowed the decline in FEV1. Long term trials are warranted to evaluate the effects of tiotropium on decline in FEV1 and to clarify its role compared with LABA.

Barr RG, et al. Inhaled **tiotropium** for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD002876 & *ACP* Journal club. AUTHORS' CONCLUSIONS: Tiotropium reduced COPD exacerbations and related hospitalisations compared to placebo and ipratropium. It also improved health-related quality-of-life and symptom scores among patients with moderate and severe disease, and may have slowed decline in FEV1. Additional long-term studies are required to evaluate its effect on mortality and change in FEV1 to clarify its role in comparison to, or in combination with, long-acting ss2-agonists and to assess its effectiveness in mild and very severe COPD. (Barr RG, Bourbeau J, Camargo Jr CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. Thorax. 2006 Jul 14; [Epub ahead of print])

Barr, R. Graham, Bluemke, David A., Ahmed, Firas S., et al. Percent Emphysema, Airflow Obstruction, and Impaired **Left Ventricular Filling**. N Engl J Med 2010 362: 217-227.

Bateman ED, Boushey HA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL Study(GOAL salmeterol/fluticasone vs fluticasone).Am J Respir Crit Care Med 2004;170:836-44.

Bateman ED, et al. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006 Mar;117(3):563-70. CONCLUSION: In pts achieving asthma control with FSC 250/50 microg twice daily, stepping treatment down to a lower dose of **FSC 100/50 microg twice** daily is more effective than switching to an inhaled corticosteroid alone.

Bavbek S, et al. Safety of **Meloxicam** in Aspirin-Hypersensitive Patients with Asthma and/or Nasal Polyps. A Challenge-Proven Study. Int Arch Allergy Immunol. 2006 Oct 2;142(1):64-69 [Epub ahead of print]

Beach J, Russell K, Blitz S, Hooton N, Spooner C, Lemiere C, Tarlo SM, Rowe BH. A systematic review of the diagnosis of **occupational asthma**. Chest. 2007 Feb;131(2

Beasley RW, Clayton TO, Crane J, Lai CK, Montefort SR, von Mutius E, Stewart AW; the ISAAC Phase Three Study Group. **Acetaminophen** Use and Risk of Asthma,

TOP

Rhinoconjunctivitis and Eczema in Adolescents: ISAAC Phase Three. Am J Respir Crit Care Med. 2010 Aug 13.
Belanger K et al. Effect of **pregnancy on maternal asthma symptoms** and medication use. *Obstet Gynecol* 2010 Mar; 115:559.
Bergen R, Black S, et al. Safety of cold-adapted live attenuated **influenza vaccine** in a large cohort of children & adolescents. Pediatr Infect Dis J. 2004 Feb;23(2):138-44.
Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of **tumor necrosis factor alpha** in refractory asthma. N Engl J Med. 2006 Feb 16;354(7):697-708.
Beta$_2$-agonists **Drug Class Review Nov/06** Oregon Health & Science University. http://www.ohsu.edu/drugeffectiveness/reports/documents/Beta%20Agonists%20Final%20Report.pdf
Birnbaum S. **Pulmonary rehabilitation**: a classic tune with a new beat, but is anyone listening? Chest. 2011 Jun;139(6):1498-502.
Bischoff EW, Hamd DH, Sedeno M, Benedetti A, Schermer TR, Bernard S, et al. Effects of written **action plan** adherence on **COPD** exacerbation recovery. Thorax 2011;66:26-31.
Bisgaard H, et al. Twelve-month safety and efficacy of inhaled fluticasone propionate in **children aged 1 to 3** years with recurrent wheezing. Pediatrics. 2004 Feb;113(2):e87-94.
Bisgaard H, et al. **Intermittent** inhaled corticosteroids in **infants** with episodic **wheezing**. N Engl J Med. 2006 May 11;354(19):1998-2005. Intermittent inhaled corticosteroid therapy had no effect on the progression from episodic to persistent wheezing and no short-term benefit during episodes of wheezing in the first three years of life. (budesonide 400ug/d)
Blais L, et al. Use of inhaled corticosteroids during the first trimester of **pregnancy** and the risk of congenital malformations among asthmatic women. Thorax. 2006 Nov 22.
Blais L, Beauchesne MF, Lemière C, Elftouh N. **High doses** of inhaled corticosteroids during the **first trimester of pregnancy** and congenital malformations. J Allergy Clin Immunol. 2009 Dec;124(6):1229-1234.e4.
Boulet LP, Bateman ED, Voves R, Muller T, Wolf S, Engelstatter R. A randomized study comparing **ciclesonide 320ug od and fluticasone** propionate 200ug bid in patients with moderate persistent asthma. Respir Med. 2007 Apr 18; [Epub ahead of print] 12 week n=474. There were no cases of oral candidiasis in patients receiving ciclesonide and nine cases (3.8%) in those receiving fluticasone propionate (p=0.002; one-sided). CONCLUSIONS: Treatment with once-daily ciclesonide and twice-daily fluticasone propionate resulted in similar improvements in lung function in patients with moderate persistent asthma. Ciclesonide showed significant improvements in oral candidiasis and HRQoL over fluticasone.
Bourbeau J, Julien M, Maltais F, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease (**COPD**): a disease-specific **self-management** intervention. Arch Intern Med 2003;163:585-91
Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, Carlsheimer A. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007 Sep 28; [Epub ahead of print] In the treatment of uncontrolled asthma, budesonide/formoterol maintenance and reliever therapy reduces the incidence of severe asthma exacerbations and hospitalisation/ER treatment with similar daily symptom control compared with sustained high-dose salmeterol/fluticasone plus SABA. This benefit is achieved with substantially less ICS exposure.
Boushey HA, Sorkness CA, King TS, et al, for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. **Daily versus as-needed corticosteroids** for mild persistent asthma. N Engl J Med 2005; 352: 1519-528 & ACP Journal Club. (InfoPOEMs: Intermittent therapy, as measured by the outcomes that matter, is as effective as continuous therapy with oral zafirlukast or inhaled budesonide for patients with very mild but persistent asthma. Note that patients had a clear plan of action for when symptoms flared up: Begin inhaled budesonide in the "yellow zone," when symptoms initially worsen, and add prednisone 0.5 mg/kg if symptoms enter the "red zone," when breathlessness is present at rest or with activities of daily living. (LOE = 1b))
Brode SK, Ling SC, Chapman KR**. Alpha-1 antitrypsin deficiency**: a commonly verlooked cause of lung disease. CMAJ. 2012 Jul 3.
Broekhuizen, Berna D. L., Sachs, Alfred P. E., Moons, Karel G. M., et al. **Diagnostic Value of Oral Prednisolone Test** for Chronic Obstructive Pulmonary Disorders. Ann Fam Med 2011 9: 104-109.
Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. **Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines**: 2010 revision. J Allergy Clin Immunol. 2010 Sep;126(3):466-76. ARIA- Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 revision. Geneva: World Health Organization (WHO); 2010 Dec 23. http://whiar.org/docs/ARIAReport_2010.pdf
Bruzzese JM, Sheares BJ, Vincent EJ, et al. Effects of a **School-based Intervention** for Urban Adolescents with Asthma: A Controlled Trial. Am J Respir Crit Care Med. 2010 Dec 7.
Bucknall CE, Miller G, Lloyd SM, et al. Glasgow supported **self-management** trial (**GSuST**) for patients with moderate to severe **COPD**: randomised controlled trial. BMJ 2012;344:e1060.
Bueving HJ, et al. Influenza **vaccination** in children with asthma: randomized double-blind placebo-controlled trial. Am J Respir Crit Care Med. 2004 Feb 15;169(4):488-93. Epub 2003 Dec 04.)
Buhl R, et al. Comparable efficacy of **ciclesonide** once daily versus fluticasone propionate twice daily in asthma. Pulm Pharmacol Ther. 2006;19(6):404-12. Epub 2005 Nov 28.
Burchett DK, Darko W, Zahra J, et al. Mixing and compatibility guide for commonly used aerosolized medications. Am J Health-Syst Pharm. 2010;67:227-30.
Bush A, Saglani S. Management of **severe asthma in children**. Lancet. 2010 Sep 4;376(9743):814-25.
Busse, W.W., Managing Asthma During **Pregnancy**: **NAEPP** Recommendations for Pharmacologic Treatment--Update **2004** http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm
Busse WW, Lemanske RF Jr, Gern JE. Role of **viral respiratory infections in asthma and asthma exacerbations**. Lancet. 2010 Sep 4;376(9743):826-34.
Busse William W., Morgan Wayne J., Gergen Peter J., et al. Randomized Trial of **Omalizumab (Anti-IgE) for Asthma in Inner-City Children**. **(ICATA)** N Engl J Med 2011; 364:1005-1015.
Butz AM, et al. Effectiveness of nebulizer use-targeted asthma education on underserved children with asthma. Arch Pediatr Adolesc Med. 2006 Jun;160(6):622-8. A nebulizer education intervention had no effect on asthma severity or health care use.
Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; **TORCH investigators**. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007 Feb 22;356(8):775-89. n=6112 The reduction in death from all causes among patients with COPD in the combination-therapy group did not reach the predetermined level of statistical significance. There were significant benefits in all other outcomes among these patients. The international, industry-supported TORCH trial, researchers randomized more than 6000 COPD patients to receive either inhaled salmeterol & fluticasone propionate 500/50ug, each drug alone, or placebo. At 3 years, rates of all-cause mortality (the primary outcome) were 12.6% with combination therapy, 13.5% with salmeterol, 16.0% with fluticasone, and 15.2% with placebo. The mortality difference between the combination-therapy and placebo groups fell just short of statistical significance (P=0.052). However, combination therapy was associated with significant improvements in health status, lung function, and the frequency of COPD exacerbations. Patients taking fluticasone, alone or in combination, had an increased rate of pneumonia (Advair 19.6%, Flovent 18.3%, Serevent 13.3%, Placebo 12.3%). (see also Pharmacist's Letter Apr/07) Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins C, Jones PW, Vestbo J, Knobil K, Yates JC, Calverley PM. Effect of Pharmacotherapy on Rate of Decline of Lung Function in COPD: Results from the TORCH Study. Am J Respir Crit Care Med. 2008 May 29. [Epub ahead of print] Pharmacotherapy with salmeterol plus fluticasone propionate, or the components, reduces the rate of decline of FEV1 in patients with moderate-to severe COPD, thus slowing disease progression. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, Vestbo J, Knobil K, Yates JC, Calverley PM. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008 Aug 15;178(4):332-8. Epub 2008 May 29. Rates of decline were similar among the active treatment arms. Pharmacotherapy with salmeterol plus fluticasone propionate, or the components, reduces the rate of decline of FEV(1) in patients with moderate-to-severe COPD, thus slowing disease progression.
Calverley PM, Rabe KF, Goehring UM, et al.; M2-124 and M2-125 study groups. **Roflumilast** in symptomatic chronic obstructive pulmonary disease: two randomised cli

TOP

Lancet. 2009 Aug 29;374(9691):685-94.
Calverley PM, Stockley RA, Seemungal TA, et al; on behalf of the Investigating New Standards for Prophylaxis in Reduction of Exacerbations (**INSPIRE**) Investigators. Reported **Pneumonia** in Patients With COPD: Findings From the INSPIRE Study. Chest. 2011 Mar;139(3):505-512.
Casaburi R, ZuWallack R. **Pulmonary rehabilitation** for management of chronic obstructive pulmonary disease. N Engl J Med. 2009 Mar 26;360(13):1329-35.
Castro M, Rubin AS, Laviolette M, et al. AIR2 Trial Study Group. Effectiveness and safety of **bronchial thermoplasty** in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010 Jan 15;181(2):116-24. Epub 2009 Oct 8. PubMed PMID: 19815809.
Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through **metered-dose inhaler with valved holding chamber** versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. J Pediatr. 2004 Aug;145(2):172-7.
Castro-Rodriguez JA, Rodrigo GJ. Efficacy of **inhaled corticosteroids in infants and preschoolers** with recurrent wheezing and asthma: a systematic review with meta-analysis. Pediatrics. 2009 Mar;123(3):e519-25. Infants and preschoolers with recurrent wheezing or asthma had less wheezing/asthma exacerbations and improve their symptoms and lung function during treatment with inhaled corticosteroids.
Castro-Rodriguez JA, Rodrigo GJ. The role of inhaled **corticosteroids and montelukast** in children with mild-moderate asthma: results of a systematic review with meta-analysis. Arch Dis Child. 2010 May;95(5):365-70. Epub 2009 Nov 27.
Cates CJ, et al. **Vaccines** for preventing influenza in people with asthma. Cochrane Database Syst Rev. 2004;(2):CD000364. Update of: Cochrane Database Syst Rev. 2000;(4):CD000364.
Cates CJ, Crilly JA, Rowe BH. Holding **chambers (spacers) versus nebulisers** for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD000052.
Cates CJ, Cates MJ, Lasserson TJ. Regular treatment with **formoterol** for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD006923.
Cates CJ, Lasserson TJ. Combination **formoterol and inhaled steroid** versus beta(2)-agonist as relief medication for chronic asthma in adults and children. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD007085. In mild asthma it is not yet known whether patients who use a budesonide/formoterol inhaler for relief of asthma symptoms derive any clinically important benefits. In more severe asthma, one study that enrolled patients who were not controlled on quite high doses of inhaled corticosteroids, and had suffered an exacerbation in the previous year, demonstrated a reduction in the risk of exacerbations that require oral corticosteroids with budesonide/formoterol for maintenance and relief in comparison with budesonide/formoterol for maintenance and terbutaline or formoterol for relief. The incidence of serious adverse events in children was also less using budesonide/formoterol for maintenance and relief in one study, which similarly enrolled children who were not controlled on medium to high doses of inhaled corticosteroids, and compared to terbutaline relief with an explorative maintenance dose of budesonide/formoterol that is not approved for treatment.
Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with **formoterol** and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006924. It is not possible, from the data in this review, to reassure people with asthma that inhaled corticosteroids with regular formoterol carries no risk of increasing mortality in comparison to inhaled corticosteroids alone as all four deaths occurred among 6,594 people using inhaled corticosteroids with formoterol. On the other hand, we have found no conclusive evidence of harm and there was only one asthma related death registered during over 3,000 patient year observation on formoterol.
Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with **salmeterol and inhaled steroids** for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006922. No significant differences have been found in fatal or non-fatal serious adverse events in trials in which regular salmeterol has been randomly allocated with inhaled corticosteroids, in comparison to inhaled corticosteroids at the same dose.
Cates CJ, Lasserson TJ. Regular treatment with **formoterol versus** regular treatment with **salmeterol** for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007695.
Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with **salmeterol and inhaled steroids** for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006922.
Cates CJ, Lasserson TJ. Combination **formoterol and budesonide as maintenance and reliever** therapy versus inhaled steroid maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD007313.
Cates CJ, Lasserson TJ. Regular treatment with **formoterol** and an inhaled corticosteroid versus regular treatment with **salmeterol** and an inhaled corticosteroid for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007694.
Cattarelli D, et al. A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed. 2006 Mar;91(2):F80-4. Epub 2005 Oct 4.
Cazzola M, Matera MG. **Beta-blockers** are safe in patients with chronic obstructive pulmonary disease, but only with caution. Am J Respir Crit Care Med. 2008 Oct 1;178(7):661-2.
Celli B, Decramer M, Leimer I, et al. Cardiovascular Safety of **Tiotropium** in Patients With COPD. Chest. 2009 Jul 10. [Epub ahead of print] Tiotropium was associated with a reduction in the risk of all-cause mortality, cardiovascular mortality and cardiovascular events.
Celli B, Decramer M, Kesten S, et al. **Mortality** in the 4-year trial of tiotropium (**UPLIFT**) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Nov 15;180(10):948-55. Epub 2009 Sep 3.
Chan Walter W.; Chiou Eric; Obstein Keith L.; et al. The Efficacy of **Proton Pump Inhibitors** for the **Treatment of Asthma** in Adults: A Meta-analysis. *Arch Intern Med*. 2011;171(7):620-629.
Chandra A, Shim C, Cohen HW, et al. Regular vs **ad-lib albuterol** for patients hospitalized with acute asthma. Chest. 2005 Sep;128(3):1115-20. CONCLUSIONS: In the management of asthma exacerbation, ad-lib administration of albuterol is therapeutically as effective as regular, scheduled administration. This method of drug administration also reduces the total dose of beta-agonists received by the hospitalized patient.
Chandra D, Stamm JA, Taylor B, et al. Outcomes of **non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease** in the United States, 1998–2008. Am J Respir Crit Care Med 2012;185:152–159
Chandratilleke MG, Carson KV, Picot J,et al. **Physical training for asthma**. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD001116. DOI: 10.1002/14651858.CD001116.pub3. This review demonstrated that physical training can improve cardiopulmonary fitness and was well tolerated among people with asthma in the included studies. As such, people with stable asthma should be encouraged to partake in regular exercise training, without fear of symptom exacerbation.
Chang A, Halstead R, Petsky H. **Methylxanthines** for prolonged non-specific cough in children. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005310.
Chang AB, Clark R, Sloots TP, Stone DG, Petsky HL, Thearle D, Champion AA, Wheeler C, Acworth JP. A **5- versus 3-day course of oral corticosteroids** for children with asthma exacerbations who are not hospitalised: a randomised controlled trial. Med J Aust. 2008 Sep 15;189(6):306-10. A 5-day course of oral prednisolone confers no advantage over a 3-day course for children with asthma exacerbations who are not hospitalised.
Chapman, Kenneth R, McIvor, Andrew. **Asthma that is unresponsive** to usual care. CMAJ 2009 0: cmaj.090089.
Chapman KR, Rennard SI, Dogra A, et al; on behalf of the **INDORSE** Study Investigators. Long-term Safety and Efficacy of **Indacaterol**, a Long-Acting {beta}2-Agonist, in Subjects With COPD: A Randomized, Placebo-Controlled Study. Chest. 2011 Jul;140(1):68-75 (52 weeks)
Chaudhuri R, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. Am J Respir Crit Care Med. 2006 Jul 15;174(2):127-33. Epub 2006 Apr 27.
Chauhan BF, Ducharme FM. **Anti-leukotriene agents** compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Databas

TOP

2012 May 16;5:CD002314. As monotherapy, inhaled corticosteroids display superior efficacy to anti-leukotrienes in adults and children with persistent asthma; the superiority is particularly marked in patients with moderate airway obstruction. On the basis of efficacy, the results support the current guidelines` recommendation that inhaled corticosteroids remain the preferred monotherapy.

Checkley, William, West, Keith P., Jr., Wise, Robert A., et al. Maternal **Vitamin A Supplementation and Lung Function** in Offspring. N Engl J Med 2010 362: 1784-1794.

Chen YZ, et al. Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: the Steroid Treatment As Regular Therapy in early asthma (START) trial. Pediatr Allergy Immunol. 2006 May;17 Suppl 17:7-13.

Chen D, Restrepo MI, Fine MJ, et al. Observational study of **inhaled corticosteroids** on outcomes for COPD patients with **pneumonia**. Am J Respir Crit Care Med. 2011 Aug 1;184(3):312-6. For

Chipps B, Zeiger RS, Murphy K, et al. Longitudinal validation of the **test for respiratory and asthma control in kids** in pediatric practices (**TRACK**) . Pediatrics. 2011 Mar;127(3):e737-47.

Chong J, Poole P, Leung B, Black PN. **Phosphodiesterase 4 inhibitors** for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002309. DOI: 10.1002/14651858.CD002309.pub3. In people with COPD, PDE4 inhibitors offered benefit over placebo in improving lung function and reducing likelihood of exacerbations, however, they had little impact on quality of life or symptoms. Gastrointestinal adverse effects and weight loss were common.

Chowdhury BA, Seymour SM, Michele TM, Durmowicz AG, Liu D, Rosebraugh CJ. The risks and benefits of **indacaterol**- the FDA's review. N Engl J Med. 2011 Dec 15;365(24):2247-9.

Ciclesonide Alvesco: New drug. Pharmacist's Letter Nov 2006.

Clearie KL, McKinlay L, Williamson PAet al. **Fluticasone/salmeterol** combination confers benefi ts in people with asthma who **smoke**. Chest. 2012;141 (2): 330 -338.

Comet R, et al. Benefits of low weekly doses of **methotrexate** in steroid-dependent asthmatic patients. A double-blind, randomized, placebo-controlled study. Respir Med. 2005 Aug 12

Cooper CB, Tashkin DP. Recent developments in inhaled therapy in stable chronic obstructive pulmonary disease. BMJ. 2005 Mar 19;330(7492):640-4.

Corren J, Lemanske RF, Hanania NA, et al. **Lebrikizumab** Treatment in Adults with Asthma. N Engl J Med. 2011 Aug 3.

Covelli H, et al. Absence of electrocardiographic findings and improved function with once-daily **tiotropium** in patients with COPD. Pharmacotherapy. 2005 Winter;25(12):1708-18.

Cox G, Thomson NC, Rubin AS, et al. AIR Trial Study Group. Asthma control during the year after bronchial **thermoplasty**. N Engl J Med. 2007 Mar 29;356(13):1327-37.

Cross Keith P, Paul Ronald I, Goldman Ran D.. **Single-dose dexamethasone** for mild-to-moderate asthma exacerbations: Effective, easy, and acceptableCan Fam Physician October 2011 57: 1134-1136

Crump, Casey, Winkleby, Marilyn A., Sundquist, Jan, et al. Risk of Asthma in Young Adults Who Were **Born Preterm:** A Swedish National Cohort Study**.** Pediatrics 2011 0: peds.2010-2603

Currie GP, Wedzicha JA. ABC of **chronic obstructive** pulmonary disease. **Acute exacerbations**. BMJ. 2006 Jul 8;333(7558):87-9.

Currie GP, Lee DK, Lipworth BJ. ABC of **chronic obstructive** pulmonary disease. Pharmacological management—**oral** treatment. BMJ. 2006 Jun 24;332(7556):1497-9.

Currie GP, Lipworth BJ. ABC of **chronic obstructive** pulmonary disease Pharmacological management--**inhaled treatment**. BMJ. 2006 Jun 17;332(7555):1439-41.

Currie GP, Douglas JG, Heaney LG. **Difficult to treat asthma** in adults. BMJ. 2009 Feb 24;338:b494. doi: 10.1136/bmj.b494.

D'Urzo AD, Tamari I, Bouchard J, Jhirad R, Jugovic P. A new **spirometry** interpretation **algorithm**. Primary Care Respiratory Alliance of Canada approach. Can Fam Physician 2011;57:1148-52.

D'Urzo AD, Tamari I, Bouchard J, Jhirad R, Jugovic P. Limitations to a **spirometry interpretation algorithm**. Can Fam Physician 2011;57:1153-6.

Dahl R, et al. EXCEL: A randomised trial comparing **salmeterol/fluticasone** propionate and formoterol/budesonide combinations in adults with persistent asthma. Respir Med. 2006 May 2; [Epub ahead of print] Twice-daily treatment with SFC and FBC over 6 months significantly improved asthma symptoms and lung function in patients with persistent asthma. The rate of exacerbations was significantly reduced over time on both treatments but SFC was found to be significantly superior to FBC in reducing the rate of moderate/severe exacerbations with sustained treatment.

Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled beta2- agonist **indacaterol** versus twice-daily formoterol in COPD. Thorax 2010;65:473-9.

Dalhousie Academic Detailing Service Resources: Update on COPD. http://cme.medicine.dal.ca/files/COPD.pdf ; Summary http://cme.medicine.dal.ca/files/COPD%20Summary.pdf

Daniels JM, Snijders D, de Graaff CS, Vlaspolder F, Jansen HM, Boersma WG. Antibiotics in Addition to Systemic **Corticosteroids for Acute Exacerbations** of COPD. Am J Respir Crit Care Med. 2009 Oct 29.

Dawood Fatimah S., Kamimoto Laurie, D'Mello Tiffany A., et al. and the Emerging Infections Program Network. Children With **Asthma** Hospitalized With Seasonal or Pandemic **Influenza**, 2003–2009. Pediatrics 2011; 128:1 e27-e32; ahead of print June 6, 2011

de Blic J, Ogorodova L, Klink R, et al. Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children. Pediatr Allergy Immunol. 2009 Feb 20. [Epub ahead of print] Treatment with SFC 50/100 mug bd compared with twice the steroid dose of FP (200 mug bd), was at least as effective in improving individual clinical outcomes and overall asthma control, in asthmatic children previously uncontrolled on low doses of ICS.

De Boeck K, Vermeulen F, Meyts I, Hutsebaut L, Franckaert D, Proesmans M. Coprescription of **Antibiotics and Asthma** Drugs in Children. Pediatrics 2011;127:1022-6.

de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. **Oral or IV Prednisolone** in the Treatment of COPD Exacerbations: A Randomized, Controlled, Double-blind Study. Chest. 2007 Dec;132(6):1741-7. Epub 2007 Jul 23. Therapy with oral prednisolone is not inferior to IV treatment in the first 90 days after starting therapy. Oral steroids are as effective as intravenous (IV) steroids for nonsevere exacerbations of chronic obstructive pulmonary disease (COPD). Because they are cheaper and less invasive, oral steroids should be the preferred treatment option. (LOE = 1b)

Decramer M, Celli B, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the **UPLIFT trial**.COPD. 2004;1(2):303-12. ?2008

Decramer M, Rutten-van Molken M, et al. Effects of **N-acetylcysteine** on outcomes in COPD (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet. 2005 May;365(9470):1552-60. (InfoPOEMs: N-acetylcysteine does not prevent chronic obstructive pulmonary disease lung-function decline or exacerbation. (LOE = 1b))

Decramer M, Celli B, Kesten S, et al. for the **UPLIFT** investigators. Effect of tiotropium on outcomes in patients with **moderate** chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet. 2009 Aug 27.

Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012 Feb 3.

Deykin A, et al. Combination Therapy with a **Long-acting {beta}-Agonist and a Leukotriene** Antagonist in Moderate Asthma. Am J Respir Crit Care Med. 2006 Sep 14; [Epub ahead of print] Patients with moderate asthma similar to those we studied should not substitute the combination of an LTRA and a LABA for the combination of ICS and LABA.

de Benedictis FM, Bush A. **Corticosteroids in respiratory diseases in children**. Am J Respir Crit Care Med. 2012 Jan 1;185(1):12-23.

de Vries et al. Reported **adverse drug reactions during the use of inhaled steroids** in children with asthma in the Netherlands. Eur J Clin Pharmacol. 2006 May;62(5):34 2006 Apr 1. Alteration of behaviour was the most frequently reported sADR. There are more indications that alterations of behaviour could be a real sADR o

TOP

fatal adrenal insufficiency was the only reported possible life threatening sADR. The association of hypertrichosis and teeth abnormalities after ICS in children has not been reported in the literature before.

Dhuper S, Chandra A, Ahmed A, et al. Efficacy and cost comparisons of bronchodilatator administration between **metered dose inhalers with disposable spacers and nebulizers** for acute asthma treatment. J Emerg Med. 2011 Mar;40(3):247-55.

Doan Q, Shefrin A, Johnson D. **Cost-effectiveness of Metered-Dose Inhalers** for Asthma Exacerbations in the Pediatric Emergency Department. Pediatrics 2011 0: peds.2010-2963

Dogaru CM, Strippoli MF, et al. **Breastfeeding** and **lung function** at school age: does maternal asthma modify the effect? Am J Respir Crit Care Med 2012;185:874–880.

Doherty S. Prescribe **systemic corticosteroids** in acute asthma. BMJ. 2009 Apr 3;338:b1234. doi: 10.1136/bmj.b1234.

Dolovich MB, Ahrens RC, Hess DR, et al. **Device selection** and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005 Jan;127(1):335-71.

Dombrowski MP, Schatz M; ACOG Committee on Practice Bulletins-Obstetrics. **ACOG practice bulletin**: clinical management guidelines for obstetrician-gynecologists number 90, February 2008: **asthma in pregnancy**. Obstet Gynecol. 2008 Feb;111(2 Pt 1):457-64.

Donaldson GC, Goldring JJ, Wedzicha JA. Influence of **Season on Exacerbation Characteristics in Patients With COPD**. Chest. 2012 Jan;141(1):94-100.

Donohue JF, Kalberg C, Emmett A, Merchant K, Knobil K. A short-term comparison of **fluticasone propionate/salmeterol** with ipratropium bromide/albuterol for the treatment of COPD. Treat Respir Med. 2004;3(3):173-81.

Donohue JF, Fogarty C, Lotvall J, et al; **INHANCE** Study Investigators. Once daily bronchodilators for chronic obstructive pulmonary disease: **indacaterol versus tiotropium**. Am J Respir Crit Care Med 2010;182:155-62.

Dransfield MT, et al.. Use of **beta blockers** & the risk of death in hospitalised patients with acute exacerbations of COPD. Thorax. 2008 Apr;63(4):301-5. Epub 2007 Oct 19. The use of beta blockers by inpatients with exacerbations of COPD is well tolerated and may be associated with reduced mortality. The potential protective effect of beta blockers in this population warrants further study.

Drug & Therapeutics Bulletin: Preventing **exacerbations** in chronic obstructive pulmonary disease. Drug & Therapeutics Bulletin. BMJ 2011;342:doi:10.1136/bmj.c7207 (24 Jan 11)

Drummond MB, Dasenbrook EC, Pitz MW, et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008 Nov 26;300(20):2407-16. Among patients with COPD, ICS therapy does not affect 1-year all-cause mortality. ICS therapy is associated with a higher risk of pneumonia.

Drummond MB, Hansel NN, Connett JE, et al. **Spirometric Predictors** of Lung Function Decline and Mortality in Early COPD. Am J Respir Crit Care Med. 2012 May 3.

Ducharme FM, Lasserson TJ, Cates CJ. Addition to **inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes** for chronic asthma. Cochrane Database Syst Rev. 2011 May 11;5:CD003137. In adults with asthma that is inadequately controlled on low doses of inhaled steroids and showing significant reversibility with beta(2)-agonists, LABA is superior to LTRA in reducing oral steroid treated exacerbations. Differences favouring LABA in lung function, functional status and quality of life scores are generally modest. There is some evidence of increased risk of SAEs with LABA. The findings support the use of a single inhaler for the delivery of LABA and inhaled corticosteroids. We are unable to draw conclusions about which treatment is better as add-on therapy for children.

Ducharme FM, Lemire C, Noya FJ, et al. Preemptive use of **high-dose fluticasone** $^{750ug\ bid}$ **for virus-induced wheezing** in young children. N Engl J Med. 2009 Jan 22;360(4):339-53. In preschool-age children with moderate-to-severe virus-induced wheezing, preemptive treatment with high-dose fluticasone as compared with placebo reduced the use of rescue oral corticosteroids. Treatment with fluticasone was associated with a smaller gain in height and weight. Given the potential for overuse, this preventive approach should not be adopted in clinical practice until long-term adverse effects are clarified.

Ducharme FM, Ni Chroinin M, Greenstone I, et al. **Addition of long-acting beta2-agonists to inhaled corticosteroids** versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev. 2010 May 12;5:CD005535.

Ducharme FM. Continuous versus **intermittent inhaled corticosteroids** for mild persistent asthma in children: not too much, not too little. Thorax. 2011 Oct 13.

Duffy N, Walker P, Diamantea F, et al. Intravenous **aminophylline** in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Thorax. 2005 Sep;60(9):713-7. Epub 2005 Jun 6.

Dzierba AL, Jelic S. Chronic obstructive pulmonary disease in the **elderly**: an update on pharmacological management. Drugs Aging. 2009;26(6):447-56.

Eder W, Ege MJ, von Mutius E. The **asthma epidemic**. N Engl J Med. 2006 Nov 23;355(21):2226-35.

Effing T, Kerstjens H, van der Valk P, et al. (Cost)-effectiveness of **self-treatment** of exacerbations on the severity of exacerbations in patients with COPD: the COPE II study. Thorax. 2009 Nov;64(11):956-62. Epub 2009 Sep 6.

Ege MJ, Mayer M, Normand AC, et al. GABRIELA Transregio 22 Study Group. **Exposure to environmental microorganisms** and childhood asthma. N Engl J Med. 2011 Feb 24;364(8):701-9.

Eisner MD, Yegin A, Trzaskoma B. Severity of asthma (SOA) score predicts clinical outcomes in patients with moderate to severe persistent asthma. Chest. 2012 Jan;141(1):58-65.

Enriquez R, et al. Cessation of asthma medication in early **pregnancy**. Am J Obstet Gynecol. 2006 Jul;195(1):149-53. Epub 2006 May 2.

Erin EM, et al. The Effects of a Monoclonal Antibody Directed against Tumor Necrosis Factor-{alpha} (**infliximab**)in Asthma. Am J Respir Crit Care Med. 2006 Oct 1;174(7):753-62. Epub 2006 Jul 13.

Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ; RSV Corticosteroid Study Group. The effect of high dose inhaled corticosteroids on wheeze in infants after **respiratory syncytial virus** infection: randomised double blind placebo controlled trial. BMJ. 2009 Mar 31;338:b897. doi: 10.1136/bmj.b897.

Ernst P, et al. Canadian Asthma Guideline Group. Safety and effectiveness of **long-acting inhaled beta**-agonist bronchodilators when taken with inhaled corticosteroids. Ann Intern Med. 2006 Nov 7;145(9):692-4.

Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in **chronic obstructive pulmonary disease** and the risk of hospitalization for **pneumonia**. Am J R Care Med. 2007 Jul 15;176(2):162-6. Epub 2007 Mar 30. The use of inhaled corticosteroids is associated with an excess risk of pneumonia hospitalization and of pneumonia hospitalization followed by death within 30 days, among elderly pat

TOP

(InfoPOEMs: In this well-conducted case-control study, elderly patients with chronic obstructive pulmonary disease (COPD) hospitalized for pneumonia were more likely to have been prescribed inhaled corticosteroids. Even though there was a dose response, we still cannot ascertain if this was cause or effect.)

Esposito-Festen J, et al. Aerosol Therapy by Pressured Metered-Dose Inhaler-**Spacer** in Sleeping Young Children: To Do or Not to Do? Chest. 2006 Aug;130(2):487-492.

Evensen AE. **Management of COPD Exacerbations**. Am Fam Physician. 2010 Mar 1;81(5):607-13.

Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al.; M2-127 and M2-128 study groups. **Roflumilast** in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet. 2009 Aug 29;374(9691):695-703.

Fan VS, et al. A **comprehensive care management program** (CCMP) to prevent **chronic obstructive pulmonary disease** hospitalizations. A randomized, controlled trial. Ann Intern Med. 2012;156:673-83. (had an unexpected excess mortality in CCMP group)

Fanta CH. **Asthma**.N Engl J Med. 2009 Mar 5;360(10):1002-14.

Farley M, Ryan P, Lynfield R, et al. Emerging Infections Program Network. Children with asthma hospitalized with **seasonal or pandemic influenza**, 2003-2009. Pediatrics. 2011 Jul;128(1):e27-32.

Ferguson GT, Calverley PM, Anderson JA, et al. Prevalence and Progression of **Osteoporosis** in Patients With COPD. Results From TORCH. Chest. 2009 Jul 6. [Epub ahead of print] In the TORCH study, no significant effect on BMD was detected for inhaled corticosteroid therapy compared with placebo.

Feuillet-Dassonval C, et al. [Written asthma **action plans**: a useful tool for self-management] Arch Pediatr. 2005 Dec;12(12):1788-96. Epub 2005 Aug 26.

FitzGerald JM, et al. Asthma control in Canada remains **suboptimal**: the Reality of Asthma Control (**TRAC**) study. Can Respir J. 2006 Jul-Aug;13(5):253-9.

FitzGerald JM, et al. Canadian Asthma Exacerbation Study Group. **Doubling the dose of budesonide** vs maintenance treatment in asthma exacerbations. Thorax. 2004Jul;59(7):550-6.

FitzGerald JM, Boulet LP, Follows RM. The **CONCEPT** trial: a 1-year, multicenter, randomized,double-blind, double-dummy comparison of a stable dosing regimen of Salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clin Ther. 2005 Apr;27(4):393-406. CONCLUSIONS: In this adult population with persistent asthma, stable dosing of SAL/FP 50/250 microg BID resulted in significantly greater increases in symptom-free days, days free of rescue medication, and morning PEE, as well as almost halving the exacerbation rate, compared with AMD of FOR/BUD 6/200 microg. The results suggest that there is a minimum daily amount of maintenance therapy necessary to prevent exacerbations in adults with persistent asthma.

Font-Ribera L et al. **Swimming pool attendance, asthma, allergies, and lung function** in the Avon Longitudinal Study of Parents and Children cohort. Am J Respir Crit Care Med 2011 Mar 1; 183:582.

Ford PA, Durham AL, Russell RE, et al. Treatment effects of **low dose theophylline combined with an inhaled corticosteroid** in COPD. Chest. 2010 Mar 18.

Ford ES, Mannino DM, Zhao G et al. Changes in **Mortality Among US Adults With COPD** in Two National Cohorts Recruited From 1971-1975 and 1988-1994. Chest. 2012 Jan;141(1):101-10.

Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. Chest. 2000 Feb;117(2):440-6. This study demonstrates that when patients with moderate asthma had reached a stable clinical condition with a high dose of budesonide, a low dose of budesonide (200 microg/d) is as effective as the standard dose (800 microg/d) in the control of symptoms and lung function over a period of several months. Furthermore, results showed that the addition of inhaled budesonide (800 microg/d) at onset of an asthmatic exacerbation has a beneficial clinical effect.

Frank PI, Morris JA, Hazell ML, Linehan MF, Frank TL. Long term prognosis in **preschool children with wheeze**: longitudinal postal questionnaire study 1993-2004. BMJ. 2008 Jun 21;336(7658):1423-6. Epub 2008 Jun 16. Using two simple predictive factors (baseline parent reported exercise induced wheeze and a history of atopic disorders), it is possible to estimate the likelihood of future asthma in children presenting with preschool wheeze. The absence of baseline exercise induced wheeze and a history of atopic disorders reduces the likelihood of subsequent asthma by a factor of five.

Frew AJ. **Sublingual immunotherapy**. N Engl J Med. 2008 May 22;358(21):2259-64. (Grass pollen sl tabs -Grazax is available in Europe)

Friedman BC, Goldman RD. **Influenza vaccination for children with asthma**. Can Fam Physician. 2010 Nov;56(11):1137-9.

Fuhr R, Magnussen H, et al. Efficacy of **Aclidinium Bromide** 400 µg Twice Daily Compared With Placebo and Tiotropium in Patients With Moderate to Severe COPD. Chest. 2012 Mar;141(3):745-52.

Gaebel K, Blackhouse G, Robertson D, Xie F, Assasi N, McIvor A, Hernandez P, Goeree R. Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary Disease [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010 (CADTH technology report; no. 127). Available:http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/000

García-Rio F, Soriano JB, Miravitlles M, et al. **Overdiagnosing Subjects With COPD Using the 0.7 Fixed Ratio**: Correlation With a Poor Health-Related Quality of Life. Chest 2011May;139(5):1072-80.

Gartlehner G, et al. Efficacy & safety of inhaled **corticosteroids in patients with COPD**: a systematic review and meta-analysis of health outcomes. Ann Fam Med. 2006 May-Jun;4(3):253-62. (InfoPOEMs: Inhaled corticosteroids prevent exacerbations in patients with mod-severe COPD. The benefit is minor, however, and steroids don't prevent exacerbations in patients with mild COPD. The prevention of exacerbations with steroids must be balanced against the higher rate of fractures and glaucoma. (LOE = 1a-))

Gershon Andrea S.; Wang Chengning; Wilton AS.; et al. **Trends in Chronic Obstructive Pulmonary Disease Prevalence, Incidence, and Mortality** in Ontario, Canada, 1996 to 2007: A Population-Based Study. Arch Intern Med. 2010;170(6):560-565.

Gershon Andrea, Croxford Ruth, To Teresa, et al. Comparison of Inhaled **Long-Acting β-Agonist and Anticholinergic** Effectiveness in Older Patients With Chronic Obstructive Pulmonary Disease: A Cohort Study. *Ann Intern Med* May 3, 2011 154:583-592; doi:10.1059/0003-4819-154-9-201105030-00003.

Gershon AS, Warner L, Cascagnette P, Victor JC, To T. **Lifetime risk of developing chronic obstructive pulmonary disease**: a longitudinal population study. Lancet. 2011 Sep 10;378(9795):991-6.

Gibson PG, Powell H, Coughlan J, et al. **Self-management** education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev. 2003;(1):CD001117.

Gibson PG, McDonald VM, Marks GB. **Asthma in older adults.** Lancet. 2010 Sep 4;376(9743):803-13.

Gildea TR, Khatri SB, Castro M. **Bronchial thermoplasty**: a new treatment for severe refractory asthma. Cleve Clin J Med 2011; 78:477–485.

Gøtzsche PC, Johansen HK. **Intravenous alpha-1 antitrypsin** augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD007851. DOI: 10.1002/14651858.CD007851.pub2. Augmentation therapy with alpha-1 antitrypsin cannot be recommended, in view of the lack of evidence of clinical benefit and the cost of treatment.

Goyal NK, Fiks AG, Lorch SA. Association of **late-preterm birth with asthma** in young children: practice-based study. Pediatrics. 2011 Oct;128(4):e830-8.

Graeme P Currie, Graham S Devereux, Daniel K C Lee, and Jon G Ayres. Recent developments in asthma management. BMJ, Mar 2005; 330: 585 - 589.

Grainge CL, Lau LCK, Ward JA, et al. Effect of **bronchoconstriction on airway remodeling** in asthma. N Engl J Med 2011; 364:2006-15.

Granger R, et al. Injectable vaccines for preventing **pneumococcal** infection in patients with COPD. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD001390. There is no evidence from randomised controlled trials that injectable pneumococcal vaccination in persons with COPD has a significant impact on morbidity or mortality. Further large randomised controlled trials would be needed to ascertain if the small benefits suggested by individual studies are real.

Green RH, et al. A randomised comparison of the effects of asthma treatment given in addition to inhaled corticosteroids on airway inflammation & airway responsiveness. Eur Respir J. 2006 Feb 2.

Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. Lancet. 1995 Jul 22;346(8969):201-6.

Guerrera M. et al. Therapeutic Uses of **Magnesium**. Am Fam Physician. 2009; 80(1):157-162.

Guilbert TW, et al. Long-term inhaled **corticosteroids in preschool children** at high risk for asthma. N Engl J Med. 2006 May 11;354(19):1985-97. In preschool children at high risk for asthma, two years of corticosteroid therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year. (fluticasone 88ug bid)

TOP

Guilleminault L, Carré P, Beau-Salinas F, et al. Asthma **Unmasked With Tumor Necrosis Factor-{alpha}-Blocking Drugs**. Chest. 2011 Oct;140(4):1068-71.

Hahn PY, Morgenthaler TY, Lim KG. Use of **exhaled nitric oxide** in predicting response to **inhaled corticosteroids for chronic cough**. Mayo Clin Proc. 2007 Nov;82(11):1350-5.

Haidl P, Schmidt F, Wiese C, Koehler D. Peak inspiratory flow rate after **methacholine challenge** in asthmatic patients and its impact on the effect of **formoterol** via different inhalers. J Aerosol Med. 2006 Fall;19(3):364-71. If patients fail to generate a PIMF of 30 l/min, 6 microg formoterol via Turbuhaler may provide inadequate relief in a severe asthma attack.

Haland G, et al. ORAACLE. Reduced **lung function** at birth and the risk of asthma at **10 years** of age. N Engl J Med. 2006 Oct 19;355(16):1682-9. Reduced lung function at birth is associated with an increased risk of asthma by 10 years of age. For some measures of lung mechanics, a reading below the median at birth was also associated with severe bronchial hyperresponsiveness (9.1% v 4.9%, P = 0.05) and use of inhaled corticosteroids at 10 years (5.9% v 2.4%, P = 0.02).

Halterman JS, et al. Improved preventive care for asthma: a randomized trial of **clinician prompting** in pediatric offices. Arch Pediatr Adolesc Med. 2006 Oct;160(10):1018-25.

Halterman Jill S.; Szilagyi Peter G.; Fisher Susan G.; et al. Randomized Controlled Trial to Improve Care for Urban Children With Asthma: Results of the **School-Based Asthma Therapy Trial**. Arch Pediatr Adolesc Med. 2011;165(3):262-268.

Hao Q, Lu Z, Dong BR, Huang CQ, Wu T. **Probiotics for preventing acute upper respiratory tract infections**. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD006895. DOI: 10.1002/14651858.CD006895.pub2. Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTIs, the rate ratio of episodes of acute URTI and reducing antibiotic use. This indicates that probiotics may be more beneficial than placebo for preventing acute URTIs.

Hanania NA., Alpan O, Hamilos DL., et al. **Omalizumab in Severe Allergic Asthma** Inadequately Controlled With Standard Therapy: A Randomized Trial. *Ann Intern Med* May 3, 2011 154:573-582.

Harrison TW, et al. **Doubling the dose of inhaled corticosteroid** to prevent asthma exacerbations: randomised controlled trial. Lancet. 2004 Jan 24;363(9405):271-5.

Hawkins NM, Petrie MC, MacDonald MR, et al. **Heart failure** and chronic obstructive pulmonary disease. The quandary of **beta-blockers** and beta-agonists. J Am Coll Cardiol 2011; 57:2127-2138.

Health Canada June/07 **VENTOLIN** IM injection and VENTOLIN I.V. infusion solution for Pregnant Women & Labour and Delivery. GlaxoSmithKline conducted a review of safety data for salbutamol. There have been 17 occurences worldwide (as of April 2007) of **myocardial ischemia** events in association with salbutamol when used to delay premature labour. There have been no Canadian cases reported to date.

Health Canada Aug/09 is informing health care professionals and Canadians that it is conducting a safety review of the potential association between the asthma drug **Xolair** (the brand name for the drug omalizumab) and an increased risk of cardiovascular problems. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_129-eng.php

Henderson-Smart DJ, De Paoli AG. **Methylxanthine treatment for apnoea in preterm infants**. *Cochrane Database Syst Rev* 2010*;* **12***:* CD000140.

Hill, Kylie, Hodder, Richard, Blouin, Maria, et al. Identifying adults at risk of COPD who need confirmatory **spirometry** in primary care: Do symptom-based questions help? Can Fam Physician 2011 57: e51-57.

Hodder, Rick, Lougheed, Diane, FitzGerald, J Mark, et al. Management of acute asthma in adults in the **emergency department: assisted ventilation**. CMAJ 2009 0: cmaj.080073

Hodder, Rick, Lougheed, M Diane, et al. Management of acute asthma in adults in the **emergency department: nonventilatory** management. CMAJ 2009 0: cmaj.080072

Hoover Wynton C, Britton LaCrecia J, Gardner Jay, et al. Rapid Onset of Iatrogenic Adrenal Insufficiency in a Patient with Cystic Fibrosis–Related Liver Disease Treated with Inhaled **Corticosteroids and a Moderate CYP3A4 Inhibitor**. Ann Pharmacother July/August 2011 45:e38; June 28

Hodyl NA, Stark M, Osei-Kumah A, Bowman M, Gibson P, Clifton VL. **Fetal glucocorticoid** regulated pathways are not affected by inhaled corticosteroid use for asthma during pregnancy. Am J Respir Crit Care Med 2011;183:716–722.

Hurst John R., Vestbo Jørgen, Antonio Anzueto, et al. . for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (**ECLIPSE**) Investigators. Susceptibility to **Exacerbation** in Chronic Obstructive Pulmonary Disease. N Engl J Med 2010; 363:1128-1138

Irvin CG, et al. Clinical Trial of Low-Dose **Theophylline and Montelukast** in Patients with Poorly Controlled Asthma. Am J Respir Crit Care Med. 2006 Sep 22. Neither montelukast nor low-dose theophylline lowered the event-rate of poor asthma control in patients with poorly-controlled asthma despite improved lung function. For patients not using ICS, low-dose theophylline improved asthma symptom control more than montelukast or placebo and provides a safe and low-cost alternative asthma treatment.

Iyer VN, Schroeder DR, Parker KO, Hyatt RE, Scanlon PD. The **nonspecific pulmonary function test**: longitudinal follow-up and outcomes. Chest. 2011 Apr;139(4):878-86.

Jackson DJ, Evans MD, Gangnon RE, et al. Evidence for a causal relationship between **allergic sensitization and rhinovirus wheezing** in early life. Am J Respir Crit Care Med 2012;185:281–285.

Jaeschke R, O'Byrne PM, Mejza F, et al.. The safety of **long-acting beta-agonists** among patients with asthma using inhaled corticosteroids: systematic review and **metaanalysis**. Am J Respir Crit Care Med. 2008 Nov 15;178(10):1009-16. Epub 2008 Sep 5. Compared with monotherapy, using long-acting beta-agonists (LABAs) plus inhaled corticosteroids in patients with asthma does not appear to increase the risk of hospitalizations. In spite of multiple studies including almost 30,000 patients and more than 8000 patient-years of follow-up, there were too few asthma-related deaths and intubations to draw conclusions about the effect of LABAs on these outcomes. (LOE = 1a)

James AL, Elliot JG, Jones RL, et al. Airway **smooth muscle hypertrophy** and hyperplasia in **asthma**. Am J Respir Crit Care Med 2012;185:1058–1064.

Jarjour NN, et al. Control of airway inflammation maintained at a lower steroid dose with 100/50 ug of fluticasone propionate/salmeterol. J Allergy Clin Immunol. 2006 Jul;118(1):44-52.Epub 2006 Jun 2.

Jarjour NN, Erzurum SC, Bleecker ER, et al. for the NHLBI Severe Asthma Research Program (SARP). Severe Asthma: Lessons Learned from the National Heart, Lung, and Blood Institute **Severe Asthma** Research Program. Am J Respir Crit Care Med. 2012 Feb 15;185(4):356-362.

Jat GC, et al. 400 µg of inhaled **budesonide** vs 200 µg of inhaled **budesonide and oral montelukast** in children with moderate persistent asthma: randomized controlled trial . Ann Allergy Asthma Immunol. 2006 Sep;97(3):397-401. The overall control of asthma with 5 mg of oral montelukast and 200 microg of inhaled budesonide is inferior to that with 400 microg of inhaled budesonide in children with moderate persistent asthma.

Jenkins C, et al. Efficacy and safety of **high-dose budesonide/formoterol (Symbicort)** compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006 May;11(3):276-86.

Jenkins C, Seccombe L, Tomlins R. **Investigating asthma symptoms in primary care**. BMJ. 2012 Apr 25;344:e2734.

Jeppesen E, Brurberg KG, Vist GE, et al. **Hospital at home for acute exacerbations of chronic obstructive pulmonary disease**. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD003573. Selected patients presenting to hospital emergency departments with acute exacerbations of COPD can be safely and successfully treated at home with support from respiratory nurses. We found evidence of moderate quality that hosp advantageous with respect to readmission rates in these patients. Treatment of acute exacerbation of COPD in hospital at home also show a trend towards reduced mortality rate when compared with conventional inpatient treatment, but these results did not reach statistical significance (mo evidence).

TOP

Johansson SG, Oman H, Nopp A, Pettersson S. The importance of **IgE antibody** levels in anti-IgE treatment. Allergy. 2006 Oct;61(10):1216-9.

Johnston SL, et al. TELICAST Investigators. The effect of **telithromycin** in acute exacerbations of asthma. N Engl J Med. 2006 Apr 13;354(15):1589-600.(InfoPOEMs: Telithromycin may add a small benefit of questionable clinical significance for adult patients with acute asthma. This comes at the price of high drug cost, increased nausea and diarrhea, and a theoretical increased risk of drug resistance in the community. Given this balance of benefits and harms, as well as recent reports of catastrophic liver failure in a small number of patients taking telithromycin, physicians should resist the temptation to prescribe this drug for asthma. (LOE = 1b))

Jones PW, Chen WH, et al. EXACT-PRO Study Group. Characterizing and quantifying the symptomatic features of **COPD exacerbations**. Chest. 2011 Jun;139(6):1388-94.

Jonkers RE, et al. Onset of relief of dyspnoea with **budesonide/formoterol or salbutamol** following **methacholine-induced** severe bronchoconstriction in adults with asthma: a double-blind, placebo-controlled study. Respir Res. 2006 Dec 4;7(1):141 [Epub ahead of print] Budesonide/formoterol and salbutamol both provided rapid relief of dyspnoea and reversal of airway obstruction in patients with asthma with experimentally induced bronchoconstriction. The perception of relief, as confirmed by objective lung function assessment, provides further evidence that budesonide/formoterol can be used as reliever medication in asthma.

Jung KS et al.Comparison of **tiotropium plus fluticasone propionate/salmeterol** with tiotropium in COPD: A randomized controlled study. Respir Med. 2011 Oct 3.

Kane Binita, Turkington Peter M, Howard Luke S, et al. Lesson of the Week: Rebound **hypoxaemia after administration of oxygen** in an acute exacerbation of chronic obstructive pulmonary disease. BMJ 2011;342:doi:10.1136/bmj.d1557 (Published 31 March 2011)

Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to **acetaminophen** and asthma in children. Obstet Gynecol. 2009 Dec;114(6):1295-306.

Kaplan AG, Balter MS, Bell AD, Kim H, McIvor RA. **Diagnosis of asthma** in adults. CMAJ. 2009 Sep 29. [Epub ahead of print]

Karner C, Cates CJ. The effect of **adding inhaled corticosteroids to tiotropium and long-acting beta(2)-agonists for chronic obstructive pulmonary disease**. Cochrane Database Syst Rev. 2011 Sep 7;9:CD009039. The relative efficacy and safety of adding inhaled corticosteroid to tiotropium and a long-acting beta(2)-agonist for chronic obstructive pulmonary disease patients remains uncertain and additional trials are required to answer this question.

Karner C, Cates CJ. **Long-acting beta(2)-agonist in addition to tiotropium** versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Apr 18;4:CD008989. The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and long-acting beta(2)-agonist compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta(2)-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus long-acting beta(2)-agonist compared to long-acting beta(2)-agonist alone. There were insufficient data to make comparisons between the different long-acting beta(2)-agonists when used in addition to tiotropium.

Karner C, Cates CJ. Combination inhaled steroid and long-acting beta(2)-agonist in addition to **tiotropium versus tiotropium or combination** alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011 Mar 16;(3):CD008532.

Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC; CAMP Research Group. Effect of long-term corticosteroid use on **bone mineral** density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics. 2008 Jul;122(1):e53-61. Multiple oral corticosteroid bursts over a period of years can produce a dosage-dependent reduction in bone mineral accretion and increased risk for osteopenia in children with asthma. Inhaled corticosteroid use has the potential for reducing bone mineral accretion in male children progressing through puberty, but this risk is likely to be outweighed by the ability to reduce the amount of oral corticosteroids used in these children.

Kerstjens HA, Bantje TA, Luursema PB, Sinninghe Damste HE, de Jong JW, Lee A, Wijker SP, Cornelissen PJ. Effects of short-acting bronchodilators added to maintenance tiotropium therapy. Chest. 2007 Nov;132(5):1493-9. Epub 2007 Sep 21. In conclusion, both short-acting bronchodilator classes were effective when added to maintenance treatment with tiotropium. The addition of the beta2-adrenergic fenoterol provided greater additional bronchodilatation than the short-acting anticholinergic ipratropium.

Kerstjens HA, Disse B, Schroder-Babo W, et al. **Tiotropium** improves lung function in patients with severe uncontrolled **asthma**: a randomized controlled trial. J Allergy Clin Immunol. 2011 Aug;128(2):308-14.

Khorfan FM, Smith P, Watt S, Barber KR. Effects of **nebulized bronchodilator** therapy on heart rate and arrhythmias in critically ill adult patients. Chest. 2011 Dec;140(6):1466-72. In critically ill adult patients, nebulized albuterol and ipratropium does not cause significant tachycardia or tachyarrhythmias. Substitution of levalbuterol for albuterol (salbutamol) to avoid tachycardia and tachyarrhythmias is unwarranted.

Kiljander TO, et al. Effects of **esomeprazole** 40 mg twice daily on asthma: a randomized placebo-controlled trial. Am J Respir Crit Care Med. 2006 May 15;173(10):1091-7. Epub 2005 Dec 15. n=770 16weeks Esomeprazole improved PEF in subjects with asthma who presented with both GERD and NOC. In subjects without both GERD and NOC, no improvement could be detected. (InfoPOEMs: In this study, esomeprazole (Nexium) was no better than placebo in improving peak expiratory flow, asthma symptoms, or quality of life in patients with stable asthma. Furthermore, esomeprazole was no better than placebo in pts with reflux, either. (LOE = 2b-))

Kiljander TO, Junghard O, Beckman O, Lind T. Effect of **Esomeprazole** 40 mg Once or Twice Daily on Asthma: A Randomized, Placebo-controlled Study. Am J Respir Crit Care Med. 2010 Jan 28.

Kit BK et al. Trends in **Preventive Asthma Medication Use** Among **Children and Adolescents**, 1988-2008. Pediatrics. 2011 Dec 5.

Konikoff MR, et al. A randomized, double-blind, placebo-controlled trial of fluticasone for pediatric **eosinophilic esophagitis**. Gastroenterology. 2006 Nov;131(5):1381-91. Epub 2006 Aug 16.

Koopmans JG, Lutter R, Jansen HM, van der Zee JS. Adding salmeterol to an ICS: long term effects on bronchial inflammation in asthma. Thorax. 2006 Apr;61(4):306-12. Epub 2006 Jan 31.

Koren G, Sarkar M, Einarson A. Safety of using **montelukast during pregnancy**. Can Fam Physician. 2010 Sep;56(9):881-2.

Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, Kramer B. Once-daily **indacaterol** vs twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J. 2010 Aug 6.

Kovesi, Thomas, Schuh, Suzanne, Spier, Sheldon, et al. Achieving control of asthma in preschoolers. CMAJ 2009 0: cmaj.071638.

Kozer E, Lotem Z, Elgarushe M, et al. RCT of **Montelukast** as Prophylaxis for Upper Respiratory Tract Infections in Children. Pediatrics. 2012 Jan 4. (12 week 4mg oral not effective)

Kravitz J, Dominici P, Ufberg J et al. **Two Days** of Dexamethasone Versus 5 Days of **Prednisone** in the Treatment of Acute Asthma: A Randomized Controlled Trial. Ann Emerg Med. 2011Feb17.

Irwin RS, et al. American College of Chest Physicians (ACCP). **Diagnosis and management of cough** executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):1S-23S. http://www.chestjournal.org/cgi/content/full/129/1_suppl/1S

Lange P, et al. Inhaled corticosteroids and decline of **lung function** in community residents with asthma. Thorax. 2006 Feb;61(2):100-4.

Lapperre T. S., Snoeck-Stroband J. B., Gosman M. M.E., et al. and the GLUCOLD (Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease) Study Group. Effect of **Fluticasone** With and Without Salmeterol on Pulmonary Outcomes in Chronic Obstructive Pulmonary Disease: A Randomized Trial. Ann Intern Med 2009; 517-527.

Laude EA, et al. The effect of helium and oxygen on exercise performance in COPD: a randomized crossover trial. Am J Respir Crit Care Med. 2006 Apr 15;173(8):865-70. Epub 2006 Jan 26. (InfoPOEMs: Inhaling a combination of 72% helium and 28% oxygen during exertion increases the comfortable walking distance and reduces the perception of exertional difficulty in patients with stable chronic obstructive pulmonary disease (COPD). (LOE = 2b))

Laugheed MD, Lemiere C, Dell S, Ducharme F, FitzGerald JM, Leigh R, et al. **Canadian Thoracic Society** Asthma Management Continuum – **2010 Consensus** Summary for children six years of age and over , and adults. Can Respir J 2010;17:15-24.

Lazarus SC, et al. **Smoking** Affects Response to **Inhaled Corticosteroids** or Leukotriene Receptor Antagonists in Asthma. Am J Respir Crit Care Med. 2007 Jan 4; [Epub ahead of print] In m

TOP

who smoke, the response to inhaled corticosteroids is attenuated, suggesting that adjustments to standard therapy may be required to attain asthma control. The greater improvement seen in some outcomes in smokers treated with montelukast suggests that leukotrienes may be important in this setting.

Lazarus SC. Clinical practice. **Emergency treatment of asthma**. N Engl J Med. 2010 Aug 19;363(8):755-64.

Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med. 2008 Sep 16;149(6):380-90. The possible association between ipratropium and elevated risk for all-cause and cardiovascular death needs further study.

Lee TA, Wilke C, Joo M, Stroupe KT, et al. Outcomes associated with **tiotropium** use in patients with chronic obstructive pulmonary disease. Arch Intern Med. 2009 Aug 10;169(15):1403-10.

Lemanske, Robert F., Jr., Mauger, David T., Sorkness, Christine A., et al. the Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute, Step-up Therapy for Children with Uncontrolled Asthma while Receiving Inhaled Corticosteroids. (**Badger**) N Engl J Med 2010 0: NEJMoa1001278. Nearly all the children had a differential response to each step-up therapy. LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up. However, many children had a best response to ICS or LTRA step-up therapy, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy.

Levalbuterol (Xopenex HFA) Medical Letter Mar 13,2006.

Lim Angelina, Stewart Kay, König Kai, et al. Systematic Review of the Safety of **Regular Preventive Asthma Medications During Pregnancy**. Ann Pharmacother July/August 2011 45:931-945.

Lin S, Munsie JP, Herdt-Losavio ML et al. Maternal Asthma Medication Use and the Risk of Selected Birth Defects. Pediatrics. 2012 Jan 16.

Lindenauer Peter K.; Pekow Penelope S.; Lahti Maureen C.; et al. Association of **Corticosteroid Dose and Route** of Administration With Risk of Treatment Failure in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (**COPD**). JAMA. 2010;303(23):2359-2367.

Littner MR, Leung FW, et al. **Lansoprazole Asthma** Study Group. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. Chest. 2005 Sep;128(3):1128-35.

Littner Michael R. In the Clinic: **Chronic Obstructive Pulmonary Disease**. *Ann Intern Med* April 5, 2011 154:ITC4-1.

Loke YK et al. **Risk of fractures with inhaled corticosteroids** in COPD: Systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax 2011 Aug; 66:699. The use of inhaled corticosteroids as a treatment for chronic obstructive pulmonary disease (COPD) in older adults increases the fracture risk somewhat, with a number needed to treat to harm of 83 over 3 years. This must be balanced against a number needed to treat of 6 per year to prevent exacerbations. (LOE = 1a)

Lokke A, et al. Developing COPD: a **25yr follow up** of the general population. Thorax. 2006 Nov;61(11):935-9. The absolute risk of developing COPD among continuous smokers is at least 25%, which is larger than was previously estimated.

Lougheed MD, Lemière C, Dell SD, et al. Canadian Thoracic Society Asthma Committee. **Canadian Thoracic Society Asthma Management Continuum--2010 Consensus Summary for children six years of age and over, and adults**. Can Respir J. 2010 Jan-Feb;17(1):15-24. http://www.respiratoryguidelines.ca/guideline/asthma

Lowe AJ, Carlin JB, et al. Paracetamol (**acetaminophen**) use in early life and asthma: prospective birth cohort study. BMJ. 2010 Sep 15;341:c4616. doi: 10.1136/bmj.c4616.

Lundback B, Ronmark E, Lindberg A, et al. Control of mild to moderate asthma over 1-year with the **combination** of salmeterol and fluticasone propionate. Respir Med. 2005 Oct 20

Macie C, Wooldrage K, Manfreda J, Anthonisen NR. Inhaled **Corticosteroids** and **Mortality** in COPD. Chest. 2006 Sep;130(3):640-6.

Mainguy V, Girard D, Maltais F, et al. Effect of **Bisoprolol** on Respiratory Function and Exercise Capacity in Chronic Obstructive Pulmonary Disease. Am J Cardiol. 2012 Apr 10.

Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community **pulmonary rehabilitation** after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. BMJ. 2004 Nov 20;329(7476):1209. Epub 2004 Oct 25.

Mancuso CA, Choi TN, Westerman H, et al. A randomized trial to **increase physical activity** in asthma patients through positive affect and self-affirmation. Arch Intern Med. doi:10.1001/archinternmed.2011.1311.

Masoli M, et al. **Moderate** dose inhaled **corticosteroids** plus salmeterol versus **higher** doses of inhaled corticosteroids in symptomatic asthma. Thorax. 2005 Sep;60(9):730-4.

Masoli M, et al. Inhaled fluticasone and **adrenal effects** in adult asthma: systematic review & meta-analysis. Eur Respir J. 2006 May 31; [Epub ahead of print]

Marciniuk DD, Goodridge D, Hernandez P, et al; **Canadian Thoracic Society (CTS)** COPD Committee Dyspnea Expert Working Group. Managing **dyspnea** in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guide. Can Respir J 2011;18(2). http://www.respiratoryguidelines.ca/sites/all/files/2011_CTS_guideline_COPD_dyspnea.pdf

Marks GB, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. J Allergy Clin Immunol. 2006 Jul;118(1):53-61. Epub 2006 May 30. House dust mite avoidance measures and dietary fatty acid modification, as implemented in this trial during infancy and early childhood, did not prevent the onset of asthma, eczema, or atopy in high-risk children.

Marra F, et al. Does **antibiotic exposure** during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006 Mar;129(3):610-8. Exposure to at least one course of antibiotics in the first year of life appears to be a risk factor for the development of childhood asthma.

Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of **beclomethasone dipropionate as rescue treatment** for children with mild persistent asthma (**TREXA**): a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; published online Feb 15. DOI:10.1016/S0140-6736(10)62145-9.

Mastronarde JG, Anthonisen NR, Castro M, et al. Efficacy of **esomeprazole** for treatment of poorly controlled asthma**.** (**SARA**) N Engl J Med. 2009 Apr 9;360(15):1487-99.

Matthay MA, Brower RG, Carson S, et al. Randomized, Placebo-Controlled Clinical Trial of an Aerosolized Beta**-2 Agonist for Treatment of Acute Lung Injury**. Am J Respir Crit Care Med. 2011 May 11.

Matsuyama W, Mitsuyama H, Watanabe M, et al. Effects of **omega-3 polyunsaturated fatty acids** on inflammatory markers in COPD. Chest. 2005 Dec;128(6):3817-27. (InfoPOEMs: This small study found that a diet rich in omega-3 fatty acids causes small improvements in chronic obstructive pulmonary disease (COPD) symptoms. (LOE = 1b))

McBride John T. The Association of **Acetaminophen and Asthma** Prevalence and Severity. Pediatrics 2011; peds.2011-1106; ahead of print November 7, 2011.

McCarney RW, et al. An overview of two Cochrane reviews of complementary treatments for chronic asthma: **acupuncture** & **homeopathy**. Respir Med. 2004 Aug;98(8):687-96.

McDonough JE, Yuan R, Suzuki M, et al. **Small-airway obstruction and emphysema in chronic obstructive pulmonary disease**. N Engl J Med 2011;365:1567-75.

McGrath KW, Icitovic N, Boushey HA, et al. for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. A Large Subgroup of Mild-to-Moderate Asthma is Persistently **Non-Eosinophilic**. Am J Respir Crit Care Med. 2012 Jan 20. (Approximately half of patients

McIvor AR, Kaplan A, Koch C, Sampalis JS. **Montelukast** as an alternative to low-dose inhaled corticosteroids in the management of **mild asthma (the SIMPLE trial)**:

TOP

open-label effectiveness trial. Can Respir J 2009;16(Suppl A):11A-21A.
McLean S, Chandler D, Nurmatov U, et al. **Telehealthcare for asthma**. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD007717. DOI: 10.1002/14651858. CD007717.pub2. Telehealthcare interventions are unlikely to result in clinically relevant improvements in health outcomes in those with relatively mild asthma, but they may have a role in those with more severe disease who are at high risk of hospital admission.
McMahon Ann W., Levenson Mark S., . McEvoy Bradley W,et al. **Age** and Risks of FDA–Approved **Long-Acting β2-Adrenergic Receptor Agonists**. Pediatrics 2011; peds.2010-1720; published ahead of print October 24, 2011
Medical Letter. **Arformoterol (Brovana)** for COPD). Jyly 2, 2007.
Medical Letter. Treatment Guidelines: Drugs for **Chronic Obstructive Pulmonary Disease**. Nov 2007. Revised **Nov 2010.**
Medical Letter. Treatment Guidelines: **Drugs for Asthma**. Dec 2008.
Medical Letter- Treatment Guidelines. **Drugs for Allergic Disorders**. Feb 2010.
Medical Letter. **Bronchial Thermoplasty** for Asthma. Aug 23, 2010.
Mehta AJ, Miedinger D, Keidel D, et al; SAPALDIA-team. **Occupational Exposure to Dusts, Gases and Fumes** and Incidence of COPD in SAPALDIA. Am J Respir Crit Care Med. 2012 Apr 6.
Mendes FA, Gonçalves RC, Nunes MP, et al. Effects of **aerobic training** on psychosocial morbidity and symptoms in patients with asthma: a randomized clinical trial. Chest. 2010 Aug;138(2):331-7.
Mets OM, Buckens CF, Zanen P, et al. Identification of chronic obstructive pulmonary disease in **lung cancer screening computed tomographic scans**. JAMA. 2011 Oct 26;306(16):1775-81.
Moen MD. **Indacaterol**: In Chronic Obstructive Pulmonary Disease. Drugs. 2010 Dec 3;70(17):2269-2280. doi: 10.2165/11203960-000000000-00000.
Moffatt MF, Gut IG, et al. GABRIEL Consortium. A large-scale, consortium-based **genomewide association study of asthma**. N Engl J Med. 2010 Sep 23;363(13):1211-21.
Mohammed S, Goodacre S. **Intravenous and nebulised magnesium** sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J. 2007 Dec;24(12):823-30.
Mometasone (Asmanex twisthaler) For Asthma. Med Letter Dec 2005;47:98-99. FDA: age ≥12 220-440ug bid or 440ug od (Fardon TC, Lee DK, Haggart K, et al. Adrenal suppression with dry powder formulations of fluticasone propionate & mometasone furoate. Am J Respir Crit Care Med. 2004 Nov 1;170(9):960-6. Epub 2004 Jun 7; Corren J, Berkowitz R, Murray JJ, Prenner B. Comparison of once-daily mometasone furoate versus once-daily budesonide in patients with moderate persistent asthma. Int J Clin Pract. 2003 Sep;57(7):567-72; Mortimer KJ, Harrison TW, Tattersfield AE. Effects of inhaled corticosteroids on bone. Ann Allergy Asthma Immunol. 2005 Jan;94(1):15-21; quiz 22-3, 79.)
Morgan WJ, et al. Inner-City Asthma Study Gp. Results of a **home-based environmental intervention** among urban children with asthma. N Engl J Med. 2004 Sep 9;351(11):1068-80.
Morse RB, Hall M, Fieldston ES, et al. Hospital-level compliance with **asthma care quality measures** at children's hospitals and subsequent asthma-related outcomes. JAMA. 2011;306(13):1454-1460.
Mortimer KJ, et al. Oral and inhaled corticosteroids and **adrenal insufficiency**: a case-control study. Thorax. 2006 May;61(5):405-8. Epub 2006 Mar 3.
Mutius E, Drazen J. A Patient with **Asthma** Seeks Medical Advice in **1828, 1928, and 2012** N Engl J Med 2012; 366:827-834.
Murk W, Risnes KR., Bracken MB. **Prenatal or Early-Life Exposure to Antibiotics** and Risk of Childhood Asthma: A Systematic Review. Pediatrics 2011; 127:6 1125-1138.
Murphy V, Namazy J, Powell H, et al. A meta-analysis of **adverse perinatal outcomes** in women with asthma. BJOG. 2011 Oct;118(11):1314-1323.
Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, Jones PW, Fitzgerald JM. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008 Nov;63(11):962-7. Epub 2008 Jul 11. TFS had significantly better quality of life and fewer hospitalisations than patients treated with TP but these improvements in health outcomes were associated with increased costs. Neither TFS nor TS are economically attractive alternatives compared with monotherapy with T. (T=tiotropium)
Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined **corticosteroid and long-acting** beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006829. Combination therapy was more effective than long-acting beta-agonists in reducing COPD exacerbation rates, although the evidence for the effects on hospitalisations was mixed, and requires further exploration. No significant impact on mortality was found even with additional information from the TORCH trial. The superiority of combination inhalers should be viewed against the increased risk of side-effects, particularly pneumonia.
Ni CM, Greenstone I, Lasserson TJ, et al. **Addition of inhaled long-acting beta2-agonists to inhaled steroids** as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD005307. In steroid-naive patients with mild to moderate airway obstruction, the combination of ICS and LABA does not significantly reduce the risk of patients with exacerbations requiring rescue oral corticosteroids over that achieved with a similar dose of ICS alone. However, it significantly improves lung function, reduces symptoms and marginally decreases rescue ss2-agonist use. Initiation of a higher dose of ICS is more effective at reducing the risk of exacerbations requiring rescue systemic corticosteroids, and of withdrawals, than combination therapy. Although children appeared to respond similarly to adults, no firm conclusions can be drawn regarding combination therapy in steroid-naive children, given the small number of children contributing data.
Ni CM, Greenstone I, Danish A, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD005535.
Ni CM, Lasserson TJ, Greenstone I, et al. Addition of **long-acting beta-agonists** to inhaled corticosteroids for chronic asthma in **children**. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007949. In children with persistent asthma, the addition of LABA to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids, but was superior for improving lung function compared to the same dose of ICS. Similarly, compared to a double dose ICS, the combination of LABA and ICS did not significantly increase the risk of exacerbations requiring oral steroids, but was associated with a significantly greater improvement in PEF and growth. The possibility of an increased risk of rescue oral steroids and hospital admission with LABA therapy needs to be further examined.
NICE Oct/10 Guidance: **Omalizumab** for the treatment of severe persistent allergic asthma in children aged 6-11. http://www.nice.org.uk/nicemedia/live/13256/51345/51345.pdf
NICE: 2010 CG101 **Chronic obstructive pulmonary disease** (update): full guideline. London: National Institute for Health and Clinical Excellence, 2010. (http://guidance.nice.org.uk/CG101/Guidance .)
Nici L, Donner C, et al., et al. **American Thoracic Society/European Respiratory Society** statement on **pulmonary rehabilitation**. Am J Respir Crit Care Med. 2006 Jun 15;173(12):1390-413.
Nici L, Lareau S, ZuWallack R. **Pulmonary Rehabilitation** in the Treatment of Chronic Obstructive Pulmonary Disease. Am Fam Physician. 2010 Sep 15;82(6):655-660.
Niewoehner DE, et al. Prevention of exacerbations of COPD with **tiotropium**, a once-daily inhaled anticholinergic bronchodilator -an RCT. Ann Intern Med. 2005 Sep 6;143(5):317-26. (InfoPOEM – Daily treatment with tiotropium for 6 months slightly decreases the number of patients experiencing a chronic obstructive pulmonary disease (COPD) exacerbation, though it doesn't decrease the number of patients who will be hospitalized for an exacerbation. (LO
Niewoehner, Dennis E. Outpatient Management of **Severe COPD**. N Engl J Med 2010 362: 1407-1416

TOP

Oborne J, Mortimer K, Hubbard RB, et al. **Quadrupling the Dose of Inhaled Corticosteroid** to Prevent Asthma Exacerbations: A Randomized, Double Blind, Placebo Controlled, Parallel Group, Clinical Trial. Am J Respir Crit Care Med. 2009 Jul 9. [Epub ahead of print] Although our primary outcome did not reach statistical significance, quadrupling the dose of inhaled corticosteroid when asthma control starts to deteriorate appears to reduce acute exacerbations of asthma and deserves further investigation.

O'byrne PM, et al. Budesonide/Formoterol combination therapy as both **maintenance and reliever** medication in asthma (**STAY** trial). Am J Respir Crit Care Med. 2005 Jan 15;171(2):129-36.

O'Byrne PM, et al. Low dose inhaled budesonide & formoterol in mild persistent asthma: the **OPTIMA** randomized trial. Am J Respir Crit Care Med. 2001 Oct 15;164(8 Pt 1):1392-7.

O'byrne PM, et al. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. Chest. 2006 Jun;129(6):1478-85. Long-term, once-daily treatment with low-dose budesonide improved both prebronchodilator and postbronchodilator FEV(1) in patients with recent-onset, persistent asthma, and reduced the loss of lung function over time (1 & 3yrs).

O'Byrne PM, Naya IP, Kallen A, et al. Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled beta2-agonists in achieving asthma control. Chest. 2008 Dec;134(6):1192-9. Epub 2008 Aug 8. Time with well-controlled asthma was improved by 19% (95% confidence interval [CI], 3 to 35%; p = 0.017) by adding formoterol, 24 microg/d, to therapy with budesonide, 200 microg/d, compared to 2% (95% CI, -9 to 12%; p=0.76) with therapy with budesonide, 800 microg/d, alone. The addition of formoterol to therapy with low-dose budesonide increases the probability of well-controlled asthma compared to a substantial increase (4X) in the dose of an ICS.

O'Byrne PM, Gauvreau G. **Phosphodiesterase-4** inhibition in COPD. Lancet. 2009Aug 29;374(9691):665-7.

O'Byrne PM, Lamm CJ, Busse WW, Tan WC, Pedersen S; START Investigators Group. The effects of inhaled **budesonide** on lung function in **smokers** and nonsmokers with mild persistent asthma. Chest. 2009 Dec;136(6):1514-20.

O'Byrne PM, Pedersen S, Carlsson LG, et al. **Risks of Pneumonia** in Asthmatic Patients Taking Inhaled Corticosteroids. Am J Respir Crit Care Med. 2010 Oct 1.

O'donnell DE, et al. Effect of **Fluticasone Propionate/Salmeterol** on Lung Hyperinflation and Exercise Endurance in COPD. Chest. 2006 Sep;130(3):647-56.

O'Driscoll BR and Beasley R. Avoidance of high concentration **oxygen in chronic obstructive pulmonary disease**. BMJ 2010 Oct 18; 341:c5549.

Ogale SS, Lee TA, Au DH, Boudreau DM, et al. **Cardiovascular Events** Associated With **Ipratropium** Bromide in COPD. Chest. 2009 Apr 10.We found an increased risk of CVEs associated with the use of ipratropium within the past 6 months. These findings are consistent with previous concerns raised about the cardiovascular safety of ipratropium bromide.

Ortiz-Alvarez O, Mikrogianakis A; **Canadian Paediatric Society**, Acute Care Committee. Managing the paediatric patient with an **acute asthma** exacerbation. Paediatr Child Health 2012;17:251-5.www.cps.ca/english/statements/AC/AC12-01.htm (accessed May 9, 2012).

Ostrom NK, Decotiis BA, et al. Comparative efficacy & safety of low-dose **fluticasone** propionate & **montelukast** in children with persistent asthma. J Pediatr.2005Aug;147(2):213-20.

Overbeek SE, et al. **Formoterol added** to low-dose budesonide has no additional antiinflammatory effect in asthmatic patients. Chest. 2005 Sep;128(3):1121-7. CONCLUSIONS: Our results demonstrate that BUD administered at a low dose has significant antiinflammatory effects in patients with mild asthma. No significant additional antiinflammatory effects could be demonstrated either by adding formoterol or by increasing the dose of BUD.

Panickar J, Lakhanpaul M, Lambert PC, et al. **Oral prednisolone** $^{10\text{-}20\text{mg od x 5days}}$ for preschool children with acute **virus-induced wheezing**. N Engl J Med. 2009 Jan 22;360(4):329-38. In preschool children (n=700) presenting to a hospital with mild-to-moderate wheezing associated with a viral infection, oral prednisolone was not superior to placebo.

Papi A, et al. **Beclomethasone/formoterol vs budesonide/formoterol** combination therapy in asthma. Eur Respir J. 2006 Nov 15; [Epub ahead of print] The new fixed combination of beclomethasone and formoterol 200/12ug in HFA Modulite((R)) pMDI is equivalent to the marketed combination of budesonide and formoterol 400/12ug in terms of efficacy and tolerability profile.

Papi A, Canonica GW, Maestrelli P, et al. BEST Study Group. Rescue use of **beclomethasone and albuterol in a single inhaler** for mild asthma. N Engl J Med. 2007 May 17;356(20):2040-52. In patients with mild asthma, the symptom-driven use of inhaled beclomethasone (250 microg) and albuterol (100 microg) in a single inhaler is as effective as regular use of inhaled beclomethasone (250 microg twice daily) and is associated with a lower 6-month cumulative dose of the inhaled corticosteroid.

Parameswaran K, Belda J, Rowe BH. Addition of **intravenous aminophylline** to beta2-agonists in adults with acute asthma. Cochrane Database Syst Rev. 2000;(4):CD002742.

Parshall MB, Schwartzstein RM, Adams L, et al. on behalf of the ATS Committee on Dyspnea. An Official American Thoracic Society (**ATS**) Statement: Update on the Mechanisms, Assessment, and Management of **Dyspnea**. Am J Respir Crit Care Med. 2012 Feb 15;185(4):435-452.

Pasqua F, Biscione G, Crigna G, et al. Combining **triple therapy** and pulmonary rehabilitation in patients with advanced **COPD**: A pilot study. Respir Med. 2009 Nov 3.

Paton J, et al. **Adrenal** responses to low dose synthetic ACTH (Synacthen) in kids receiving high dose inhaled fluticasone. Arch Dis Child. 2006Oct;91(10):808-13. Epub 2006Mar 23.

Paul I. M., Maselli J. H., Hersh A. L., et al. **Antibiotic Prescribing** During Pediatric Ambulatory Care Visits for Asthma. *Pediatrics*, 2011; DOI: 10.1542/peds.2011-0218

Pauwels RA, et al. **START** Investigators Group. Early intervention with **budesonide** in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003Mar 29;361(9363):1071-6.

Pauwels RA, et al. Effect of inhaled **formoterol and budesonide** on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (**FACET**) International Study Group. N Engl J Med. 1997 Nov 13;337(20):1405-11. Erratum in: N Engl J Med 1998 Jan 8;338(2):139.

Pauwels RA, et al; **RELIEF** Study investigators. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J. 2003 Nov;22(5):787-94.

Pavord ID, Cox G, Thomson NC, et al Safety and Efficacy of **Bronchial Thermoplasty** in Symptomatic, Severe Asthma. Am J Respir Crit Care Med. 2007 Sep 27; [Epub ahead of print] Bronchial thermoplasty is associated with a short-term increase in asthma-related morbidity. However, there is preliminary evidence of long-lasting improvement in asthma control.

Pearlman DS, et al. Once-daily **ciclesonide** improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. J Allergy Clin Immunol. 2005 Dec;116(6):1206-12.

Pedersen S, et al. A comparative study of inhaled **ciclesonide** 160 microg/day and fluticasone 176 microg/day in children with asthma. Pediatr Pulmonol. 2006 Oct;41(10):954-61.

Peters SP, Kunselman SJ, Icitovic N, et al. **Tiotropium** bromide step-up therapy for adults with uncontrolled **asthma**. (**TALC**) N Engl J Med 2010. DOI: 10.1056/NEJMoa1008770. n=174, 14 wk

Petsky HL, et al. Tailored interventions based on **exhaled nitric oxide** versus clinical symptoms for asthma in children & adults. Cochrane Database Syst Rev. 2009Oct7;(4):CD006340.

Petsky HL, Cates CJ, Lasserson TJ, et al. A systematic review and meta-analysis: tailoring asthma treatment on **eosinophilic markers** (exhaled nitric oxide or sputum eosinophils). Thorax. 2012 Mar;67(3):199-208.

Philp JC, Maselli J, Pachter LM, Cabana MD. **Complementary and Alternative** Medicine Use and Adherence With **Pediatric Asthma** Treatment. Pediatrics. 2012 Apr 9.

Pinnock H, Shah R. Asthma. BMJ. 2007 Apr 21;334(7598):847-50.

Pinnock Hilary, Kendall Marilyn, Murray Scott A, et al. **Living and dying with severe chronic obstructive pulmonary disease**: multi-perspective longitudinal qualitative study. BMJ 2011;342:doi:10.1136/bmj.d142 (Published 24 Jan 2011)

Poels PJ, et al. **Spirometry** in chronic obstructive pulmonary disease. BMJ. 2006 Oct 28;333(7574):870-1.

TOP

Pollart SM., Compton RM, Elward KS. Management of **Acute Asthma Exacerbations**. Am Fam Physician. 2011;84(1):40-47.
Poole P, Black PN. **Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease**. Cochrane Database Syst Rev. 2010 Feb 17;2:CD001287.
Postma DS, O`Byrne PM, Pedersen S. Comparison of the effect of low-dose **ciclesonide and fixed-dose fluticasone propionate and salmeterol** combination on long-term asthma control. Chest. 2011 Feb;139(2):311-8.
Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of **fraction of exhaled nitric oxide** (**FENO**): a double-blind, randomised controlled trial. Lancet 2011; 378: 983–90.
Price D, Musgrave SD, Shepstone L, et al. **Leukotriene antagonists** as first-line or add-on asthma-controller therapy. N Engl J Med. 2011 May 5;364(18):1695-707.
Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated **BODE index** and the **ADO** index**.** Lancet. 2009 Aug 29;374(9691):704-11.
Punnoose AR, Burke AE, Golub RM. JAMA **patient page. Childhood asthma**. JAMA. 012 Jan 25;307(4):421.
Qaseem A, Snow V, Shekelle P, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2007 Nov 6;147(9):633-8.
Qaseem A, Wilt TJ, Weinberger SE, et al. for the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society, and the European Respiratory Society. **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease**: A Clinical Practice Guideline **Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society**. Ann Intern Med. 2011 Aug 2;155(3):179-191.
Quon BS, FitzGerald JM, Lemière C, Shahidi N, Ducharme FM. **Increased versus stable doses of inhaled corticosteroids** for exacerbations of chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD007524. DOI: 10.1002/14651858.CD007524.pub2. There is very little evidence from trials in children. In adults with asthma on daily maintenance ICS, a self-initiated ICS increase to 1000 to 2000 mcg/day at the onset of an exacerbation is not associated with a statistically significant reduction in the risk of exacerbations requiring rescue oral corticosteroids. More research is needed to assess the effectiveness of increased ICS doses at the onset of asthma exacerbations (particularly in children).
Qureshi F, et al. Clinical efficacy of racemic **albuterol vs levalbuterol** for the treatment of acute pediatric asthma. Ann Emerg Med. 2005 Jul;46(1):29-36. (InfoPOEMs: Levalbuterol (Xopenex) is no more effective and no safer than albuterol in the treatment of moderate asthma exacerbations in children. These results are similar to the results printed on the product labeling for levalbuterol. In another study of severe asthma, there were fewer hospitalizations with levalbuterol than with albuterol treatment in patients (J Pediatr 2003:143:731-36). Given the 15-fold higher price of levalbuterol, it makes little sense to use it when albuterol is as effective. (LOE = 1b))
Rabe KF, et al. **Budesonide/formoterol** in a **single inhaler** for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006 Feb;129(2):246-56.
Rabe KF, et al. Effect of **budesonide/formoterol** for **reliever** therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 2006 Aug 26;368(9537):744-53.
Rabe KF, et al. **Roflumilast**--an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2005 Aug 13-19;366(9485):563-71.
Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a **combination of tiotropium and formoterol** to salmeterol and fluticasone in moderate COPD. Chest. 2008 Apr 10; [Epub ahead of print] Tiotropium plus formoterol were superior in lung function over the day compared to salmeterol plus fluticasone in patients with moderate COPD. Long-term studies in severe COPD are warranted to assess the relative efficacy of different treatment combinations.
Ram FS, Picot J, Lightowler J, Wedzicha JA. **Non-invasive positive pressure ventilation** for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004;(3):CD004104.
Ramsay CF, Pearson D, Mildenhall S, Wilson AM. Oral **montelukast in acute asthma exacerbations**: a randomised, double-blind, placebo-controlled trial. Thorax. 2010 Oct 18
Rees J. **Asthma** control in adults. BMJ. 2006 Apr 1;332(7544):767-71.
Restrepo RD, Wettstein R, Wittnebel L, Tracy M. AARC clinical practice guideline: **incentive spirometry**: 2011. Respir Care 2011 Oct;56(10):1600-4.
Rice KL, Dewan N, Bloomfield HE, et al. **Disease management program** for **chronic obstructive pulmonary disease:** a randomized controlled trial. Am J Respir Crit Care Med. 2010 Oct 1;182(7):890-6.
Ritz T, Rosenfield D, Steptoe A. Physical activity, lung function, and shortness of breath in daily life of individuals with asthma. Chest. 2010 May 14.
Rodrigo GJ, Castro-Rodriguez JA. **Anticholinergics** in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax. 2005 Aug 10. Conclusions: This review strongly suggests that the addition of multiple doses of inhaled ipratropium bromide to beta2-agonists seems indicated as the standard treatment in children, adolescent and adult patients with moderate to severe exacerbations of asthma in the emergency setting.
Rodrigo GJ, Nannini LJ. **Tiotropium** for the treatment of stable chronic obstructive pulmonary disease: A systematic review with meta-analysis. Pulm Pharmacol Ther. 2006 Mar 2
Rodrigo GJ. Rapid effects of **inhaled corticosteroids** in **acute asthma**: an evidence-based evaluation. Chest. 2006 Nov;130(5):1301-11. Data suggests that ICS present early beneficial effects (1 to 2 h) when they were used in multiple doses administered in time intervals </= 30 min over 90 to 120 min.
Rodrigo GJ, Castro-Rodriguez JA, Nannini LJ, et al. **Tiotropium** and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. Respir Med. 2009 Jun 23. [Epub ahead of print] Compared with control (placebo or salmeterol), tiotropium did not significantly increase the risk of adverse major cardiovascular events among COPD patients. Subgroup analysis suggested that smoking history can modify the risk of cardiovascular adverse events.
Rodrigo GJ, Castro-Rodriguez JA, Plaza V. Safety and Efficacy of Combined Long-Acting {beta}-Agonists and Inhaled Corticosteroids vs **Long-Acting {beta}-Agonists** Monotherapy for Stable COPD: A Systematic Review. Chest. 2009 Jul 24. [Epub ahead of print] Compared with LABAs, the magnitude of LABAs/ICS benefits did not reach the criteria for predefined clinical important effects, and were associated with serious adverse effects.
Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous **omalizumab** versus placebo as add on therapy to corticosteroids for children and adults with asthma: a systematic review. Chest. 2010 Aug 5. Data indicate that the efficacy of add on omalizumab in patients with moderate to severe allergic asthma is accompanied by an acceptable safety profile.
Rodrigo G, Pollack C, Rodrigo C, Rowe BH. **Heliox** for nonintubated acute asthma patients. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD002884.
Romieu I, Fabre A, Fournier A, Kauffmann F, Varraso R, Mesrine S, et al. **Postmenopausal hormone therapy** and **asthma onset** in the E3N cohort. Thorax. 2010 Feb 8.
Rossi A et al. Acute effects of **indacaterol** on lung hyperinflation in moderate COPD: A comparison with tiotropium. Respir Med. 2012 Jan;106(1):84-90.
Rutten FH et al; **Beta-Blocker**s May Reduce Mortality & Risk of Exacerbations in Patients With **Chronic Obstructive Pulmonary Disease**. Arch Intern Med. 2010;170(1
Ryan D, Price D, Musgrave SD, et al. Clinical and cost effectiveness of **mobile phone supported self monitoring** of asthma: multicentre randomised controlled trial. BM

TOP

Mar 23;344:e1756.
Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose **omalizumab** in patients with H1-antihistamine-refractory **chronic idiopathic urticaria**. J Allergy Clin Immunol. 2011 Sep;128(3):567-73.e1.
Salpeter S, Ormiston T, Salpeter E. Cardioselective **beta-blockers** for COPD. Cochrane Database Syst Rev. 2005 Oct 19;4:CD003566. Cardioselective beta- blockers, given to patients with COPD in the identified studies did not produce adverse respiratory effects. Given their demonstrated benefit in conditions such as heart failure, coronary artery disease and hypertension, cardioselective beta-blockers should not be routinely withheld from patients with COPD.
Salpeter SR, et al. Meta-analysis: **anticholinergics**, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med. 2006 Oct;21(10):1011-9. (InfoPOEMs: Anticholinergic treatment in patients with chronic obstructive pulmonary disease (COPD) produces better results than treatment with a beta-2 agonist. Studies comparing anticholinergic treatment with placebo have shown a greater decrease in the number of exacerbations. Studies comparing beta-2 agonist treatment with placebo have shown less benefit. In direct comparison with each other, there were 2.5 more exacerbations for every 100 patients treated with a beta-2 agonist instead of an anticholinergic. (LOE = 1a))
Salpeter SR, Buckley NS. Systematic Review of Clinical Outcomes in COPD: beta-Agonist Use Compared With **Anticholinergics** and Inhaled **Corticosteroids**. Clin Rev Allergy Immunol. 2006 Oct;31(2-3):219-30. In conclusion, inhaled anticholinergic bronchodilators and corticosteroids should be used to improve long-term clinical outcomes in patients with COPD. beta-Agonists increase respiratory deaths in COPD, possibly as a result of poorer disease control.
Salpeter SR, Wall AJ, Buckley NS. **Long-acting beta-agonists** with and without inhaled corticosteroids and **catastrophic asthma events**. Am J Med. 2010 Apr;123(4):322-8.e2.
Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in **non-smokers**. Lancet. 2009 Aug 29;374(9691):733-43.
Sander N, et al. **Dose counting** and the use of pressurized metered-dose inhalers: canisters running on empty. Ann Allergy Asthma Immunol. 2006 Jul;97(1):34-8.
Sanford M. **Roflumilast**: in chronic obstructive pulmonary disease. Drugs. 2010 Aug 20;70(12):1615-27. doi: 10.2165/11205930-000000000-00000.
Sano Y, Adachi M, Kiuchi T, Miyamoto T. Effects of nebulized sodium **cromoglycate** on adult patients with severe refractory asthma. Respir Med. 2005 Aug 8
Sauni R, Uitti J, Jauhiainen M, Kreiss K, Sigsgaard T, Verbeek JH. **Remediating buildings damaged by dampness and mould** for preventing or reducing respiratory tract symptoms, infections and asthma. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD007897. DOI: 10.1002/14651858.CD007897.pub2. We found moderate to very low-quality evidence that repairing mould-damaged houses and offices decreases asthma-related symptoms and respiratory infections compared to no intervention in adults.
Scarfone RJ, Zorc JJ, Angsuco CJ. Emergency physicians' prescribing of asthma controller medications. Pediatrics. 2006 Mar;117(3):821-7.
Schatz M, Dombrowski MP. Clinical practice. **Asthma in pregnancy**. N Engl J Med. 2009 Apr 30;360(18):1862-9.
Schuh S, et al. High-dose inhaled fluticasone does not replace **oral prednisolone** in children with mild to moderate acute asthma. Pediatrics. 2006 Aug;118(2):644-50.
Schuh S, et al. A comparison of inhaled fluticasone and **oral prednisone** for children with severe acute asthma. N Engl J Med. 2000 Sep 7;343(10):689-94.
Schuh S, Willan AR, Stephens D, et al. Can Montelukast Shorten Prednisolone Therapy in Children with Mild to Moderate Acute Asthma? A Randomized Controlled Trial. J Pediatr. 2009 Aug 3. Montelukast does not represent an adequate alternative to corticosteroids after outpatient stabilization in mild to moderate acute asthma.
Schuh S, Zemek R, Plint A, et al. **Magnesium** Use in Asthma Pharmacotherapy: A Pediatric Emergency Research Canada Study. Pediatrics. 2012 Apr 16.
Scicchitano R, et al. Efficacy & safety of **budesonide/formoterol single inhaler** vs a higher dose of budesonide in mod-severe asthma. Curr Med Res Opin. 2004 Sep;20(9):1403-18.
Seemungal TA, Wilkinson TM, Hurst JR, et al. **Long-term erythromycin** therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med. 2008 Dec 1;178(11):1139-47.
Sethi S, Jones PW, Theron MS, et al. PULSE Study group. **Pulsed moxifloxacin** for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respir Res. 2010 Jan 28;11:10. Erratum in: Respir Res. 2010;11:88.
Seymour JM, Moore L, Jolley CJ, et al. Outpatient **pulmonary rehabilitation** following acute exacerbations of COPD. Thorax. 2010 May;65(5):423-8.
Sharma Gulshan; Kuo Yong-Fang; Freeman Jean L.; et al. Outpatient Follow-up Visit and 30-Day **Emergency Department Visit and Readmission** in Patients Hospitalized for Chronic Obstructive Pulmonary Disease. Arch Intern Med. 2010;170(18):1664-1670.
Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily **budesonide** in patients with **early onset**, mild persistent asthma: results of the inhaled Steroid Treatment As Regular Therapy in early asthma (START) study. Annals of Allergy, Asthma and Immunology 2005; 94:48-54
Shefrin AE, Goldman RD. Use of **dexamethasone and prednisone** in acute asthma exacerbations in pediatric patients. Can Fam Physician. 2009 Jul;55(7):704-6. Both prednisone (1 to 2 mg/kg daily for 5 days) and dexamethasone (0.3 to 0.6 mg/kg daily for 1 to 5 days) are effective in reducing hospital admissions and unscheduled return to care, with minimal side effects.
Shorr AF, Sun X, Johannes RS, et al. Validation of a Novel **Risk Score** for Severity of Illness in **Acute Exacerbations of COPD**. (**BAP-65**) Chest. 2011 Nov;140(5):1177-83.
Short PM, Lipworth SIW, Elder DHJ, et al. Effect of **β blockers in treatment** of chronic obstructive pulmonary disease: a retrospective cohort study. BMJ 2011;342. (10 May 2011)
Short PM, Williamson PA, Elder DH, et al. The impact of **tiotropium on mortality** and exacerbations when added to inhaled corticosteroids and long-acting β-agonist therapy in COPD. Chest. 2012 Jan;141(1):81-6. The study suggests that the addition of tiotropium to ICSs and LABA therapy may confer benefits in reducing all-cause mortality, hospital admissions, and oral corticosteroid bursts in patients with COPD.
Silveira D'Avila R, Piva JP, Jose Cauduro Marostica P, Luis Amantea S. Early administration of two intravenous bolus of aminophylline added to the standard treatment of children with acute asthma. Respir Med. 2007 Sep 13; [Epub ahead of print] In children aged 2-5 years admitted to a PER with asthma, two intravenous doses of 5mg/kg of aminophylline given 6h apart did not change the length of stay in hospital, the number of nebulizations given or the duration of oxygen therapy required. We are unable to tell whether there would be benefit with higher doses of aminophylline designed to give levels in the usual therapeutic range.
Silverman M, et al. Safety and tolerability of inhaled budesonide in children (3yrs) in the Steroid Treatment As Regular Therapy in early asthma (**START**) trial. Pediatr Allergy Immunol. 2006 May;17 Suppl 17:14-20.
Silverman, Edwin K., Sandhaus, Robert A. **Alpha1-Antitrypsin Deficiency.** N Engl J Med 2009 360: 2749-2757
Silvers KM, Frampton CM, Wickens K, et al. **Breastfeeding** Protects against Current Asthma up to 6 Years of Age. J Pediatr. 2012 Jan 28.
Sin DD, Tashkin D, Zhang X, Radner F, Sjöbring U, Thorén A, Calverley PM, Rennard SI. Budesonide and the risk of **pneumonia**: a meta-analysis of individual patient data. Lancet. 2009 Aug 29;374(9691):712-9.
Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a system

TOP

and meta-analysis. JAMA. 2008 Sep 24;300(12):1439-50. **Inhaled anticholinergics** are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD.

Singh S, Amin AV, Loke YK. Long-term Use of Inhaled **Corticosteroids and the Risk of Pneumonia** in Chronic Obstructive Pulmonary Disease: A Meta-analysis. Arch Intern Med. 2009 Feb 9;169(3):219-229. Inhaled corticosteroids were associated with a significantly increased risk of any pneumonia (relative risk [RR], 1.60; 95% confidence interval [CI], 1.33-1.92 [P < .001]; I(2) = 16%) and serious pneumonia (1.71; 1.46-1.99 [P < .001]; I(2) = 0%) but without a significantly increased risk of pneumonia-related mortality (1.27; 0.80-2.03 [P = .31]; I(2) = 0%) or overall mortality (0.96; 0.86-1.08 [P = .51]; I(2) = 0%). Among patients with COPD, inhaled corticosteroid use for at least 24 weeks is associated with a significantly increased risk of serious pneumonia, without a significantly increased risk of death.

Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with **salmeterol/fluticasone propionate and tiotropium** bromide versus individual components in moderate to severe COPD. Thorax. 2008 Jul;63(7):592-8. Epub 2008 Feb 1.

Singh S, Loke YK, Enright PL, Furberg CD. **Mortality associated with tiotropium mist inhaler** not studied: Spriva HandiHaler in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis of randomised controlled trials. BMJ 2011;342:d3215.

Skoner DP, Maspero J, Banerji D; and the Ciclesonide Pediatric Growth Study Group. Assessment of the Long-term Safety of Inhaled **Ciclesonide** on **Growth** in Children With Asthma. Pediatrics. 2007 Dec 10; [Epub ahead of print]n=661 1yr. Ciclesonide demonstrated no detectable effect on childhood growth velocity, even at the highest dosage, which may ease concerns about systemic adverse events.

Skoner DP, Meltzer EO, Milgrom H, et al. Effects of **Inhaled Mometasone Furoate on Growth Velocity** and Adrenal Function: A Placebo-Controlled Trial in Children 4-9 Years Old with Mild Persistent Asthma. J Asthma. 2011 Aug 22. One year of treatment with a total daily dose of 100 µg of MF-DPI in the morning resulted in no significant difference, whereas a total daily dose of 200 µg of MF-DPI was associated with some changes in growth velocity when compared with placebo.

Slatore CG, Bryson CL, Au DH. The association of inhaled corticosteroid use with serum **glucose** concentration in a large cohort. Am J Med. 2009 May;122(5):472-8. Inhaled steroids are not associated with an increase in serum glucose concentrations in patients without diabetes. In patients with diabetes, slightly higher serum glucose levels were associated with higher doses of corticosteroids, increasing an average 1.82 mg/dL (0.101 mmol/L) for every 100 mcg increase in dose of steroid (in triamcinolone equivalents). This increase could be clinically relevant with high doses; fluticasone 1000 mcg per day would increase glucose an average of 72.8 mg/dL (4.04 mmol/L). The increase was higher in patients receiving medication for diabetes, an average 2.65 mg/dL (0.147 mmol/L). (LOE = 1b)

Slats AM, et al. Improvement in bronchodilation following deep inspiration after a course of **high-dose oral prednisone** in asthma. Chest. 2006 Jul;130(1):58-65.

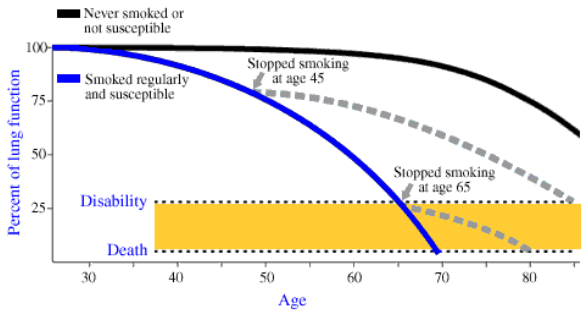
Smith AD, Cowan JO, Brassett, KP, et al. Use of exhaled **nitric oxide** measurements to guide treatment in chronic asthma. N Engl J Med 2005;352:2163-72. (InfoPOEMs: Using exhaled nitric oxide measurements to adjust inhaled corticosteroid doses allows patients to use a lower dose than the traditional approach based on symptoms and spirometry. Although there was no statistically significant differences regarding patient-oriented outcomes, all trends were consistent in favor of the fraction of nitric oxide measurement . (LOE = 1b-))

Smith C, Goldman RD. **Nebulizers versus pressurized metered-dose inhalers** in preschool children with wheezing. Can Fam Physician. 2012 May;58(5):528-30.

Smith, Scott D. **Diagnosis** of asthma in adults. CMAJ 2009 0: cmaj.080006

Smith FG, Perkins GD, Gates S, et al, for the **BALTI-2** study investigators. Effect of intravenous **β-2 agonist** (salbutamol) treatment on clinical outcomes in acute respiratory distress syndrome- ARDS (BALTI-2): a multicentre, randomised controlled trial. Lancet 2011; online Dec 12.

Smoking Cessation benefits: Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977 Jun 25;1(6077):1645-8.



Sonnenschein-van der Voort A, Jaddoe V, Raat H et al. **Fetal and Infant Growth** and Asthma Symptoms in Preschool Children: The Generation R Study. Am. J. Respir. Crit. Care Med. 2012; 185: 731-737.

Sood A, Qualls C, Schuyler M, et al. Low **Serum Adiponectin** Predicts Future Risk for Asthma in Women. Am J Respir Crit Care Med. 2012 Apr 6.

Soriano JB, Zielinski J, Price D. **Screening** for and early detection of chronic obstructive pulmonary disease. Lancet. 2009 Aug 29;374(9691):721-32.

Sorkness CA, et al. for the Childhood Asthma Research and Education Network of the NHLBI. Long-term comparison of 3 controller regimens (**fluticasone** 100 mug twice daily (fluticasone monotherapy), fluticasone 100 mug/salmeterol 50 mug in the morning and salmeterol 50 mug in the evening (PACT combination), and montelukast 5 mg in the evening) for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller Trial. (**PACT**) J Allergy Clin Immunol. 2006 Nov 29; [Epub ahead of print] Therefore, of the regimens tested, the PACT study findings favor fluticasone monotherapy in treating children with mild-moderate persistent asthma with FEV(1) >/= 80% predicted, confirming current guideline recommendations.

Sovani MP, et al. A benefit-risk assessment of inhaled **long-acting beta2-agonists** in the management of obstructive pulmonary disease. Drug Saf. 2004;27(10):689-715.

Søyseth V, Johnsen HL, et al. The Incidence of **Work-related Asthma-like Symptoms and Dust Exposure in Norwegian Smelters**. Am J Respir Crit Care Med. 2012 A

TOP

Spencer S, Evans DJ, Karner C, et al. **Inhaled corticosteroids** versus long-acting beta(2)-agonists for **chronic obstructive pulmonary disease**. Cochrane Database Syst Rev. 2011 Oct 5;10:CD007033. Placebo-controlled trials have established the benefits of both long-acting beta-agonist and inhaled corticosteroid therapy for COPD patients as individual therapies. This review, which included trials allowing comparisons between LABA and ICS, has shown that the two therapies confer similar benefits across the majority of outcomes, including the frequency of exacerbations and mortality. Use of long-acting beta-agonists appears to confer a small additional benefit in terms of improvements in lung function compared to inhaled corticosteroids. On the other hand, inhaled corticosteroid therapy shows a small advantage over long-acting beta-agonist therapy in terms of health-related quality of life, but inhaled corticosteroids also increase the risk of pneumonia.

Stallberg B, et al. **Potency ratio** fluticasone (Flixotide Diskus)/budesonide (Pulmicort Turbuhaler). Respir Med. 2006 Aug 2. From these data the potency difference between the present drug inhaler combinations, Flixotide Diskus & Pulmicort Turbuhaler, was calculated to be between 1.50:1 (95% CI 1.10:1-2.05:1) & 1.75:1 (CI 1.26:1-2.43:1) depending on if patients with insufficient steroid-response were excluded from the calculations or not. In these steroid-naive patients, the potency difference was evident only at low daily doses, below 200mcg.

Stelmach R, et al. Effect of treating **allergic rhinitis** with corticosteroids in patients with mild-to-moderate persistent asthma. Chest. 2005 Nov;128(5):3140-7.

Stephenson Anne; Seitz Dallas; Bell Chaim M.; et al. Inhaled **Anticholinergic Drug Therapy and the Risk of Acute Urinary Retention** in Chronic Obstructive Pulmonary Disease: A Population-Based Study. Arch Intern Med. 2011;171(10):914-920.

Stoller JK, Aboussouan LS. A Review of **Alpha-1 Antitrypsin Deficiency**. Am J Respir Crit Care Med. 2011 Sep 29.

Stordal K, et al. **Acid suppression** does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. Arch Dis Child. 2005 Sep;90(9):956-60. (InfoPOEMs: Suppressing acid in asthmatic children with minimal symptoms of reflux does not improve asthma. This study does not address whether this holds true for children with clinically significant reflux. (LOE = 2b))

Stout JW, et al. Classification of **asthma severity** in children: the contribution of pulmonary function testing. Arch Pediatr Adolesc Med. 2006 Aug;160(8):844-50.

Strunk RC, et al; for the **CAMP** Research Group. Mild to moderate asthma affects lung growth in children and adolescents. J Allergy Clin Immunol. 2006 Nov;118(5):1040-7. Mild to moderate asthma results in a pattern of airway obstruction that increases in magnitude from age 5 to 18 years.

Strunk RC, Sternberg AL, Szefler SJ, Zeiger RS, Bender B, Tonascia J; on behalf of the Childhood Asthma Management Program (**CAMP**) Research Group. Long-Term Budesonide or Nedocromil Treatment, Once Discontinued, Does Not Alter the Course of Mild to Moderate Asthma in Children and Adolescents. J Pediatr. 2009 Jan 22. [Epub ahead of print] Clinically meaningful improvements in the control of asthma and in airway responsiveness achieved during continuous treatment with inhaled corticosteroids do not persist after continuous treatment is discontinued.

Strunk RC, Bloomberg GR. **Omalizumab** for asthma. N Engl J Med. 2006 Jun 22;354(25):2689-95.

Subbarao P, Mandhane PJ, Sears MR. Asthma: **epidemiology, etiology and risk factors**. CMAJ. 2009 Sep 14. [Epub ahead of print]

Suissa S, Kezouh A, Ernst P. Inhaled Corticosteroids and the Risks of **Diabetes Onset and Progression**. Am J Med. 2010 Sep 24.

Summaries for patients. Chronic obstructive pulmonary disease: a clinical practice guideline. Ann Intern Med. 2011 Aug 2;155(3):I-35.

Sze MA, Dimitriu PA, Hayashi S, et al. The **lung tissue microbiome** in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;185:1073–1080.

Tan WC, et al. in **Caucasian versus Asian** patients with asthma: 3-year results of the **START** study.Respirology. 2006 Nov;11(6):767-775.

Tantisira KG, Lasky-Su J, Harada M, et al. **Genomewide association between GLCCI1** and response to **glucocorticoid therapy** in asthma. N Engl J Med 2011.

Tashkin DP, Celli B, Senn S, et al. **UPLIFT** Study Investigators. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2008 Oct 5. [Epub ahead of print] In patients with COPD, therapy with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV(1). (Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP. Mortality in the 4 Year Trial of Tiotropium (UPLIFT) in Patients with COPD. Am J Respir Crit Care Med. 2009 Sep 3.)

Tattersfield AE, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. Lancet. 2001 Jan 27;357(9252):257-61.

Tattersfield AE, et al. Exacerbations of **asthma**: a descriptive study of 425 severe exacerbations. The **FACET** International Study Group. Am J Respir Crit Care Med. 1999 Aug;160(2):594-9.

Teach SJ, et al. Improved asthma outcomes in a high-morbidity pediatric population: results of an emergency **department-based** randomized clinical trial. Arch Pediatr Adolesc Med. 2006 May;160(5):535-41.

Tegethoff M, Greene N, et al. **Inhaled Glucocorticoids during Pregnancy** and Offspring Pediatric Diseases: A National Cohort Study. Am J Respir Crit Care Med. 2011 Dec 28.

Teper AM, Colom AJ, Kofman CD, et al. Effects of inhaled **fluticasone** propionate in **children** less than 2 years old with recurrent wheezing. Pediatr Pulmonol. 2004 Feb;37(2):111-5.

Thakkar K, Boatright RO, Gilger MA, et al. **Gastroesophageal reflux and asthma in children: a systematic review.** Pediatrics. 2010 Apr;125(4):e925-30. Epub 2010 Mar 29.

To T, Wang C, Guan J, McLimont S, Gershon AS. What is the **Lifetime Risk** of Physician **Diagnosed** Asthma in Ontario, Canada? Am J Respir Crit Care Med. 2009 Nov 19.

Tofts RPH, Ferrer G, Oliveira E. How should one investigate a **chronic cough**? *Cleveland Clinic Journal of Medicine* 2011; 78(2):84-85, 89; doi:10.3949/ccjm.77a.10033.

Tomerak A, Vyas H, Lakenpaul M, et al. Inhaled beta2-agonists for treating non-specific **chronic cough** in children. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005373.

Townshend J, Hails S, McKean M. Management of asthma in **children**. BMJ. 2007 Aug 4;335(7613):253-7.

Townshend J, Hails S, McKean M. Diagnosis of asthma in **children**. BMJ. 2007 Jul 28;335(7612):198-202.

Trappenburg JC, Monninkhof EM, Bourbeau J, Trooster T, Schrijvers AJ, Verheij TJ, et al. Effect of an **action plan** with ongoing support by a case manager on exacerbation-related outcome in patients with **COPD**: a multicentre randomised controlled trial. Thorax 2011;66:977-84.

Turpeinen M, Nikander K, Pelkonen AS, et al. **Daily versus as-needed inhaled corticosteroid** for mild persistent asthma (The Helsinki early intervention childhood asthma study). Arch Dis Child. 2008 Aug;93(8):654-9. Epub 2007 Jul 18.

Upham BD, Mollen CJ, Scarfone RJ, Seiden J, Chew A, Zorc JJ. **Nebulized budesonide added** to standard pediatric emergency department treatment of acute asthma: a randomized, double-blind trial. Acad Emerg Med. 2011 Jul;18(7):665-73. Nebulized budesonide added to standard therapy in the treatment of acute asthma in children did not significantly improve asthma severity scores or reduce hospital admissions. (LOE = 1b)

Uronis H, McCrory DC, Samsa G, et al. Symptomatic **oxygen** for non-hypoxaemic chronic obstructive pulmonary disease**.** Cochrane Database Syst Rev. 2011 Jun 15;6:CD006429. Oxygen can relieve dyspnoea in mildly and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy.

U.S. Preventive Services Task Force. Screening for Chronic Obstructive Pulmonary Disease Using **Spirometry**: U.S. Preventive Services Task Force Recommendation St... Ann Intern Med. 2008 Mar 3; [Epub ahead of print] Do not screen adults for COPD using spirometry

TOP

VA/DoD Department of Veterans Affairs and Department of Defense. COPD Guideline 2007 . At www.healthquality.va.gov/Chronic_Obstructive_Pulmonary_Disease_COPD.asp on 27 Nov 2010.

Vaes AW, Annegarn J, Meijer K, et al. The Effects of a "New" **Walking Aid** on Exercise Performance in Patients With COPD: A Randomized Crossover Trial. Chest. 2012 May;141(5):1224-32. (modern draisine vs a rollator)

Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, et al. the **COMBO** study Group. Combination Therapy **Salmeterol/Fluticasone versus Doubling Dose of Fluticasone** in Children with Asthma. Am J Respir Crit Care Med. 2010 Jul 9.

Vaidyanathan S, Williamson P, Clearie K, et al. **Fluticasone Reverses Oxymetazoline Induced Tachyphylaxis** of Response and Rebound Congestion. Am J Respir Crit Care Med. 2010 Mar 4.

Van den Bruel A, Gailly J, Neyt M. Does **tiotropium** lower exacerbation and hospitalization frequency in COPD patients: results of a meta-analysis. BMC Pulm Med. 2010 Sep 21;10(1):50.

van der Meer V, et al. **Internet-based self-management plus education compared with usual care in asthma: a randomized trial.** Ann Intern Med. 2009 Jul 21;151(2):110-20.

van Gestel YR, Hoeks SE, Sin DD, et al. The Impact of Cardioselective Beta-Blockers on Mortality in Patients with COPD and Atherosclerosis. Am J Respir Crit Care Med. 2008 Jun 19. [Epub ahead of print] Cardioselective beta-blockers were associated with reduced mortality in COPD patients undergoing vascular surgery. In carefully selected patients with COPD, the use of cardioselective beta-blockers appears to be safe and associated with reduced mortality.

van Noord JA, et al. Effects of **tiotropium with and without formoterol** on airflow obstruction and resting hyperinflation in patients with COPD. Chest. 2006 Mar;129(3):509-17.

Vennera MD, et al. behalf of the Spanish Registry. **Omalizumab** Therapy in Severe Asthma: Experience from the Spanish Registry-Some New Approaches. J Asthma. 2012 Mar 23.

Vestbo J, et al.; TRISTSAN study group. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax. 2005 Apr;60(4):301-4.

Vestbo J, Anderson W, Coxson HO, et al. ; **ECLIPSE** investigators. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J. 2008 Apr;31(4):869-73. Epub 2008 Jan 23.

Vestbo J, Edwards LD, Scanlon PD, et al. **Changes in forced expiratory volume in 1 second** over time in COPD. N Engl J Med 2011. DOI: 10.1056/NEJMoa1105482

Vogelmeier C, et al. **Budesonide/formoterol maintenance & reliever**: an effective asthma treatment option? Eur Respir J. 2005 Nov;26(5):819-28. Erratum in: ERJ Dec;26(6):1191.

Vogelmeier C, Hederer B, Glaab T, et al. **Tiotropium versus salmeterol** for the prevention of exacerbations of COPD. **POET-COPD**. N Engl J Med 2011;364:1093-103.

Vogt Hartmut, Lindström Karolina, Bråbäck Lennart, et al. **Preterm Birth and Inhaled Corticosteroid Use** in 6- to 19-Year-Olds: A Swedish National Cohort Study. Pediatrics 2011; 127:6 1052-1059; published ahead of print May 9, 2011, doi:10.1542/peds.2010-3083

von Leupoldt A, Taube K, Lehmann K, et al. The impact of **anxiety and depression on outcomes of pulmonary rehabilitation** in patients with COPD. Chest. 2011 Mar 31.

Vuillermin PJ, Robertson CF, Carlin JB, Brennan SL, Biscan MI, South M. **Parent initiated prednisolone** (1mg/kg od x 3-5 days)for acute asthma in children of school age: randomised controlled crossover trial. BMJ 2010;340:c843.

Wagena EJ, Knipschild PG, et al. Efficacy of bupropion & nortriptyline for **smoking cessation** among people at risk for or with chronic obstructive pulmonary disease. Arch Intern Med. 2005 Oct 24;165(19):2286-92. CONCLUSIONS: Bupropion SR treatment is an efficacious aid to smoking cessation in patients with COPD. Nortriptyline treatment seems to be a useful alternative.

Wahidi MM, Kraft M. **Bronchial thermoplasty** for severe asthma. Am J Respir Crit Care Med. 2012 Apr 1;185(7):709-14.

Wahn U, et al. Relationship between pretreatment specific IgE and the response to **omalizumab** therapy. Allergy. 2009 Jul 21. [Epub ahead of print]

Walker S, Monteil M, Phelan K, Lasserson TJ, et al. **Anti-IgE omalizumab** for chronic asthma in adults & children. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003559.

Walters J, Walters E, Wood-Baker R. Oral **corticosteroids** for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005374. CONCLUSIONS: There is no evidence to support the long-term use of oral steroids at doses less than 10-15 mg prednisolone though some evidence that higher doses (>/= 30 mg prednisolone) improve lung function over a short period. Potentially harmful adverse effects e.g.. diabetes, hypertension, osteoporosis would prevent recommending long-term use at these high doses in most patients.

Walters JA, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic **corticosteroids for acute exacerbations** of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD001288. Treatment of an exacerbation of COPD with oral or parenteral corticosteroids significantly reduces treatment failure and the need for additional medical treatment and shortens hospital stay. It increases the rate of improvement in lung function and dyspnoea and the improvement continues during treatment, but there is a significantly increase in the risk of an adverse drug event occurring. The optimal dose and length of treatment regime needs to be better defined.

Walters JA, Turnock AC, Walters EH, et al. **Action plans** with limited patient education only for exacerbations of **chronic obstructive pulmonary disease.** Cochrane Database Syst Rev. 2010 May 12;5:CD005074.

Waschki B, Kirsten A, et al. **Physical Activity** Is the Strongest Predictor of All-Cause Mortality in Patients With COPD: A Prospective Cohort Study. Chest. 2011 Aug;140(2):331-42.

Watson WT, Gillespie C, et al. Small-group, interactive **education** and the effect on asthma control by children and their families. CMAJ. 2009 Aug 17. [Epub ahead of print]

Weatherall M, Wijesinghe M, et al. Meta-analysis of the risk of **mortality with salmeterol** and the effect of concomitant inhaled corticosteroid therapy. Thorax. 2010 Jan;65(1):39-43.

Wedzicha JA, Calverley PM, Seemungal TA, **INSPIRE** Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008 Jan 1;177(1):19-26. Epub 2007 Oct 4. n=1,323 patients mean age, 64 yr, post-bronchodilator FEV1, 39% predicted were randomized in this 2-year trial. We found no difference in exacerbation rate between salmeterol/fluticasone propionate and tiotropium. More patients failed to complete the study while receiving tiotropium. A small statistically significant beneficial effect was found on health status, with an unexpected finding of lower deaths in salmeterol/fluticasone propionate-treated patients.

Wells KE, Peterson EL, Ahmedani BK, et al. The relationship between combination inhaled **corticosteroid and long-acting β-agonist** use and severe asthma exacerbations in a diverse population. J Allergy Clin Immunol. 2012 May;129(5):1274-1279.e2.

Welsh EJ, Bara A, Barley E, Cates CJ. **Caffeine** for asthma. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD001112.

Wen MC, et al. Efficacy and tolerability of anti-asthma **herbal medicine** intervention in adult patients with moderate-severe allergic asthma. J Allergy Clin Immunol. 200

TOP

Sep;116(3):517-24. CONCLUSION: Anti-asthma herbal medicine intervention appears to be a safe and effective alternative medicine for treating asthma. In contrast with prednisone, **ASHMI** had no adverse effect on adrenal function and had a beneficial effect on T(H)1 and T(H)2 balance.

Wechsler ME, Wong DA, Miller MK, Lawrence-Miyasaki L. **Churg-strauss syndrome** in patients treated with **omalizumab**. Chest. 2009 Aug;136(2):507-18. Epub 2009 May 1.

Wechsler ME, Kunselman SJ, Chinchilli VM, et al. National Heart, Lung and Blood Institute's Asthma Clinical Research Network. Effect of **beta2-adrenergic receptor polymorphism** on response to longacting beta2 agonist in asthma (LARGE trial): a **genotype-stratified**, randomised, placebo-controlled, crossover trial. Lancet. 2009 Nov21;374(9703):1754-64.

Wechsler ME, Kelley JM, Boyd IOE, et al. Active **albuterol (salbutamol)** or placebo, sham acupuncture, or no intervention in asthma. N Engl J Med 2011;365:119-26

Welsh EJ, Cates CJ. **Formoterol versus short-acting beta-agonists as relief medication for adults and children with asthma.** Cochrane Database Syst Rev. 2010 Sep 8;9:CD008418. In adults, formoterol was similar to short-acting beta(2)-agonists when used as a reliever, and showed a reduction in the number of exacerbations requiring a course of oral corticosteroids. Clinicians should weigh the relatively modest benefits of formoterol as-needed against the benefits of single inhaler therapy and the potential danger of long-term use of long-acting beta(2)-agonists in some patients. We did not find evidence to recommend changes to guidelines that suggest that long-acting beta(2)-agonists should be given only to patients already taking inhaled corticosteroids.There was insufficient information reported from children in the included trials to come to any conclusion on the safety or efficacy of formoterol as relief medication for children with asthma.

Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of **budesonide/formoterol added to tiotropium** in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Oct 15;180(8):741-50. Epub 2009 Jul 30. (n=660 over 12 weeks)

Williams Kirsten M.; Chien Jason W.; Gladwin Mark T.; et al. **Bronchiolitis Obliterans** After Allogeneic Hematopoietic Stem Cell Transplantation. JAMA. 2009;302(3):306-314.

Wilt TJ, Niewoehner D, Kim C, et al. Use of **spirometry** for case finding, diagnosis, and management of chronic obstructive pulmonary disease (**COPD**). Evid Rep Technol Assess (Summ). 2005 Aug;(121):1-7. http://hiru.mcmaster.ca/PLUS_BATCHES/batch173_110905/8314.pdf

Wolthers OD, Walters EG. Short-Term Lower Leg Growth in 5- to 11-Year-Old Asthmatic Children Using Beclomethasone Dipropionate Inhalers With Chlorofluorocarbon or Hydrofluoroalkane Propellants: A 9-Week, Open-Label,Randomized, Crossover, Noninferiority Study. Clin Ther. 2011 Jul 22.

Wong CH, et al. **Gastro-oesophageal reflux** disease in 'difficult-to-control' asthma: prevalence and response to treatment with acid suppressive therapy. Aliment Pharmacol Ther. 2006 May 1;23(9):1321-7.

Wong CX, Carson KV, Smith BJ. **Home care by outreach nursing for chronic obstructive pulmonary disease.** Cochrane Database Syst Rev. 2011 Mar 16;3:CD000994. Outreach nursing programmes for COPD improved disease-specific HRQL.

Wong CX, Carson KV, Smith BJ. **Home care by outreach nursing for chronic obstructive pulmonary disease**. Cochrane Database Syst Rev. 2012 Apr 18;4:CD000994. Outreach nursing programmes for COPD improved disease-specific HRQL. However the effect on hospitalisations was heterogeneous, reducing admissions in one study, but increasing them in others, therefore we could not draw firm conclusions for this outcome.

Woods ER, Bhaumik U, Sommer SJ, et al. **Community asthma initiative**: evaluation of a quality improvement program for comprehensive asthma care. Pediatrics. 2012 Mar;129(3):465-72.

Wouters EF, Postma DS, Fokkens B, et al. **COSMIC** (COPD and Seretide: a Multi-Center Intervention and Characterization) Study Group. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with **COPD** causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax. 2005 Jun;60(6):480-7. CONCLUSIONS: Withdrawal of FP in COPD patients using SFC resulted in acute and persistent deterioration in lung function and dyspnoea and in an increase in mild exacerbations and percentage of disturbed nights. This study clearly indicates a key role for ICS in the management of COPD as their discontinuation leads to disease deterioration, even under treatment with a LABA.

Writing Committee for the American Lung Association Asthma Clinical Research Centers. Holbrook JT, Wise RA, Gold BD, et al. **Lansoprazole** for children with poorly controlled asthma: a randomized controlled trial. JAMA. 2012;307(4):373-381. PPIs does not improve symptom control in children with asthma.

Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD002991. Patients and clinicians should balance the potential benefits of inhaled steroids in COPD (reduced rate of exacerbations, reduced rate of decline in quality of life), against the known increase in local side effects (oropharyngeal candidiasis and hoarseness). The risk of long term adverse effects is unknown.

Yang, Ya-Wen, Chen, Yi-Hua, Wang, Kuo-Hsien, et al. Risk of **herpes zoster** among patients with chronic obstructive pulmonary disease: a population-based study. CMAJ 2011 183: E275-280.

Zeiger RS, Szefler SJ, Phillips BR, et al.; for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Response profiles to **fluticasone** and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol. 2006 Jan;117(1):45-52.

Zeiger RS et al. **Daily or intermittent budesonide** in preschool children with recurrent wheezing. (**MIST**) N Engl J Med 2011 Nov 24; 365:1990.

Zemek RL, et al. Systematic review of randomized controlled trials examining **written action plans** in children: what is the plan? Arch Pediatr Adolesc Med. 2008 Feb;162(2):157-63. Although there are limited data to firmly conclude that provision of an action plan is superior to none, there is clear evidence suggesting that symptom-based plans are superior to peak flow-based plans in children and adolescents.

Zemek R, Plint A, Osmond MH et al. **Triage Nurse Initiation of Corticosteroids** in Pediatric Asthma Is Associated With Improved Emergency Department Efficiency. Pediatrics. 2012 Mar 19

Zhang L, Axelsson I, Chung M, Lau J. **Dose Response of Inhaled Corticosteroids in Children** With Persistent Asthma: A Systematic Review. Pediatrics. 2010 Dec 6.

Zhou Yumin, Hu Guoping, Wang Dali, et al. **Community based integrated intervention** for prevention and management of chronic obstructive pulmonary disease (COPD) in Guangdong, China: cluster randomised controlled trial. BMJ 341:doi:10.1136/bmj.c6387 (Published 1 Dec 2010).

Web sites:

Asthma UK www.asthma.org.uk; Allergy UK www.allergyuk.org; Lung & Asthma Information Agency www.laia.ac.uk.

Canadian Asthma Consensus Guidelines web site http://www.asthmaguidelines.com

Canadian Network For Asthma Care (CNAC) http://www.cnac.net?english/clinics.html

TOP

TOP

INHALATIONAL DEVICES and MONITORING TOOLS

References:

A Guide to Spirometry for Primary Care Physicians by Dr. J. Lowry

Burchett DK, Darko W, Zahra J, et al. Mixing and compatibility guide for commonly used aerosolized medications. Am J Health-Syst Pharm. 2010;67:227-30.

Choosing a Spacer Device for MDIs. Pharmacist's Letter Sept. 2008.

Daman HR. Pulmonary function testing: use of the peak expiratory flow rate in an out-patient or office setting. J Asthma. 1984;21(5):331-7.

Dhuper S, Chandra A, Ahmed A, et al. Efficacy and cost comparisons of bronchodilatator administration between **metered dose inhalers with disposable spacers and nebulizers** for acute asthma treatment. J Emerg Med. 2011 Mar;40(3):247-55.

Doan Q, Shefrin A, Johnson D. **Cost-effectiveness of Metered-Dose Inhalers** for Asthma Exacerbations in the Pediatric Emergency Department. Pediatrics 2011 0: peds.2010-2963

Dolovich MB, Ahrens RC, Hess DR, et al. Device selection & outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005 Jan;127(1):335-71.

Dolovich MB, Dhand R. **Aerosol drug delivery**: developments in device design and clinical use. Lancet. 2011 Mar 19;377(9770):1032-45.

Pharmacist's Letter. Tips for correct use of Metered-dose Inhalers (MDIs). June 2007.

RxFiles Asthma Pharmacotherapy 2003; RxFiles Asthma & COPD Pharmacotherapy Comparison Chart 2006 www.RxFiles.ca

Sander N, et al. Dose counting & the use of pressurized metered-dose inhalers: canisters running on empty. Ann Allergy Asthma Immunol. 2006 Jul;97(1):34-8.

Schultz A et al. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. Pediatrics 2010 Dec; 126:e1493.

Self TH, Pinner NA, Sowell RS, Headley AS. Does it really matter what volume to exhale before using asthma inhalation devices?. J Asthma. 2009 Apr;46(3):212-6. Both patients and health care professionals need education to help ensure correct use of MDI and other asthma inhalation devices, including instruction to first **exhale** gently to functional residual capacity (FRC) or residual volume (RV) before inhaling the medication.

Sims MW. **Aerosol therapy** for obstructive lung diseases: device selection and practice management issues. Chest. 2011 Sep;140(3):781-8.

Smith C, Goldman RD. **Nebulizers versus pressurized metered-dose inhalers** in preschool children with wheezing. Can Fam Physician. 2012 May;58(5):528-30.

www.inspiratory.com "In-check DIAL" bibliography

TOP

Extras: **Rimonabant ACOMPLIA** –(not in Canada) cannabinoid receptor 1 blocker; 36% complete smoking cessation in final 4 wks of a 10 wk trial Dose: 20mg/d SE: nausea, **depression**, anxiety & ↓ weight. [xlviii,xlix,l] ??Clonidine use
Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch Gen Psychiatry. 2009 Nov;66(11):1253-62. {Nicotine lozenge, bupropion, and bupropion plus lozenge produced effects that were comparable with those reported in previous research, the nicotine patch plus lozenge produced the greatest benefit relative to placebo for smoking cessation.}

e-Cigaretes: 1) nicotine containing electronic cigarettes (misnomer as aerosolizing delivery device + cartridge). They are illegal in Canada. Current controversies with regulation in the USA. Counsel patients to avoid; alternate products/approaches available for smoking cessation. 2) Concerns: a) risk becoming starter product & skirt smoke free laws, b) potential toxicities, c) lack evidence for benefit as smoking cessation aid & strong potential to ↑ addiction, d) diversion of devices for use in delivering alternate drugs of abuse. e) short term use found to have adverse physiological effects, increased flow resistance and decreased FeNO. f.) toxic and carcinogenic compounds still delivered in e-cigarettes but in lower concentration than traditional cigarettes

Cytisine: Derived from an extract of golden rain acacia seeds; (1.5 mg oral tablets) in 740 adults who smoked ≥ 10 cigarettes/day and were willing to attempt to stop smoking permanently. Patients were randomized to cytisine vs. placebo for 25 days. The dose was 6 tablets for the first 3 days, followed by 5 tablets/day on days 4-12, 4 tablets/day on days 13-16, 3 tablets/day on days 17-20, and finally 2 tablets/day on days 21-25. All patients received minimal counseling during 4 clinical visits and 3 telephone calls over 12 months. Cytisine is currently available in Russia and Poland (at the equivalent of $6 to $15 per course). [West 2011]

References TOBACCO / SMOKING CESSATION PHARMACOTHERAPY:

[1] MicroMedex 2011; Lexi Drugs 2011
[2] Therapeutic Choices 5th edition 2007
[3] Henningfield J, Reginald V, August R, et al. Pharmacotherapy for Nicotine Dependence. CA Cancer J Clin 2005;55:281-299
[4] Morales-Suarez-Varela MM, Bille C, Christensen K, Olsen J. Smoking habits, nicotine use, and congenital malformations. Obstet Gynecol. 2006 Jan;107(1):51-7.
[5] Ludvig J, Miner B, Eisenberg M. Smoking Cessation in patients with coronary artery disease. AHJ 2004;149(4):565-570.
[6] Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation.Cochrane Database Syst Rev. 2004;(3):CD000146.
[7] Silagy C, Lancaster T, Stead L, et al. Nicotine replacement therapy for smoking cessation. The Cochrane Database of Systemic Reviews 2004;3
[8] Lam W, Sze PC, Sacks HS, Chalmers TC. Meta-analysis of randomised controlled trials of nicotine chewing-gum. Lancet. 1987 Jul 4;2(8549):27-30.
[9] Jorenby DE, A controlled trial of sustained-release **bupropion, a nicotine patch, or both** for smoking cessation. N Engl J Med. 1999 Mar 4;340(9):685-91. .
[10] Chatkin JM, Mariante de Abreu C, Haggstram FM, et al.. Abstinence rates and predictors of outcome for smoking cessation: do Brazilian smokers need special strategies? Addiction. 2004 Jun;99(6):778-84.
[11] Simon JA, Duncan C, Carmody TP, Hudes ES. Bupropion for smoking cessation: a randomized trial. Arch Intern Med. 2004 Sep 13;164(16):1797-803.
[12] Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med. 1996 Dec 12;335(24):1792-8. (n=584, 14 wks)
[13] http://heartdisease.about.com/cs/riskfactors/a/rimonabant_p.htm
[14] Hughes J, Stead L, Lancaster T. Antidepressants for Smoking Cessation. The Cochrane Database of Systemic Reviews 2004;4. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD000031.
[15] Paluck EC, McCormack JP, Ensom MH, Levine M, Soon JA, Fielding DW. Outcomes of bupropion therapy for smoking cessation during routine clinical use. Ann Pharmacother. 2006 Feb;40(2):185-90.
[16] Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J. 2003 May;24(10):946-55.(n=629, 52 wks)
[17] Regier L, Jensen B. Can Zyban be given with SSRIs in RxFiles Q&A Summary. Accessed at: http://www.rxfiles.ca/acrobat/zyban%2Dssri%2Dq%26a.pdf
[18] Medical Letter 2006. 48;66-68.
Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. **Cochrane** Database Syst Rev. 2010 Dec 8;12:CD006103. **Varenicline** at standard dose increased the chances of successful long-term smoking cessation between two- and threefold compared with pharmacologically unassisted quit attempts. Lower dose regimens also conferred benefits for cessation, while reducing the incidence of adverse events. More participants quit successfully with varenicline than with bupropion. Two open-label trials of varenicline versus NRT suggested a modest benefit of varenicline but confidence intervals did not rule out equivalence. Limited evidence suggests that varenicline may have a role to play in relapse prevention. The main adverse effect of varenicline is nausea, but mostly at mild to moderate levels and tending to subside over time. Possible links with serious adverse events, including depressed mood, agitation and suicidal thoughts, have been reported but are so far not substantiated.There is a need for further independent community-based trials of varenicline, to test its efficacy and safety in smokers with varying co-morbidities and risk patterns. There is a need for further trials of the efficacy of treatment extended beyond 12 weeks. **Cytisine** may also increase the chances of quitting, but the evidence at present is inconclusive.
[19] Gonzales D, Rennard SI, Nides M, et al; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):47-55. (InfoPOEMs: Varenicline (Chantix) therapy for 12 weeks is significantly more effective than placebo at maintaining smoking abstinence at 52 weeks. Varenicline may also be marginally more effective than bupropion SR. Reported success rates are likely to be higher than real-world settings. (LOE = 1b))
[20] Jorenby DE, Hays JT, Rigotti NA, et al.; Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):56-63.
[21] Tonstad S, Tonnesen P, Hajek P, et al. Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):64-71.
[22] Wisner KL, Hanusa BH, Perel JM, Peindl KS, et al. Postpartum depression: a randomized trial of sertraline versus nortriptyline. J Clin Psychopharmacol. 2006 Aug;26(4):353-60.
[23] Weissman AM, Levy BT, Hartz AJ, et al. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry. 2004 Jun;161(6):1066-78.
[24] Wagena E, et al. Efficacy of Bupropion & Nortriptyline for Smoking Cessation Among People at Risk for or with Chronic Obstructive Pulmonary Disease. Arch Intern Med 2005;165:2286-2292 (n=225; 12 wks).
[25] Haggstram FM, Chatkin JM, et al. A controlled trial of nortriptyline, bupropion SR & placebo for smoking cessation: preliminary results. Pulm Pharmacol Ther. 2006;19(3):205-9. Epub 2006 Mar 6.
[26] Henningfield J, Reginald V, August R, et al. Pharmacotherapy for Nicotine Dependence. CA Cancer J Clin 2005;55:281-299.
[27] Lyon ER. A review of the effects of nicotine on schizophrenia and antipsychotic medications. Psychiatr Serv 1999 Oct;50(10):1346-50
[28] Critchley J, Capewell S. Mortality Risk Reduction Associated with Smoking Cessation in Patients with Coronary Heart Disease. JAMA 2003; 290(1):86-97.
[29] Weblinks: http://www.healthknowledgecentral.org/onepagers/smoking.pdf; http://www.quitnet.com/Library/Guides/NRT/lozenge_specifics.jtml
[30] Ranney L, Melvin C, Lux L et al. Systematic Review: Smoking cessation Intervention Strategies for adults and adults in special populations. Ann Intern Med. 2006 Sep 5; [Epub ahead of print] Early Release – Accessed online at http://www.annals.org/cgi/content/full/0000605-200612050-00142v1
[31] Critchley J, Capewell S. Mortality Risk Reduction Associated with Smoking Cessation in Patients with Coronary Heart Disease. JAMA 2003; 290(1):86-97.
[32] Godtfredsen N, Prescott E, Osler M. Effect of Smoking Reduction on Lung Cancer Risk. JAMA 2005;294:1505-1510(n=19,714; 31 yrs)
[33] Doll R, Peto R, Boneham J. Mortality in relation to smoking:50 years observations on male British doctors.BMJ 2004;328:1519-1529 (n=34,439, 50yrs)
Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. Worldwide burden of disease from exposure to **second-hand** smoke: a retrospective analysis of data from 192 countries. Lancet. 2010 Nov 25.
[34] Wilson K, Gibson N, Willan A, Cook D. Effect of Smoking Cessation on Mortality After Myocadial Infarction: Meta-analysis of Cohort Studies. Arch Intern Med 2000; 160; 939-944
[35] Johnson BA, Ait-Daoud N, Akhtar FZ, Javors MA. Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: an RCT. Arch Intern Med. 2005 Jul 25;165(14):1600-5.
[36] An LC, et al. Benefits of **telephone** care over primary care for smoking cessation: a randomized trial.Arch Intern Med. 2006 Mar 13;166(5):536-42. (InfoPOEMs: A telephone-based counseling program is effective at helping self-selected older men quit smoking. The men in this study were veterans who had smoked for an average of 40 years, and 1 in 8 was able to quit for at least 6 months. (LOE = 1b))
[37] Chaudhuri R, et al. Effects of Smoking Cessation on Lung Function and Airway Inflammation In Smokers with Asthma. Am J Respir Crit Care Med. 2006 Apr 27; [Epub ahead of print] Six weeks after smoking cessation, smokers with asthma achieved considerable improvement in lung function and a fall in sputum neutrophil count compared to smokers who continued to smoke. These findings highlight the importance of smoking cessation in asthma.
[38] Houston TK, et al. Active and passive smoking and development of **glucose intolerance** among young adults in a prospective cohort: CARDIA study. BMJ. 2006 May 6;332(7549):1064-9. Epub 2006 Apr 7.
[39] Lancaster T, Hajek P, Stead LF, West R, Jarvis MJ. Prevention of relapse after quitting smoking: a systematic review of trials. Arch Intern Med. 2006 Apr 24;166(8):828-35
[40] Zhu SH, et al. Evidence of real-world effectiveness of a telephone quitline for smokers.N Engl J Med. 2002 Oct 3;347(14):1087-93.
[41] Healton CG, et al. Smoking, obesity, & their co-occurrence in the USA: cross sectional analysis. BMJ. 2006 May 12; 23.5% of adults were obese, 22.7% smoked, and **4.7% smoked and were obese**.
[42] Tobacco Use: Prevention, Cessation, and Control. Agency for Healthcare Research and Quality; US Department of Heath and Human Services http://www.ahrq.gov/clinic/tp/tobusetp.htm
[43] Shaw LJ, Raggi P, Callister TQ, Berman DS. Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers. Eur Heart J. 2006 Apr;27(8):968-75. Epub 2006 Jan 27.
[44] Teo KK, et al.; behalf of the INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet. 2006 Aug 19;368(9536):647-58.
[45] Wen W, et al. **Environmental tobacco** smoke and mortality in Chinese women who have never smoked: prospective cohort study. BMJ. 2006 Aug 19;333(7564):376. Epub 2006 Jul 12.
[46] Anthonisen NR, et al; **Lung Health Study** Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005 Feb 15;142(4):233-9. Summary for patients in: Ann Intern Med. 2005 Feb 15;142(4):I12.
[47] Heatherton, TF, Kozlowski LT, Frecker, RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: A revision of the **Fagerstrom** Tolerance Questionnaire. Brit J Add. 1991; 86:1119-1127. {Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom tolerance questionnaire. J Behav Med. 1989;12:159-82.} http://www.wfts.org/programs_and_services/images/Fagerstrom_Test.pdf

Modified Fagerström Test for Nicotine Dependence

TOP

1. How soon after you wake up do you smoke your first cigarette?
Within 5 minutes (3 points)
5 to 30 minutes (2 points)
31 to 60 minutes (1 point)
After 60 minutes (0 points)

2. Do you find it difficult not to smoke in places where you shouldn't, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?
Yes (1 point)
No (0 points)

3. Which cigarette would you most hate to give up; which cigarette do you treasure the most?
The first one in the morning (1 point)
Any other one (0 points)

4. How many cigarettes do you smoke each day?
10 or fewer (0 points)
11 to 20 (1 point)
21 to 30 (2 points)
31 or more (3 points)

5. Do you smoke more during the first few hours after waking up than during the rest of the day?
Yes (1 point)
No (0 points)

6. Do you still smoke if you are so sick that you are in bed most of the day, or if you have a cold or the flu and have trouble breathing?
Yes (1 point)
No (0 points)

Scoring: 7 to 10 points = highly dependent; 4 to 6 points = moderately dependent; less than 4 points = minimally dependent.

FIGURE 1. Modified Fagerström test for evaluating intensity of physical dependence on nicotine.
Adapted with permission from Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86:1119-27.

TOBACCO / SMOKING CESSATION PHARMACOTHERAPY Extra articles:

Agboola S, McNeill A, Coleman T, Leonardi Bee J. A systematic review of the effectiveness of **smoking relapse prevention** interventions for abstinent smokers. Addiction. 2010 Aug;105(8):1362-80.

Akuete K, Oh SS, Thyne S, et al. Ethnic Variability in **Persistent Asthma After In Utero** Tobacco Exposure. Pediatrics. 2011 Aug 22.

Alpert Hillel R, Connolly Gregory N, Biener Lois. A prospective cohort study **challenging the effectiveness (NRT treatment)** of population-based medical intervention for smoking cessation. Tob Control tobaccocontrol-2011-050129. Online First: 10 January 2012.

Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A,Robinson G, Beasley R. THE EFFECTS OF **CANNABIS** ON PULMONARY STRUCTURE, FUNCTION AND SYMPTOMS. Thorax. 2007 Jul 31; [Epub ahead of print] Smoking cannabis was associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. In contrast, cannabis smoking was seldom associated with macroscopic emphysema. The 1:**2.5 to 5 dose equivalence between cannabis joints and tobacco cigarettes** for adverse effects on lung function is of major public health significance.

Allen MH, Debanné M, Lazignac C, et al. Effect of Nicotine Replacement Therapy on Agitation in Smokers With **Schizophrenia**: A Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry. 2011 Jan 18.

Alverson, Clinton J., Strickland, Matthew J., Gilboa, Suzanne M., et al. **Maternal Smoking and Congenital Heart Defects** in the Baltimore-Washington Infant Study. Pediatrics 2011 127: e647-e653

Alwan S, Reefhuis J, Botto LD, Rasmussen SA, Correa A, Friedman JM; National Birth Defects Prevention Study. Maternal use of **bupropion** and risk for **congenital heart defects**. Am J Obstet Gynecol. 2010 Apr 22.

American Lung Association. An emerging deadly trend: **waterpipe tobacco** use. Tobacco policy trend alert. 2007. Available at: http://slati.lungusa.org/reports/Trend%20Alert_Waterpipes.pdf Accessed July 8, 2010.

Aubin HJ, Bobak A, Britton JR, et a. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial. Thorax. 2008 Feb 8; [Epub ahead of print] The Week 52 CAR (NRT,Weeks 8-52; varenicline,Weeks 9-52) was 26.1% for varenicline and 20.3% for NRT (OR 1.40, 95% CI, 0.99 to 1.99, p=0.056). Varenicline significantly reduced craving (p<0.001), withdrawal symptoms (p<0.001) and smoking satisfaction (p<0.001) versus NRT. The outcomes of this registered clinical trial (NCT00143325) established that abstinence from smoking was greater, and craving, withdrawal symptoms and smoking satisfaction less, at the end of treatment with varenicline than with transdermal nicotine.

Audrain-McGovern Janet, Stevens Sarah, Murray Pamela J., et al. The Efficacy of **Motivational Interviewing Versus Brief Advice** for Adolescent Smoking Behavior Change. Pediatrics 2011; 128:1 e101-e111; doi:10.1542/peds.2010-2174.

Avdalovic MV, Murin S. **Electronic cigarettes**: no such thing as a free lunch...Or puff. Chest. 2012 Jun;141(6):1371-2.

Aveyard P, West R. **Managing smoking cessation**. BMJ. 2007 Jul 7;335(7609):37-41.

Aveyard P, Johnson C, Fillingham S, Parsons A, Murphy M. **Nortriptyline** plus nicotine replacement versus placebo plus **nicotine** replacement for smoking cessation: pragmatic randomised controlled trial. BMJ. 2008 Apr 27; [Epub ahead of print] Nortriptyline and nicotine replacement therapy are both effective for smoking cessation but the effect of the combination is less than either alone and evidence is lacking that combination treatment is more effective than either alone.

Baardman ME, Kerstjens-Frederikse WS, et al. Combined adverse effects of maternal **smoking and high body mass index** on heart development in offspring: evidence for interaction? Heart. 2012 Jan 30.

Bartecchi C, et al. Reduction in the incidence of acute myocardial infarction associated with a **citywide smoking ordinance**. Circulation. 2006 Oct 3;114(14):1490-6. Epub 2006 Sep 25. (InfoPOEMs: This observational study found that a citywide smoking ban was associated with a reduction in the incidence of acute myocardial infarction (AMI) by approximately 70 per 100,000 person-years (that is, approximately 1 fewer AMI for every 1400 persons per year). Share this information with local politicians and other community leaders who are resisting curbs on smoking. Another study by the Centers for Disease Control and Prevention found that a smoking ban in El Paso, Texas, had no negative economic consequences for bars and restaurants.* *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5307a2.htm (LOE = 4))

Basu Sanjay, Stuckler David, Bitton Asaf. Projected effects of **tobacco smoking on worldwide tuberculosis** control: mathematical modelling analysis. BMJ 2011;343:d5506 doi: 10.1136/bmj.d5506

Batty GD, Shipley MJ, Kivimaki M, et al. Impact of smoking cessation advice on **future smoking behavior**, morbidity, and mortality: up to **40 years of follow-up** of the first randomized controlled trial of a general population sample. Arch Intern Med. 2011;171(21):1950-1951.

Bjerregaard BK, et al. The effect of **occasional smoking** on smoking-related cancers : In the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control. 2006 Dec;17(10):1305-9.

Boffetta Paolo, Straif Kurt. Use of **smokeless tobacco** and risk of myocardial infarction and stroke: systematic review with meta-analysis. BMJ 2009;339:b3060, doi: 10.1136/bmj.b3060 (Published 18 August 2009) An association was detected between use of smokeless tobacco products and risk of fatal myocardial infarction and stroke, which does not seem to be explained by chance.

Bolliger CT, Issa JS, Posadas-Valay R, et al. Effects of **varenicline** in adult smokers: a **multinational** (Latin America, Africa & Middle East), 24-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2011 Apr;33(4):465-77.

Bonser RS, Taylor R, Collett D, Thomas HL, Dark JH, Neuberger J, on behalf of members of the Cardiothoracic Advisory Group to NHS Blood and Transplant and the Association of Lung Transplant Physicians (UK). Effect of **donor smoking on survival after lung** transplantation: a cohort study of a prospective registry. Lancet 2012.

Borland R. Electronic cigarettes as a method of tobacco control. BMJ. 2011 Sep 30;343:d6269.

Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and **Colorectal Cancer**: A Meta-analysis. JAMA. 2008 Dec 17;300(23):2765-78. Cigarette smoking is significantly associated with colorectal cancer incidence and mortality.

Brand JS, Chan MF, Dowsett M, et al. Cigarette **Smoking and Endogenous Sex Hormones** in Postmenopausal Women. J Clin Endocrinol Metab. 2011 Aug 10.

Britton J. **Taxing tobacco profits** to prevent the smoking epidemic. The Lancet. Published online March 4, 2011 DOI:10.1016/S0140-6736(10)62040-5

Burke H, Leonardi-Bee J, Hashim A et al. **Prenatal and Passive Smoke Exposure** and Incidence of Asthma and Wheeze: Systematic Review and Meta-analysis. Pediatrics. 2012 Mar 19.

Burstein AH, et al. Pharmacokinetics, safety, and tolerability after single and multiple oral doses of **varenicline** in elderly smokers. J Clin Pharmacol. 2006 Nov;46(11):1234-40. Thus, no dose adjustment is necessary based on age alone.

Cahill K, Stead LF, Lancaster T. **Nicotine receptor partial agonists** for smoking cessation. **Cochrane** Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub2. Varenicline increased the odds of successful long-term smoking cessation approximately threefold compared with pharmacologically unassisted quit attempts.In trials reported so far, more participants quit successfully with varenicline than with bupropion. The effectiveness of varenicline as an aid to relapse prevention has not been clearly established. The main adverse effect of varenciline is nausea, but this is mostly at mild to moderate levels and tends to reduce with habituation.There is a need for independent trials of varenicline versus placebo, to test the early findings. There is also a need for direct comparisons with nicotine replacement therapy, and for further trials with bupropion, to establish the relative efficacy of the treatments.Cytisine may also increase the chances of quitting, but the evidence at present is inconclusive.

Cahill K, Moher M, Lancaster T. **Workplace interventions** for smoking cessation. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD003440. We found strong evidence that interventions directed towards individual smokers increase the likelihood of quitting smoking. These include individual and group counselling and pharmacological treatment to overcome nicotine addiction. All these interventions show similar effects whether offered in the workplace or elsewhere. Self-help interventions and social support are less effective. Although people taking up these interventions are more likely to stop, the absolute numbers who quit are low.2. There was limited evidence that participation in programmes can be increased by competitions and incentives organized by the employer.3. We failed to detect an effect of comprehensive programmes in reducing the prevalence of smoking.

Cahill K, Lancaster T, Green N. **Stage-based interventions** for smoking cessation. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD004492. DOI: 10.1002/14651858.CD004492.pub4.

Cahill K, Stead LF, Lancaster T. **Nicotine receptor partial agonists** for smoking cessation. **Cochrane** Database Syst Rev. 2010 Dec 8;12:CD006103. **Varenicline** at standard dose increased the chances of successful long-term smoking cessation between two- and threefold compared with pharmacologically unassisted quit attempts. Lower dose regimens also conferred benefits for cessation, while reducing the incidence of adverse events. More participants quit successfully with varenicline than with bupropion. Two open-label trials of varenicline versus NRT suggested a modest benefit of varenicline but confidence intervals did not rule out equivalence. Limited evidence suggests that varenicline may have a role to play in relapse prevention. The main adverse effect of varenicline is nausea, but mostly at

TOP

mild to moderate levels and tending to subside over time. Possible links with serious adverse events, including depressed mood, agitation and suicidal thoughts, have been reported but are so far not substantiated. There is a need for further independent community-based trials of varenicline, to test its efficacy and safety in smokers with varying co-morbidities and risk patterns. There is a need for further trials of the efficacy of treatment extended beyond 12 weeks. **Cytisine** may also increase the chances of quitting, but the evidence at resent is inconclusive.

Cahill K, Stead LF, Lancaster T. **Nicotine receptor partial agonists for smoking cessation**. Cochrane Database of Systematic Reviews **2012**, Issue 4. Art. No.: CD006103. Cytisine increases the chances of quitting, although absolute quit rates were modest in two recent trials. Varenicline at standard dose increased the chances of successful long-term smoking cessation between two- and threefold compared with pharmacologically unassisted quit attempts. Lower dose regimens also conferred benefits for cessation, while reducing the incidence of adverse events. More participants quit successfully with varenicline than with bupropion. Two open-label trials of varenicline versus NRT suggested a modest benefit of varenicline but confidence intervals did not rule out equivalence. Limited evidence suggests that varenicline may have a role to play in relapse prevention. The main adverse effect of varenicline is nausea, but mostly at mild to moderate levels and tending to subside over time. Possible links with serious adverse events, including serious psychiatric or cardiovascular events, cannot be ruled out.

Callaghan, Russell C, Veldhuizen, Scott, Leatherdale, Scott, Murnaghan, Donna, Manske, Steve Use of **contraband cigarettes** among adolescent daily smokers in Canada. CMAJ 2009 0: cmaj.090665.

Callinan JE, Clarke A, Doherty K, Kelleher C. **Legislative smoking bans** for reducing secondhand smoke exposure, smoking prevalence and tobacco consumption. Cochrane Database Syst Rev. 2010 Apr 14;4:CD005992.

Campbell R, Starkey F, Holliday J, et al. An informal **school-based peer-led intervention** for smoking prevention in adolescence (ASSIST): a cluster randomised trial. Lancet. 2008 May 10;371(9624):1595-602. The results suggest that, if implemented on a population basis, the ASSIST intervention could lead to a reduction in adolescent smoking prevalence of public-health importance.

Carandang RA, Barton B, Rordorf GA, et al. Nicotine replacement therapy **after subarachnoid hemorrhage** is not associated with increased vasospasm. Stroke. 2011 Nov;42(11):3080-6.

Carpenter MJ, Hughes JR, Gray KM, et al. **Nicotine therapy sampling** to induce quit attempts among smokers unmotivated to quit: a randomized clinical trial. Arch Intern Med. 2011;171(21): 1901-1907.

Cao Yin; Kenfield Stacey; Song Yan; et al. Cigarette Smoking Cessation and Total and Cause-Specific **Mortality: A 22-Year Follow-up** Study Among US Male Physicians (**PHS**). Arch Intern Med. 2011;171(21):1956-1959.

Carson KV, Verbiest MEA, Crone MR, et al. **Training health professionals** in smoking cessation. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD000214. DOI: 10.1002/14651858.CD000214.pub2. Training health professionals to provide smoking cessation interventions had a measurable effect on the point prevalence of smoking, continuous abstinence and professional performance. The one exception was the provision of nicotine gum or replacement therapy, which did not differ between groups.

CDC, Morbidity and Mortality Weekly Report (MMWR). **Cigarette Use Among High School Students** --- United States, 1991—2009. July 9, 2010. For current frequent cigarette use, the prevalence increased from 12.7% in 1991 to 16.8% in 1999, declined to 9.7% in 2003, and then declined more gradually, to 7.3% in 2009. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5926a1.htm?s_cid=mm5926a1_w

CDC Aug/10 Tobacco Use Among **Middle and High School Students** --- United States, 2000—2009 http://www.cdc.gov/mmwr/pdf/wk/mm5933.pdf

CDC-From the Centers for Disease Control and Prevention **Smoking in Top-Grossing Movies**—United States, 1991-2009 *JAMA*. 2010;304(24):2692-2694.

CDC Sep/11 Vital Signs: Current Cigarette **Smoking Among Adults Aged ≥18 Years** --- United States, 2005—2010 (drop from 20.9% to 19.3%) **http://www.cdc.gov/mmwr/preview/mmwrhtml/mm60e0906a1.htm?s_cid=mm60e0906a1_x**

Cesaroni G, Forastiere F, Agabiti N, et al. Effect of the **Italian smoking ban on population rates of acute coronary events**. Circulation 2008; DOI: 10.1161/circulationaha.107.729889.

Chandler MA, Rennard SI. **Smoking cessation**. Chest. **2010** Feb;137(2):428-35.

Chapman S, Mackenzie R. The global research neglect of **unassisted smoking cessation**: causes and consequences. PLoS Med. 2010 Feb 9;7(2):e1000216.

Chen R, Zhang D, Chen Y, et al. Passive smoking and risk of **cognitive impairment** in women who never smoke. Arch Intern Med. 2012 Feb 13;172(3):271-3.

Chen LS, Baker TB, Piper ME, et al. Interplay of **genetic risk factors (CHRNA5-CHRNA3-CHRNB4)** and cessation treatments in smoking cessation success. Am J Psychiatry 2012

Chung HY, Machado P, van der Heijde D, et al. Smokers in **early axial spondyloarthritis** have earlier disease onset, more disease activity, inflammation and damage, and poorer function and healthrelated quality of life: results from the DESIR cohort. Ann Rheum Dis. Published Online First: 11 Oct 2011.

Christakis NA, Fowler JH. The collective dynamics of smoking in a **large social network**. N Engl J Med. 2008 May 22;358(21):2249-58. Network phenomena appear to be relevant to smoking cessation. Smoking behavior spreads through close and distant social ties, groups of interconnected people stop smoking in concert, and smokers are increasingly marginalized socially

Civljak M, Sheikh A, Stead LF, et al. **Internet-based interventions** for smoking cessation. Cochrane Database Syst Rev. 2010 Sep 8;9:CD007078.

Clearie KL, McKinlay L, Williamson PAet al. **Fluticasone/salmeterol** combination confers benefi ts in people with **asthma** who smoke. Chest. 2012;141 (2): 330 -338.

Cobb Nathan K., Abrams David B. **E-Cigarette** or Drug-Delivery Device? Regulating Novel Nicotine Products. N Engl J Med 2011; 365:193-195.

Coleman HG, Bhat S, Johnston BT, et al. Tobacco Smoking Increases the Risk of **High-Grade Dysplasia and Cancer Among Patients With Barrett's Esophagus**. Gastroenterology. 2011 Nov 4.

Coleman T, Cooper S, Thornton JG, et al. A randomized trial of **nicotine-replacement therapy patches in pregnancy**. N Engl J Med 2012;366:808-18.

Colivicchi F, Mocini D, Tubaro M, et al. Effect of smoking relapse on outcome **after acute coronary syndromes**. Am J Cardiol. 2011 Sep 15;108(6):804-8.

Conen David, Everett Brendan M., Kurth Tobias, et al. Smoking, Smoking Status, and Risk for Symptomatic **Peripheral Artery Disease** in Women: A Cohort Study. Ann Intern Med June 7, 2011 154:719-726.

Connolly, Gregory N., Richter, Patricia, Aleguas, Alfred, Jr, et al. **Unintentional Child Poisonings** Through Ingestion of Conventional and Novel Tobacco Products. Pediatrics 2010 0: peds.2009-2835

Cook MB, Shaheen NJ, Anderson LA, et al. Cigarette Smoking Increases **Risk of Barrett's Esophagus**: An Analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. Gastroenterology. 2012 Jan 11.

Cosgrove KP, Esterlis I, McKee SA, et al. Sex Differences in Availability of **β2*-Nicotinic Acetylcholine Receptors** in Recently Abstinent Tobacco Smokers. Arch Gen Psychiatry. 2012 Apr;69(4):418-27.

Cressman AM, Pupco A, Kim E, et al. **Smoking cessation therapy during pregnancy**. Can Fam Physician. 2012 May;58(5):525-7.

De Pergola G, Ciampolillo A, Alò D, et al. **Free Triiodothyronine** is associated with smoking habit, independently of obesity, body fat distribution, insulin, and metabolic parameters. J Endocrinol Invest. 2010 Jul 13.

Decramer M; on behalf of the **European Respiratory Roadmap** Initiative. The European Respiratory Roadmap. Lancet. 2011 Jun 22. (for smoking legislation)

Desai NR, Mega JL, Jiang S, et al. Interaction between cigarette smoking and clinical benefit of clopidogrel. J Am Coll Cardiol 2009; 53:1273-1278.

DiPaula BA, Thomas MD. Worsening **psychosis induced by varenicline** in a hospitalized psychiatric patient. Pharmacotherapy. 2009 Jul;29(7):852-7.

Drugs in Pregnancy and Lactation. 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Philadelphia, PA: 2011.

Dugas E, Tremblay M, Low NC, et al. **Water-pipe smoking** among North American youths. Pediatrics. 2010;125:1184-1189. Abstract

Duijts L, Jaddoe VW, van der Valk RJ, et al. **Fetal exposure to maternal and paternal smoking** and the risks of wheezing in preschool children: the generation R study. Chest. 2012 Apr;141(4):876-85.

E-Cigarette- http://en.wikipedia.org/wiki/E-cigarette ; (FDA and Public Health Experts Warn About Electronic Cigarettes July,2009 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm)

Ebbert J, Montori VM, Erwin PJ, et al. Interventions for **smokeless tobacco** use cessation. Cochrane Database Syst Rev. 2011 Feb 16;2:CD004306. Varenicline and behavioural interventions may help ST users to quit. Behavioural interventions incorporating telephone counselling or an oral examination are likely to increase abstinence rates.

Eder L, Shanmugarajah S, Thavaneswaran A et al. The association between smoking and the development of **psoriatic arthritis** among psoriasis patients. Ann Rheum Dis. 2012 Feb;71(2):219-24.

Eisenberg MJ, Filion KB, Yavin D, Bélisle P, Mottillo S, Joseph L, Gervais A, O'Loughlin J, Paradis G, Rinfret S, Pilote L. Pharmacotherapies for smoking cessation: a **meta-analysis** of randomized controlled trials. CMAJ. 2008 Jul 15;179(2):135-44. Varenicline, bupropion and the 5 nicotine replacement therapies were all more efficacious than placebo at promoting smoking abstinence at 6 and 12 mon

Ekblad M, Gissler M, Lehtonen L, Korkeila J. **Prenatal smoking exposure** and the risk of psychiatric morbidity into young adulthood. Arch Gen Psychiatry. 2010 Aug;67(8):841-9.

Ellerbeck EF, Mahnken JD, Cupertino AP, et al. Effect of varying levels of **disease management** on smoking cessation: a randomized trial. Ann Intern Med. 2009 Apr 7;150(7):437-46.

Els Charl, Kunyk Diane, Sidhu Harkirat. Smoking cessation and **neuropsychiatric adverse events**: Are family physicians caught between a rock and a hard place? Can Fam Physician June 2011 57: 647-649.

Elton-Marshall, Tara, Leatherdale, Scott T., Burkhalter, Robin. **Tobacco, alcohol and illicit drug use among Aboriginal youth** living off-reserve: results from the Youth Smoking Survey. CMAJ 2011 183: E480-486

Etter JF. **Cytisine** for smoking cessation: a literature review and a meta-analysis. Arch Intern Med. 2006 Aug 14-28;166(15):1553-9.

Etter JF, Huguelet P, et al. **Nicotine gum** treatment before smoking cessation: a randomized trial. Arch Intern Med. 2009 Jun 8;169(11):1028-34. Starting nicotine gum treatment 4 weeks before the target quit date was no more effective than starting treatment on the quit date.

Fagerström Karl, Gilljam Hans, Metcalfe Michael, et al. **Stopping smokeless tobacco with varenicline**: randomised double blind placebo controlled trial. BMJ 341:doi:10.1136/bmj.c6549 (Published 6 Dec 2010).

Fang X, Wang X, Bai C. **COPD in China**: The Burden and Importance of Proper Management. Chest. 2011 Apr;139(4):920-9.

Farley AC, Hajek P, Lycett D, et al. Interventions for **preventing weight gain** after smoking cessation. Cochrane Database Syst Rev. 2012 Jan 18;1:CD006219. Although some pharmacotherapies tested to limit PCWG show evidence of short-term success, other problems with them and the lack of data on long-term efficacy limits their use. Weight management education only, is not effective and may reduce abstinence. Personalised weight management support may be effective and not reduce abstinence, but there are too few data to be sure.

FDA Chantix/**Champix** Warning Feb/2008: 491 **suicide** reports; **39 completed**. **Canada**: **46 psychiatric** adverse reactions reported from April 1-Nov23/07

FDA and Public Health Experts Warn About **Electronic Cigarettes** July,2009 Laboratory analysis of electronic cigarette samples has found that they contain carcinogens and toxic chemicals such as diethylene glycol, an ingredient used in antifreeze. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm

FDA Aug, 2009 — Announced the launch of a new division, the **Center for Tobacco Products**, "in an historic effort to curb the hundreds of thousands of deaths caused by those products each year." The new center will oversee the Family Smoking Prevention and Tobacco Control Act, signed into law by President Barack Obama in June 2009.

FDA May/11 has decided to oversee **electronic cigarettes** the same way it does tobacco products.

FDA June/11 drug safety communication: **Chantix (varenicline) may increase the risk of certain cardiovascular adverse events** in patients with cardiovascular disease.

FDA Quit Smoking package **images** 2011 http://www.fda.gov/downloads/TobaccoProducts/Labeling/UCM259401.pdf

FDA July/11 has approved an updated drug label for the smoking cessation aid Chantix (**varenicline**) to include information about the efficacy and safety of the drug in two patient populations who may benefit greatly from giving up smoking—those with cardiovascular disease and those with chronic obstructive pulmonary disease (COPD).

FDAOct/11 has reviewed the results from two FDA-sponsored epidemiological studies that evaluated the risk of **neuropsychiatric adverse** events associated with the smoking cessation drug **Chantix (varenicline).** Neither study found a difference in risk of neuropsychiatric hospitalizations between Chantix and nicotine replacement therapy (NRT; e.g., NicoDerm patches). However, both studies had a number of study design limitations, including only assessing neuropsychiatric events that resulted in hospitalization, and not having a large enough sample size to detect rare adverse events (see 10/24/2011 Drug Safety Communication below for more information). Healthcare professionals and patients should continue to follow the recommendations in the physician label and the patient Medication Guide.

TOP

and to monitor for neuropsychiatric symptoms when prescribing or using Chantix. The drug manufacturer is conducting a large safety clinical trial of Chantix to assess neuropsychiatric adverse events, and results from this study are expected in 2017.

Ferguson J, Docherty G, Bauld L, Lewis S, Lorgelly P, Boyd KA, et al. Effect of offering different levels of support and **free nicotine replacement therapy via an English national telephone quitline**: randomised controlled trial. BMJ 2012;344:e1696.

Filion KB, Abenhaim HA, Mottillo S, et al. The effect of smoking cessation **counselling in pregnant women**: a meta-analysis of randomised controlled trials. BJOG. 2011 Nov;118(12):1422-8.

Fiore MC, Baker TB. Clinical practice. **Treating smokers in the health care setting**. N Engl J Med. 2011 Sep 29;365(13):1222-31

Forinash Alicia B, Pitlick Jamie M, Clark Kylie, et al. **Nicotine Replacement Therapy Effect on Pregnancy Outcomes.** Articles Ahead of Print published on 1 November 2010, DOI 10.1345/aph.1P279.

Free C, Knight R, Robertson S, et al. Smoking cessation support delivered via **mobile phone text messaging (txt2stop)**: a single-blind, randomised trial. Lancet 2011; published online June 30. DOI:10.1016/S0140-6736(11)60701-0.

Freedman R. **Exacerbation of schizophrenia by varenicline**. Am J Psychiatry. 2007 Aug;164(8):1269.

Freedman ND, Silverman DT, Hollenbeck AR, et al. Association between smoking and risk of **bladder cancer** among men and women. JAMA. 2011 Aug 17;306(7):737-45.

Frey P, Waters DD, Demicco DA, et al. Impact of **Smoking on Cardiovascular Events** in Patients With Coronary Disease Receiving Contemporary Medical Therapy (from the Treating to New Targets [TNT] and the Incremental Decrease in End Points Through Aggressive Lipid Lowering [IDEAL] Trials). Am J Cardiol. 2010 Dec 1.

Garza D et al. A double-blind randomized placebo-controlled pilot study of **neuropsychiatric adverse events in abstinent smokers treated with varenicline** or placebo. Biol Psychiatry 2011 Jun 1; 69:1075. (limited efficacy & side effects)

Geerts CC, Bots ML, van der Ent CK, et al. **Parental Smoking** and Vascular Damage in Their 5-year-old Children. Pediatrics. 2012 Jan;129(1):45-54.

Gellert C, Schottker B, Brenner H. **Smoking and all-cause mortality** in older people: systematic review and meta-analysis. Arch Intern Med. 2012; 172(11):837-844.

Gerber Y, Rosen LJ, Goldbourt U, et al. Smoking status and long-term survival after first acute **myocardial infarction**. J Am Coll Cardiol 2009; 54:2382-2387.

Goto K, Nikolsky E, Lansky AJ, et al. Impact of Smoking on Outcomes of Patients **With ST-Segment Elevation Myocardial Infarction** (from the HORIZONS-AMI Trial). Am J Cardiol. 2011 Aug 23.

Graham Amanda L.; Cobb Nathan K.; Papandonatos George D.; et al. A Randomized Trial of Internet and Telephone Treatment for Smoking Cessation. Arch Intern Med. 2011;171(1):46-53.

Gray KM, Upadhyaya HP. Tobacco smoking in individuals with **attention-deficit hyperactivity disorder**: epidemiology and pharmacological approaches to cessation. CNS Drugs. 2009;23(8):661-8. doi: 10.2165/00023210-200923080-00003.

Gray Ron, Bonellie Sandra R, Chalmers James, et al. Contribution of smoking during pregnancy to inequalities in **stillbirth and infant death** in Scotland 1994-2003: retrospective population based study using hospital maternity records.BMJ 2009;339:b3754, doi: 10.1136/bmj.b3754 (Published 1 October 2009)

Gu D, Kelly TN, Wu X, et al. **Mortality attributable to smoking in China**. N Engl J Med. 2009 Jan 8;360(2):150-9. The leading causes of smoking-related deaths were as follows: cancer, 268,200 (95% CI, 214,500 to 321,900); cardiovascular disease, 146,200 (95% CI, 79,200 to 213,100); and respiratory disease, 66,800 (95% CI, 20,300 to 113,300). Our study documents that smoking is a major risk factor for mortality in China. Continued strengthening of national programs and initiatives for smoking prevention and cessation is needed to reduce smoking-related deaths in China.

Gunnell AS, et al. Synergy between Cigarette Smoking and **Human Papillomavirus** Type 16 in Cervical Cancer In situ Development. Cancer Epidemiol Biomarkers Prev. 2006 Oct 20; [Epub ahead of print]

Gunnell D, Irvine D, Wise L, et al. **Varenicline and suicidal behaviour**: a cohort study based on data from the General Practice Research Database. BMJ 2009;339:b3805, doi: 10.1136/bmj.b3805 (Published 1 October 2009)

Gunnerbeck A, Wikström AK, Bonamy AK, Wickström R, Cnattingius S. Relationship of **Maternal Snuff Use** and Cigarette Smoking With **Neonatal Apnea**. Pediatrics. 2011 Aug 28.

Hackshaw Allan, Rodeck Charles, Boniface Sadie. Maternal smoking in pregnancy and **birth defects**: a systematic review based on 173 687 malformed cases and 11.7 million controls Hum. Reprod. Update (2011) dmr022 online July 11, 2011 doi:10.1093/humupd/dmr022

Hajek P, Stead LF, West R, Jarvis M, Lancaster T. **Relapse prevention** interventions for smoking cessation. Cochrane Database Syst Rev. 2009;(1):CD003999.

Hajek Peter; McRobbie Hayden J.; Myers Katie E.; et al. Use of **Varenicline for 4 Weeks Before** Quitting Smoking: Decrease in Ad Lib Smoking and Increase in Smoking Cessation Rates. Arch Intern Med. 2011;171(8):770-777.

Hall SM, Humfleet GL, Reus VI, Muñoz RF, Cullen J. Extended nortriptyline and psychological treatment for cigarette smoking. Am J Psychiatry. 2004 Nov;161(11):2100-7.

Hammond, David, Chaiton, Michael, Lee, Alex, Collishaw, Neil. **Destroyed documents**: uncovering the science that Imperial Tobacco Canada sought to conceal. CMAJ 2009 0: cmaj.080566.

Hanewinkel, Reiner, Isensee, Barbara, Sargent, James D., et al. **Cigarette Advertising** and Teen Smoking Initiation. Pediatrics 2011 127: e271-e278.

Harvard Study Confirms **Rise in Nicotine Delivery of Cigarettes** A reanalysis of data released last summer confirms that the nicotine yield from cigarettes increased about 11% from 1998 to 2005. A Harvard School of Public Health review of the data, which are annually reported to the Massachusetts Department of Public Health by cigarette manufacturers, was released online. It found the nicotine increase across brands from the four major manufacturers and in all categories of cigarettes, such as menthol and ultralight. The report said the nicotine boost was accomplished both by increasing the amount of nicotine in the cigarettes and by redesigning them to burn more slowly, so users take more puffs per cigarette. http://www.hsph.harvard.edu/nicotine/trends.pdf

Haslemo T, et al. The effect of variable cigarette consumption on the interaction with **clozapine** and **olanzapine**. Eur J Clin Pharmacol. 2006 Nov 7; [Epub ahead of print] A daily consumption of 7-12 cigarettes is probably sufficient for maximum induction of clozapine and olanzapine metabolism. A 50% lower starting dose of both drugs in non-smokers seems rational to avoid side effects.

Hawk LW Jr, Ashare RL, Lohnes SF, et al. The effects of **extended pre-quit varenicline** (4 weeks vs 1 week) treatment on smoking behavior and short-term abstinence: a randomized clinical trial. Clin Pharmacol Ther. 2012 Feb;91(2):172-80.

Hays JT, Ebbert JO. **Varenicline** for tobacco dependence. N Engl J Med. 2008 Nov 6;359(19):2018-24.

Hays JT, Ebbert JO. **Adverse effects and tolerability** of medications for the treatment of tobacco use and dependence. Drugs. 2010 Dec 24;70(18):2357-72.

Health Canada July/07 Unauthorized Smoking Cessation Product **Resolve** May Pose Health Risk - Consumer Information. The product contains an unacceptable amount of an ingredient labelled as "CESTEMENOL-350." Consuming excessive amounts of this ingredient might result in damage to the kidney, liver or red blood cells.

Health Canada June/08 Pfizer Canada in collaboration with Health Canada would like to notify healthcare professionals of important safety information regarding **CHAMPIX**, and post-marketing reports of serious **neuropsychiatric adverse events**, including depressed mood, agitation, hostility, changes in behaviour, suicidal ideation and suicide, as well as worsening of pre-existing psychiatric illness (previously diagnosed or not). Since introduction of CHAMPIX in Canada, in April 2007 through April 30, 2008, a total of **226 Canadian cases** of neuropsychiatric adverse events have been reported. For the same time period, there have been **708 534 prescriptions filled** for CHAMPIX in Canada1. All patients attempting to quit smoking with CHAMPIX, their families & caregivers should be alerted about the need to monitor for symptoms of neuropsychiatric adverse events. Patients should be instructed to stop taking CHAMPIX and contact their healthcare provider immediately if they have or if their families or caregivers observe depressed mood, agitation, hostility or changes in behavior, that are not typical for the patient, or if the patient has suicidal ideation or suicidal behavior. Patients with concomitant psychiatric conditions, even if well controlled, or with a history of psychiatric symptoms, should be diligently monitored.

Health Canada Mar/09 is advising Canadians not to purchase or use **electronic smoking products**, as these products may pose health risks and have not been fully evaluated for safety, quality and efficacy by Health Canada. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_53-eng.php (FDA and Public Health Experts Warn About Electronic Cigarettes http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm)

Health Canada June/10 **CHAMPIX** (varenicline tartrate) - Changes to the Canadian Product Monograph - Pfizer Canada Inc. Changes include: 1- a boxed warning highlighting recommendations about neuropsychiatric adverse events, 2- a warning about rare reports of serious allergic and skin reactions, 3- a guidance for prescribers about information to be shared with their patients prior to and during treatment, and 4- an additional dosing option for CHAMPIX.

Health Canada Jan/12 is informing Canadians that our **review of Champix** is now complete and the label has been updated with new information with respect to cardiovascular safety. Champix (brand name for varenicline tartrate) is a prescription drug used to help patients quit smoking in combination with supportive counselling. Health Canada evaluated data from a quit-smoking clinical trial involving 700 smokers with cardiovascular disease (approximately 350 who received Champix and 350 who received a placebo or "sugar pills"). Cardiovascular disease is a broad term for any condition that affects the heart and/or blood vessels, including heart attack and stroke. Although a slightly increased number of patients experienced serious heart-related events in the group treated with Champix compared to the group treated with placebo, the study was not adequately designed to be able to test the cardiovascular safety of Champix. The small study size combined with other study design weaknesses make it impossible to draw conclusions based on these data. The possibility of an increased risk of heart attack or stroke in patients with cardiovascular disease can neither be confirmed nor ruled out at this time.

Hegaard HK, Kjaergaard H, Møller LF, Wachmann H, Ottesen B. **Multimodal** intervention raises smoking cessation rate during **pregnancy**. Acta Obstet Gynecol Scand 2003;82:813-9.

Hissaria P, Roberts-Thomson PJ, Lester S, et al. Cigarette smoking in patients with **systemic sclerosis** - reduces overall survival. Arthritis Rheum. 2011 Mar 24. doi: 10.1002/art.30352.

Horn K, Dino G, Branstetter SA, Zhang J, Noerachmanto N, Jarrett T, Taylor M. Effects of **physical activity** on teen smoking cessation. Pediatrics. 2011 Oct;128(4):e801-11.

Hovell MF, Wahlgren DR, Liles S, et al. **Coaching and Cotinine Feedback** to Preteens to Reduce Their Secondhand Smoke Exposure: a Randomized Trial. Chest. 2011 Apr 7.

Howe M, Leidal A, Montgomery D, Jackson E. Role of Cigarette Smoking and **Gender in Acute Coronary Syndrome Events**. Am J Cardiol. 2011 Sep 15. (increased in **female** smokers)

Hui M, Doherty M, Zhang W. Does **smoking protect against osteoarthritis**? Meta-analysis of observational studies. Ann Rheum Dis. 2011 Jul;70(7):1231-7. The protective effect of smoking in OA observed in some epidemiological studies is likely to be **false**.

Hum Ashley M., Robinson Leslie A., Jackson Ashley A., et al. **Physician Communication Regarding Smoking and Adolescent** Tobacco Use. Pediatrics 2011; peds.2010-1195; published ahead of print May 16, 2011, doi:10.1542/peds.2010-1195

Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained- release bupropion and placebo for smoking cessation. N Engl J Med 1997;337:1195-202. (**low dose is effective**)

Huxley RR, Woodward M. Cigarette smoking as a risk factor for **coronary heart disease in women** compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011; DOI: DOI:10.1016/S0140-6736(11)60781-2.

Jia H, Lubetkin EI. Trends in **quality-adjusted life-years** lost contributed by smoking and obesity. Am J Prev Med 2010; DOI: 10.1016/j.amepre.2009.09.043.

Jiménez-Ruiz C, Berlin I, Hering T. **Varenicline**: a novel pharmacotherapy for smoking cessation. Drugs. 2009;69(10):1319-38. doi: 10.2165/00003495-200969100-00003.

Johannessen A, Bakke PS, Hardie JA, et al. Association of exposure to **environmental tobacco smoke in childhood** with chronic obstructive pulmonary disease and respiratory symptoms in adults. Respirology. 2012 Jan 16.

Jones LL, Hassanien A, Cook DG, Britton J, Leonardi-Bee J. **Parental Smoking and the Risk of Middle Ear Disease** in Children: A Systematic Review and Meta-analysis. Arch Pediatr Adolesc Med. 2011 Sep 5.

Joseph AM, Fu SS, Lindgren B, et al. **Chronic disease management** for tobacco dependence: a randomized, controlled trial. Arch Intern Med. 2011; 171(21):1894-1900.

Kabir Zubair, Connolly Gregory N., Alpert Hillel R. **Secondhand Smoke** Exposure and **Neurobehavioral Disorders** Among Children in the United States. Pediatrics 2011; peds.2011-0023; published ahead of print July 11, 2011, doi:10.1542/peds.2011-0023

Källberg H, Ding B, Padyukov L, et al. EIRA Study Group. Smoking is a major preventable risk factor for **rheumatoid arthritis**: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis. 2010 Dec 13.

Karagueuzian Hrayr S., White Celia, Sayre James, et al. **Cigarette Smoke Radioactivity [polonium 210 (210Po)]** and Lung Cancer RiskNicotine Tob Res (2011) first published online September 27, 2011 doi:10.1093/ntr/ntr145.

Keating GM, Siddiqui MA. **Varenicline** : A Review of its Use as an Aid to Smoking Cessation Therapy. CNS Drugs. 2006;20(11):945-960.

Kenfield SA, Stampfer MJ, Rosner BA, et al. Smoking and smoking cessation in relation to **mortality in women**. JAMA 2008; 299: 2037-2047.

Kenfield Stacey A., Stampfer Meir J., Chan June M., et al. **Smoking and Prostate Cancer Survival** and Recurrence. JAMA. 2011;305(24):2548-2555.doi:10.1001/jama.2011.879.

King BA, Dube SR, Tynan MA. **Secondhand Smoke Exposure** in Cars Among Middle and High School Students--United States, 2000-2009. Pediatrics. 2012 Feb 6.

Kleykamp BA, Heishman SJ. The **older smoker**. JAMA. 2011 Aug 24;306(8):876-7.

Kohen I, Kremen N. **Varenicline-induced manic episode** in a patient with bipolar disorder. Am J Psychiatry. 2007 Aug;164(8):1269-70.

TOP

Koplan KE, David SP, Rigotti NA. **Smoking cessation** -10minute Consultation. BMJ. 2008 Jan 26;336(7637):217.

Kroon LA. **Drug interactions** with smoking. Am J Health Syst Pharm. 2007 Sep 15;64(18):1917-21.

Kwok MK, Schooling CM, Ho LM, Leung S, Mak KH, McGhee SM, Lam TH, Leung GM. Early life **second hand smoke** exposure and serious infectious morbidity during the first eight years: evidence from Hong Kong's "Children of 1997" birth cohort. Tob Control. 2008 May 27. [Epub ahead of print]

Ladapo Joseph A.; Jaffer Farouc A.; Weinstein Milton C.; et al. Projected Cost-effectiveness of Smoking Cessation Interventions in **Patients Hospitalized With Myocardial Infarction**. *Arch Intern Med*. 2011;171(1):39-45.

Lai, Hak-Kan, Ho, Sai-Yin, Wang, Man-Ping, Lam, Tai-Hing. **Secondhand Smoke** and Respiratory Symptoms Among Adolescent Current Smokers. Pediatrics 2009 124: 1306-1310.

Lai DT, Cahill K, Qin Y, Tang JL. **Motivational interviewing** for smoking cessation. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006936.

Lamprecht B, McBurnie MA, Vollmer WM, et al. for the BOLD Collaborative Research Group. **COPD in Never Smokers**: Results From the Population-Based Burden of Obstructive Lung Disease Study. Chest. 2011 Apr;139(4):752-763.

Lancaster T, Stead LF. **Individual behavioural counselling** for smoking cessation. Cochrane Database Syst Rev. 2005;(2):CD001292.

Land T, Rigotti N, Levy D, et al. A longitudinal study of **Medicaid coverage for tobacco dependence treatments** in Massachusetts and associated decreases in hospitalizations for cardiovascular disease. PLOS Med 2010; DOI:10.1371/journal.pmed.1000375.

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. **Smoking and mental illness**: a population-based prevalence study. JAMA. 2000; 284(20):2606-2610.

Lazarus SC, et al. Smoking Affects Response to **Inhaled Corticosteroids** or **Leukotriene Receptor Antagonists** in Asthma. Am J Respir Crit Care Med. 2007 Jan 4; [Epub ahead of print] In mild asthmatics who smoke, the response to inhaled corticosteroids is attenuated, suggesting that adjustments to standard therapy may be required to attain asthma control. The greater improvement seen in some outcomes in smokers treated with montelukast suggests that leukotrienes may be important in this setting.

Larzelere M, Williams D. **Promoting Smoking Cessation** Am Fam Physician. 2012 Mar 15;85(6):591-598.

Leistikow BN, Kabir Z, Connolly GN, Clancy L, Alpert HR. Male tobacco smoke load and non-lung **cancer mortality** associations in Massachusetts. BMC Cancer. 2008 Nov 24;8:341. The lung/non-lung cancer death rate associations suggest that all-sites cancer death rate SAFs in year 2003 **were 73%** (Sensitivity Range [SR] 61-82%) for all ages and 74% (SR 61-82%) for ages 30-74 years.

Leonardi-Bee, Jo, Britton, John, Venn, Andrea. **Secondhand Smoke** and Adverse **Fetal Outcomes in Nonsmoking Pregnant Women**: A Meta-analysis. Pediatrics 2011 127: 734-741

Lessov-Schlaggar Christina N., Wahlgren Dennis R., Liles Sandy, et al. Sensitivity to **Secondhand Smoke** Exposure Predicts **Future Smoking Susceptibility**. Pediatrics 2011; peds.2010-3156; published ahead of print July 11, 2011, doi:10.1542/peds.2010-3156

Leung Chi C.; Lam Tai H.; Ho Kin S.; et al. **Passive Smoking and Tuberculosis**. Arch Intern Med. 2010;170(3):287-292.

Levine Michele D.; Perkins Kenneth A.; Kalarchian Melissa A.; et al. **Bupropion and Cognitive Behavioral Therapy** for Weight-Concerned Women Smokers. Arch Intern Med. 2010;170(6):543-550.

Levy DE, Winickoff JP, Rigotti NA. **School absenteeism** among children living with smokers. Pediatrics. 2011 Oct;128(4):650-6.

Li W, Han J, Qureshi AA. **Smoking and risk of incident psoriatic arthritis** in US women. Ann Rheum Dis Published Online First: 8 Nov 2011. doi:10.1136/ annrheumdis-2011-200416

Lightwood JM, Glantz SA. Declines in Acute **Myocardial Infarction** After Smoke-Free Laws and Individual Risk Attributable to Secondhand Smoke. Circulation. 2009 Sep 21. [Epub ahead of print]

Lin HH, Ezzati M, Chang HY, Murray M. Association between tobacco smoking and **active tuberculosis** in Taiwan: prospective cohort study. Am J Respir Crit Care Med. 2009 Sep 1;180(5):475-80. Epub 2009 Jun 19.

Lovato C, Watts A, Stead LF. Impact of **tobacco advertising and promotion** on increasing adolescent smoking behaviours. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD003439. DOI: 10.1002/14651858.CD003439.pub2. Longitudinal studies consistently suggest that exposure to tobacco advertising and promotion is associated with the likelihood that adolescents will start to smoke.

Luo J, Margolis KL, Wactawski-Wende J, et al. Association of active and passive **smoking with risk of breast cancer** among postmenopausal women: a prospective cohort study. BMJ. 2011 Mar 1;342:d1016. doi: 10.1136/bmj.d1016.

Maisonneuve P, et al. Impact of smoking on patients with idiopathic chronic **pancreatitis**. Pancreas. 2006 Aug;33(2):163-8.

Mackay D et al. **Smoke-free legislation** and hospitalizations for childhood asthma. N Engl J Med 2010 Sep 16; 363:1139.

Mackay DF, Nelson SM, Haw SJ, et al. Impact of Scotland's Smoke-Free Legislation on **Pregnancy Complications**: Retrospective Cohort Study. PLoS Med 9(3): e1001175.

Mahmoudi M, Coleman CI, Sobieraj DM. Systematic review of the **cost-effectiveness of varenicline vs. bupropion** for smoking cessation. Int J Clin Pract. 2012 Feb;66(2):171-82.

McCauley L, Markin C, Hosmer D. An unexpected consequence of **electronic cigarette use**. Chest. 2012 Apr;141(4):1110-3. (lipoid pneumonia)

McCowan LM, et at.; SCOPE consortium. Spontaneous **preterm birth and small for gestational age infants** in women who stop smoking early in pregnancy: prospective cohort study. BMJ. 2009 Mar 26;338:b1081. doi: 10.1136/bmj.b1081. Erratum in: BMJ. 2009;338. doi: 10.1136/bmj.b1558.

McFall Miles, Saxon Andrew J., Malte Carol A., et al. for the CSP 519 Study Team. Integrating Tobacco Cessation **Into Mental Health Care for Posttraumatic Stress Disorder**: A Randomized Controlled Trial. JAMA. 2010;304(22):2485-2493.doi:10.1001/jama.2010.1769.

Medical Letter: **Treatment Guidelines- Drugs for Tobacco Dependence**. Sept 2008.

Medical Letter. **Safety** of Smoking Cessation Drugs. Aug,2009.

Mennella JA, Yourshaw LM, Morgan LK. Breastfeeding and smoking: short-term effects on **infant feeding and sleep**.Pediatrics. 2007 Sep;120(3):497-502. An acute episode of smoking by lactating mothers altered infants' sleep/wake patterning.

Menzies D, et al. Respiratory symptoms, pulmonary function, and markers of inflammation among **bar workers** before and after a legislative **ban** on smoking in public places. JAMA. 2006 Oct 11;296(14):1742-8.

Meyers DG, Neuberger JS, He J et al. Cardiovascular effect of bans on **smoking in public places**. A systematic review and meta-analysis. J Am Coll Cardiol 2009; 54: 1249-1255.

Milidou I, Henriksen TB, Jensen MS, et al. **Nicotine replacement therapy during pregnancy** and **infantile colic** in the offspring. Pediatrics. 2012 Mar;129(3):e652-8.

Miller M, Cho JY, Pham A, et al. **Persistent airway inflammation and emphysema progression** on CT scan in ex-smokers observed for 4 years. Chest. 2011 Jun;139(6):1380-7.

Mills E et al. Smoking cessation **reduces postoperative complications**: A systematic review and meta-analysis. Am J Med 2011 Feb; 124:144.

Mirkhel A, et al. Frequency of **aspirin resistance** in a community hospital. Am J Cardiol. 2006 Sep 1;98(5):577-9. Epub 2006 Jun 30. In conclusion, this study estimates aspirin resistance prevalence and shows a strong association of smoking with platelet hyperactivity in a diverse community hospital population. Nonresponders to 81 mg/day frequently responded to 325 mg/day or to the addition of clopidogrel.

Moshammer H, et al. **Parental smoking** and lung function in children: an international study. Am J Respir Crit Care Med. 2006 Jun 1;173(11):1255-63. Epub 2006 Feb 16.

Mohiuddin SM, Mooss AN, Hunter CB, et al. **Intensive smoking cessation** intervention **reduces mortality** in high-risk smokers with cardiovascular disease. Chest. 2007 Feb;131(2):446-52. At 24 month, continuous abstinence smoking cessation rate was 33% in the intensive-treatment group and 9% in the usual-care group ($p < 0.0001$). Over the 2-year follow-up period, 41 patients in the usual-care group were hospitalized compared to 25 patients in the intensive-tx group (relative risk reduction [RRR], 44%; 95% confidence interval [CI], 16 to 63%; $p = 0.007$). The all-cause mortality rate was 2.8% in the intensive-tx group and 12.0% in the usual-care group (RRR, 77%; 95% CI, 27 to 93%; $p = 0.014$). **Absolute risk reduction in mortality was 9.2% with a number needed to treat of 11.**

Monuteaux MC, Spencer TJ, Faraone SV, et al. A randomized, placebo-controlled clinical trial of bupropion for the prevention of smoking in children and adolescents with **attention-deficit/hyperactivity disorder**. J Clin Psychiatry. 2007 Jul;68(7):1094-101. While bupropion was not associated with a lower rate of smoking in youth with ADHD, post hoc analyses suggest that stimulant treatment was. Future controlled studies should investigate the role of stimulants in the prevention of smoking in children and adolescents with ADHD.

Moolgavkar SH, Holford TR, Levy DT et al. Impact of Reduced Tobacco Smoking on **Lung Cancer Mortality** in the United States During 1975-2000. J Natl Cancer Inst. 2012 Mar 14.

Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of **nicotine replacement therapy assisted reduction** to stop smoking: systematic review and meta-analysis. BMJ. 2009 Apr 2;338:b1024. doi: 10.1136/bmj.b1024.

Moore TJ, Glenmullen J, Furberg CD. **Thoughts and Acts of Aggression/Violence** Toward Others Reported in Association with **Varenicline** (September) (FREE). Ann Pharmacother. 2010 Jul 20.

Moore TJ, Furberg CD, Glenmullen J, Maltsberger JT, Singh S, 2011 **Suicidal Behavior and Depression in Smoking** Cessation Treatments. PLoS ONE 6(11): e27016. doi:10.1371/journal.pone.0027016

Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release **bupropion for adolescent** smoking cessation. Arch Pediatr Adolesc Med. 2007 Nov;161(11):1068-74. Sustained-release bupropion hydrochloride, 300 mg/d, plus brief counseling demonstrated short-term efficacy for adolescent smoking cessation. Abstinence rates were lower than those reported for adults, with rapid relapse after medication discontinuation.

Muscat JE, Ahn K, Richie JP Jr et al. **Nicotine dependence phenotype** and lung cancer risk. Cancer. 2011 Dec 1;117(23):5370-6.

Myers Katie; Hajek Peter; Hinds Charles; et al. **Stopping Smoking Shortly Before Surgery and Postoperative Complications**: A Systematic Review and Meta-analysis. Arch Intern Med. 2011;0(2011):archinternmed.2011.97.

Nathisuwan S, Dilokthornsakul P, Chaiyakunapruk N, et al. Assessing Evidence of **Interaction Between Smoking and Warfarin**: A Systematic Review and Meta-analysis. Chest. 2011 May;139(5):1130-9. National Institutes of Health State-of-the-Science Conference Statement: **Tobacco Use**: Prevention, Cessation, and Control. Ann Intern Med. 2006 Sep 5; [Epub ahead of print]

Nides M, et al. Smoking cessation with **varenicline**, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Arch Intern Med. 2006 Aug 14-28;166(15):1561-8. (InfoPOEMs: Approximately 1 in 7 highly motivated patients will not be smoking 1 year after taking varenicline (Chantix) 1 mg twice daily for 6 weeks. Lower doses did not work. Side effects will be common and will not be tolerated by some patients. (LOE = 1b-))

Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. Worldwide burden of disease from exposure to **second-hand** smoke: a retrospective analysis of data from 192 countries. Lancet. 2010 Nov 25.

Ockene I and Salmoirago-Blotcher E. **Varenicline** for smoking cessation in patients with **coronary heart disease**. Circulation 2010; 121:188-190.

Oncken C, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, **varenicline**, for smoking cessation. Arch Intern Med. 2006 Aug 14-28;166(15):1571-7.

Oncken C, Dornelas E, Greene J, et al. Nicotine **Gum for Pregnant Smokers**: A Randomized Controlled Trial. Obstet Gynecol. 2008 Oct;112(4):859-867. Although nicotine gum did not increase quit rates, use of nicotine gum increased birth weight and gestational age, two key parameters in predicting neonatal wellbeing.

Okuyemi KS, Nollen NL, Ahluwalia JS. **Interventions** to facilitate smoking cessation. Am Fam Physician. 2006 Jul 15;74(2):262-71. Review. Summary for patients in: Am Fam Physician. 2006 Jul 15;74(2):276.

O'Malley SS, et al. A controlled trial of **naltrexone augmentation** of nicotine replacement therapy for smoking cessation. Arch Intern Med. 2006 Mar 27;166(6):667-74.

Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their **lung age**: the Step2quit randomised controlled trial. BMJ. 2008 Mar 6; [Epub ahead of print] Telling smokers their lung age significantly improves the likelihood of them quitting smoking, but the mechanism by which this intervention achieves its effect is unclear.

Parsons A, Daley A, Begh R, Aveyard P. Influence of **smoking cessation after diagnosis** of early stage **lung cancer** on prognosis: systematic review of observational studies with meta-analysis. BMJ 2010;340:b5569, doi: 10.1136/bmj.b5569 (Published 21 January 2010)

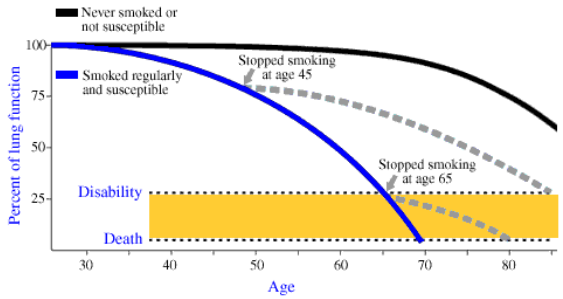
Pawson R, Wong G, Owen L. Myths, facts and conditional truths: What is the evidence on the risks associated with **smoking in cars carrying children**? CMAJ. 2011 Jul 12;183(10):E680-4.

Pbert L, Druker S, Difranza JR, et al. Effectiveness of a **School Nurse-Delivered Smoking-Cessation Intervention** for Adolescents. Pediatrics. 2011 Oct 17.

Pell JP, Haw S, Cobbe S, et al. **Smoke-free legislation** and hospitalizations for acute coronary syndrome. N Engl J Med. 2008 Jul 31;359(5):482-91. The number of admissions for acute coronary syndrome decreased after the implementation of smoke-free legislation. A total of 67% of the decrease involved nonsmokers. However, fewer admissions among smokers also contributed to the overall reduction.

TOP

Pharmacists Letter. New Regimen for Nicorette Gum: **Reduce-to-Quit** (RTQ). Aug 2007.
Piano Mariann R., Benowitz Neal L., FitzGerald Garret A., et al., and on behalf of the American Heart Association (AHA) Council on Cardiovascular Nursing Impact of **Smokeless Tobacco Products** on Cardiovascular Disease: Implications for Policy, Prevention, and Treatment: A Policy Statement From the American Heart Association. Circulation 122: 1520-1544; published online before print as doi:10.1161/CIR.0b013e3181f432c3
Pierce John P., Messer Karen, White Martha M., et al. **Prevalence of Heavy Smoking** in California and the United States, 1965-2007. *JAMA*. 2011;305(11):1106-1112.doi:10.1001/jama.2011.334
Piper Megan E.; Smith Stevens S.; Schlam Tanya R.; et al. A Randomized Placebo-Controlled Clinical Trial of **5 Smoking Cessation Pharmacotherapies**. Arch Gen Psychiatry. 2009;66(11):1253-1262. While the nicotine lozenge, bupropion, and bupropion plus lozenge produced effects that were comparable with those reported in previous research, the nicotine patch plus lozenge produced the greatest benefit relative to placebo for smoking cessation.
Planer David; Lev Ishay; Elitzur Yair; et al. **Bupropion** for Smoking Cessation in Patients With **Acute Coronary Syndrome**. Arch Intern Med. 2011;0(2011):archinternmed.2011.72. (Not increase smoking abstinence)
Pletcher MJ, et al. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Arch Intern Med. 2006 Sep 25;166(17):1915-22.
Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute phase reactants and cigarette smoking status predict radiographic progression in the spine in early **axial spondyloarthritis**. Arthritis Rheum. Published Online First: 29 Nov 2011.
Polakowski LL, Akinbami LJ, Mendola P. Prenatal Smoking Cessation and the Risk of Delivering **Preterm and Small-for-Gestational-Age Newborns**. Obstet Gynecol. 2009 Aug;114(2, Part 1):318-325.
Pollak KI, Oncken CA, et al. Nicotine replacement and behavioral therapy for smoking cessation in **pregnancy**. Am J Prev Med. 2007 Oct;33(4):297-305.
Prochaska JJ, Hilton JF. Risk of **cardiovascular serious adverse events associated with varenicline** use for tobacco cessation: systematic review and meta-analysis. BMJ. 2012 May 4;344:e2856.
Prochazka AV, Kick S, Steinbrunn C, Miyoshi T, Fryer GE. A randomized trial of **nortriptyline combined with transdermal nicotine** for smoking cessation. Arch Intern Med. 2004 Nov 8;164(20):2229-33.
Prochazka AV, Weaver MJ, Keller RT, Fryer GE, Licari PA, Lofaso D. A randomized trial of **nortriptyline** for smoking cessation. Arch Intern Med. 1998 Oct 12;158(18):2035-9.
Prokhorov Alexander V.; Hudmon Karen Suchanek; Marani Salma; et al. Engaging Physicians and Pharmacists in Providing **Smoking Cessation Counseling**. Arch Intern Med. 2010;170(18):1640-1646.
Raad D, Gaddam S, Schunemann HJ, et al. Effects of **Water-Pipe Smoking** (WPS) on Lung Function: A Systematic Review and Meta-analysis. Chest. 2011 Apr;139(4):764-74.
Ranney L, Melvin C, Lux L, McClain E, Lohr KN. Systematic Review: Smoking Cessation **Intervention** Strategies for Adults and Adults in Special Populations. Ann Intern Med. 2006 Sep 5; [Epub ahead of print]
Reda AA, Kaper J, Fikrelter H, et al. Healthcare **financing systems** for increasing the use of tobacco dependence treatment. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004305. Full financial interventions directed at smokers when compared to no financial interventions could increase the proportion quitting, quit attempts and utilization of pharmacotherapy by smokers. Although the absolute differences were small the costs per additional quitter were low.
Reynolds K, Liese AD, Anderson AM, et al. Prevalence of Tobacco Use and Association between Cardiometabolic Risk Factors and Cigarette **Smoking in Youth with Type 1 or Type 2 Diabetes Mellitus**. J Pediatr. 2011 Apr;158(4):594-601.e1.
Retnakaran R, et al. Cigarette smoking and **cardiovascular risk** factors among Aboriginal Canadian youths. CMAJ. 2005 Oct 11;173(8):885-9.
Rigotti NA, et al. Bupropion for smokers hospitalized with acute **cardiovascular disease**. Am J Med. 2006 Dec;119(12):1080-7. Bupropion improved short-term but not long-term smoking cessation rates over intensive counseling and appeared to be safe in hospitalized smokers with acute cardiovascular disease.
Rigotti NA, Munafo MR, and Stead LF. Smoking cessation interventions for **hospitalized smokers**. A systematic review. Arch Intern Med 2008; 168:1950-1960. Offering smoking cessation counseling to all hospitalized smokers is effective as long as supportive contacts continue for more than 1 month after discharge. Adding nicotine replacement therapy to counseling may further increase smoking cessation rates and should be offered when clinically indicated, especially to hospitalized smokers with nicotine withdrawal symptoms.
Rigotti N A, Pipe AL, Benowitz NL, et al. Efficacy and safety of **varenicline** for smoking cessation in patients with cardiovascular disease (**CVD**). Circulation 2010; 121:221-229.
Rodondi N, Collet TH, Nanchen D, et al. Impact of **carotid plaque screening** on smoking cessation and other cardiovascular risk factors: a randomized controlled trial. Arch Intern Med. doi:10.001/archinternmed.2011.1326.
Rodriguez Josanna, Jiang Rui, Johnson W. Craig, Et al. The Association of **Pipe and Cigar** Use With Cotinine Levels, Lung Function, and Airflow Obstruction: A Cross-sectional Study. *Ann Intern Med* February 16, 2010 152:201-210
Roosaar A, Johansson AL, Sandborgh-Englund G, Axéll T, Nyrén O. Cancer and mortality among users and nonusers of **snus**. Int J Cancer. 2008 Jul 1;123(1):168-73. A statistically significant increase in the incidence of the combined category of oral and pharyngeal cancer among daily users of snus (incidence rate ratio 3.1, 95% confidence interval 1.5-6.6) was found. Overall mortality was also slightly increased (hazard ratio 1.10, 95% confidence interval 1.01-1.21). Although the combined previous literature on snus and oral cancer weigh toward no association, this population-based prospective study provided suggestive evidence of snus-related risks that cannot be lightly ignored.
Rosen LJ, Noach MB, Winickoff JP et al. **Parental Smoking Cessation** to Protect Young Children:A Systematic Review and Meta-analysis. Pediatrics. 2012 Jan;129(1):141-52
Rusanen Minna; Kivipelto Miia; Quesenberry Charles P., et al. Heavy Smoking in Midlife and Long-term Risk of **Alzheimer Disease and Vascular Dementia**. Arch Intern Med. 2010;0(2010):archinternmed.2010.393.
Sabia S, Elbaz A, Dugravot A, et al. Impact of Smoking on **Cognitive Decline** in Early Old Age: The Whitehall II Cohort Study. Arch Gen Psychiatry. 2012 Feb 6.
Schroeder SA. A 51-year-old woman with **bipolar disorder** who wants to quit smoking. JAMA. 2009 Feb 4;301(5):522-31. Epub 2009 Jan 6.
Schnoll Robert A., Patterson Freda, Wileyto E. Paul, Et al. Effectiveness of **Extended-Duration Transdermal Nicotine Therapy**: A Randomized Trial. Ann Intern Med February 2, 2010 152:144-151; doi:10.1059/0003-4819-152-3-201002020-00005
Schultz AS et al. A qualitative investigation of **smoke-free policies on hospital property**. CMAJ. 2011 Dec 13;183(18):E1334-44.
SDIS – Guidelines for NRT during pregnancy and lactation. Available at: http://www.usask.ca/pharmacy-nutrition/services/sdis.shtml
Seung-Kwon Myung; Diana D. McDonnell; Gene Kazinets; Hong Gwan Seo; Joel M. Moskowitz Effects of **Web- and Computer-Based Smoking Cessation Programs**: Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2009;169(10):929-937.
Sheffer MA, Baker TB, Fraser DL, et al. **Fax referrals, academic detailing**, and tobacco quitline use a randomized trial. Am J Prev Med. 2012 Jan;42(1):21-8.
Shields B, Hill A, Bilous M, Knight B, Hattersley AT, Bilous RW, Vaidya B. Cigarette smoking during pregnancy is associated with alterations in maternal and fetal thyroid function. J Clin Endocrinol Metab. 2008 Nov 18. [Epub ahead of print] Cigarette smoking is associated with changes in maternal thyroid function throughout the pregnancy and in fetal thyroid function as measured in cord blood samples.
Sibbald M, Yan AT, Huang W, et al. Association between smoking, outcomes, and early **clopidogrel** use in patients with acute coronary syndrome: Insights from the Global Registry of Acute Coronary Events. *Am Heart J* 2010; 160:855-861. (no effect)
Siegel M. A Lost Opportunity for Public Health - The FDA Advisory Committee Report on **Menthol**. N Engl J Med. 2011 May 4.
Sims Michelle, Maxwell Roy, Bauld Linda, Gilmore Anna. Short term impact of smoke-free legislation in England: retrospective analysis of hospital admissions for **myocardial infarction**. BMJ 2010;340:c2161
Singh S, Loke YK, Spangler JG, et al. Risk of serious adverse **cardiovascular events associated with varenicline**: a systematic review and meta-analysis. CMAJ. 2011 Jul 4.
Smith PM, Burgess E. Smoking cessation initiated during hospital stay for **patients with coronary artery disease**: a randomized controlled trial. CMAJ 2009; 180:1297-1303.
Smith Stevens S.; McCarthy Danielle E.; Japuntich Sandra J.; et al. Comparative Effectiveness of 5 Smoking Cessation Pharmacotherapies in Primary Care Clinics. *Arch Intern Med*. 2009;169(22):2148-2155. Bupropion SR + lozenge was superior to all of the monotherapies (odds ratio, 0.46-0.56); patch + lozenge was superior to patch and bupropion monotherapies (odds ratio, 0.56 and 0.54, respectively).
Smoking Cessation benefits: Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977 Jun 25;1(6077):1645-8.



Soria R, et al. A randomised controlled trial of **motivational** interviewing for smoking cessation. Br J Gen Pract. 2006 Oct;56(531):768-74. (InfoPOEMs: In this study with several biases favoring the intervention, motivational interviewing appears to be more effective than brief advice in promoting smoking cessation. (LOE = 2b))
Stapleton JA, Watson L, Spirling LI, et al. **Varenicline** in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those **with mental illness**. Addiction. 2008 Jan;103(1):146-54. Epub 2007 Nov 19. (n=412 over 6weeks) In this setting and with group support varenicline appears to improve success rates over those achieved with NRT, and is equally effective and safe in those with and without a mental illness.
Stead L, Lancaster T. Interventions to reduce harm from **continued tobacco use**. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005231. There is insufficient evidence about long-term benefit to give firm support the use of interventions intended to help smokers reduce but not

TOP

quit tobacco use.
Stead LF, Perera R, Bullen C, Mant D, et al. **Nicotine replacement therapy** for smoking cessation. **Cochrane** Database Syst Rev. 2008 Jan 23;(1):CD000146. All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50-70%, regardless of setting.The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT.
Stead LF, et al. **Physician advice** for smoking cessation. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD000165. Simple advice has a small effect on cessation rates. Assuming an unassisted quit rate of 2 to 3%, a brief advice intervention can increase quitting by a further 1 to 3%. Additional components appear to have only a small effect, though there is a small additional benefit of more intensive interventions compared to very brief interventions.
Stewart ST, Cutler DM, Rosen AB. Forecasting the effects of obesity and smoking on U.S. **life expectancy**. N Engl J Med. 2009 Dec 3;361(23):2252-60. PubMed
Steinberg MB, Schmelzer AC, Richardson DL, Foulds J. The case for treating **tobacco dependence as a chronic disease**. Ann Intern Med. 2008 Apr 1;148(7):554-6.
Steinberg MB, Greenhaus S, Schmelzer AC, Bover MT, Foulds J, Hoover DR, et al. **Triple-combination pharmacotherapy** for medically ill smokers: a randomized trial. Ann Intern Med. 2009 Apr 7;150(7):447-54. Flexibly dosed triple-combination pharmacotherapy for up to 6 months was more effective than standard-duration nicotine patch therapy for outpatient smokers with medical illnesses.
Stone KC, LaGasse LL, Lester BM, et al. **Sleep problems in children** with prenatal substance exposure: the Maternal Lifestyle study. Arch Pediatr Adolesc Med. 2010 May;164(5):452-6.
Strandberg-Larsen K, et al. Use of nicotine replacement therapy during **pregnancy** and stillbirth: a cohort study. BJOG. 2008 Oct;115(11):1405-10. Epub 2008 Aug 20. Our study does not indicate that use of NRT during pregnancy increases the risk of stillbirth.
Strandberg AY, Strandberg TE, Pitkala K, et al. The effect of smoking in midlife on health-related quality of life in old age. A 26-year prospective study. Arch Intern Med 2008; 168:1968-1974. During the 26-year follow-up of this socioeconomically homogeneous male cohort, HRQoL deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. Never-smokers lived longer than heavy smokers, and their extra years were of better quality.
Stranges S, et al. Lifetime cumulative exposure to **secondhand** smoke and risk of myocardial infarction in never smokers: results from the Western new york health study, 1995-2001. Arch Intern Med. 2006 Oct 9;166(18):1961-7. Exposure to SHS has declined sharply among nonsmokers in recent years. In the absence of high levels of recent exposure to SHS, cumulative lifetime exposure to SHS may not be as important a risk factor for MI as previously thought.
Surgeon General: A Report of "How Tobacco **Smoke Causes Disease**: The Biology and Behavioral Basis for Smoking-Attributable Disease". Executive Summary 2010 http://www.surgeongeneral.gov/library/tobaccosmoke/report/executivesummary.pdf
Swamy GK, Roelands JJ, Peterson BL, et al. Predictors of adverse events among **pregnant** smokers exposed in a nicotine replacement therapy trial. Am J Obstet Gynecol. 2009 Oct;201(4):354.e1-7. Epub 2009 Aug 7.
Syamlal G, Mazurek JM, Malarcher AM. Current cigarette smoking **prevalence among working adults**—United States, 2004—2010.MMWR Morb Mortal Wkly Rep 2011; 60:1305-1309.
Tahiri M, Mottillo S, Joseph L, et al. **Alternative Smoking Cessation Aids**: A Meta-analysis of Randomized Controlled Trials. Am J Med. 2012 Jun;125(6):576-84.
Tanski SE, Wilson KM. Children and **secondhand smoke**: clear evidence for action. Pediatrics. 2012 Jan;129(1):170-1.
Tashkin DP, Rennard S, Hays JT, et al. Effects of **Varenicline on Smoking Cessation in Mild-to-Moderate COPD**: A Randomized Controlled Trial. Chest. 2010 Sep 23.
Thomsen T, Tønnesen H, Møller AM. Effect of preoperative smoking cessation interventions on postoperative complications and smoking cessation. Br J Surg. 2009 May;96(5):451-61.
Thomsen T, Villebro N, Møller AM. Interventions for **preoperative smoking cessation**. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD002294. There is evidence that preoperative smoking interventions including NRT increase short-term smoking cessation and may reduce postoperative morbidity. The optimal preoperative intervention intensity remains unknown. Based on indirect comparisons and evidence from two small trials, interventions that begin four to eight weeks before surgery, include weekly counselling, and use NRT are more likely to have an impact on complications and on long-term smoking cessation.
Tolstrup JS, Kristiansen L, Becker U, et al. Smoking and risk of acute and chronic **pancreatitis** among women and men: a population-based cohort study. Arch Intern Med. 2009 Mar 23;169(6):603-9. In this population of Danish men and women, smoking was independently associated with increased risk of pancreatitis.
Tran K, Asakawa K, Cimon K, et al. Pharmacologic-based strategies for smoking cessation: **clinical and cost-effectiveness analyses. Canadian Agency for Drugs and Technologies in Health(CADTH)**.2010Sep:1-548.
Tsoi DT, Porwal M, Webster AC. Efficacy and safety of **bupropion** for smoking cessation and reduction in **schizophrenia**: systematic review and meta-analysis. Br J Psychiatry. 2010 May;196(5):346-53.
Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with **schizophrenia**. Cochrane Database Syst Rev. 2010 Jun 16;(6):CD007253.
Tverdal A, Bjartveit K. Health consequences of **reduced daily cigarette** consumption. Tob Control. 2006 Dec;15(6):472-80. Long-term follow-up provides no evidence that heavy smokers who cut down their daily cigarette consumption by >50% reduce their risk of premature death significantly. In health education and patient counselling, it may give people false expectations to advise that reduction in consumption is associated with reduction in harm.
Tynan M, Babb S, MacNeil A, Griffin M. **State smoke-free laws** for worksites, restaurants, and bars—United States, 2000-2010. MMWR Morb Mortal Wkly Rep April 22, 2011; 60: 472-475.
Uhl GR, Liu QR, Drgon T, et al. **Molecular genetics** of successful smoking cessation: convergent genome-wide association study results. Arch Gen Psychiatry. 2008 Jun;65(6):683-93.
U.S. Preventive Services Task Force **USPSTF. Counseling and interventions** to prevent tobacco use and tobacco-caused disease in adults and pregnant women: USPSTF reaffirmation recommendation statement. Ann Intern Med. 2009 Apr 21;150(8):551-5.
Ussher MH, Taylor A, Faulkner G. **Exercise interventions** for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD002295. DOI: 10.1002/14651858.CD002295.pub3. Only one of the 15 trials offered evidence for exercise aiding smoking cessation at a 12-month follow up.
van Domburg RT, op Reimer WS, Hoeks SE, Kappetein AP, Bogers AJ. **Three life-years gained** from smoking cessation after coronary artery bypass surgery: a 30-year follow-up study. Am Heart J. 2008 Sep;156(3):473-6. Epub 2008 Jun 26.
Vardavas CI, Anagnostopoulos N, Kougias M, et al. Short-term Pulmonary Effects of Using an **Electronic Cigarette**: Impact on Respiratory Flow Resistance, Impedance, and Exhaled Nitric Oxide. Chest. 2012 Jun;141(6):1400-6.
Volpp KG, Troxel AB, Pauly MV, Glick HA, et al. A randomized, controlled trial of **financial incentives** for smoking cessation.N Engl J Med. 2009 Feb 12;360(7):699-709.
Vozoris NT. **Mentholated cigarettes** and cardiovascular and pulmonary diseases: a population-based study. Arch Intern Med. 2012 Apr 9;172(7):590-1.
Wahawisan Joy, Kolluru Srikanth, et al. **Methadone Toxicity Due to Smoking Cessation**—A Case Report on the Drug-Drug Interaction Involving Cytochrome P450 Isoenzyme 1A2. Ahead of Print on 1 June 2011, DOI 10.1345/aph.1P759. Ann Pharmacother ;45:e34.
Wang H, O'Reilly EJ, Weisskopf MG, et al. Smoking and risk of **amyotrophic lateral sclerosis**: a pooled analysis of 5 prospective cohorts. Arch Neurol. 2011 Feb;68(2):207-13.
Washko George R, Hunninghake Gary M., Fernandez Isis E., et al. for the COPDGene Investigators. **Lung Volumes and Emphysema** in Smokers with Interstitial Lung Abnormalities. N Engl J Med 2011; 364:897-906.
Weeks SG, Glantz SA, De Marco T, Rosen AB, Fleischmann KE. **Secondhand smoke** exposure and quality of life in patients with **heart failure**. Arch Intern Med. 2011;171(21):1887-1893.
Wertz MS, Kyriss T, Paranjape S, Glantz SA. The **Toxic Effects of Cigarette Additives**. Philip Morris' Project Mix Reconsidered: An Analysis of Documents Released through Litigation. PLoS Med. 2011 Dec;8(12):e1001145.
West R, Sohal T. "Catastrophic" pathways to smoking cessation: findings from national survey. BMJ. 2006 Feb 25;332(7539):458-60. Epub 2006 Jan 27.
West Robert, Zatonski Witold, Cedzynska Magdalena, et al. Placebo-Controlled Trial of **Cytisine** for Smoking Cessation. N Engl J Med 2011;365:1193-20.
Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2007 Dec 12;298(22):2654-64. Active smoking is associated with an increased risk of type 2 diabetes.
Williams KE, Reeves KR, Billing CB Jr, Pennington AM, Gong J. A double-blind study evaluating the long-term (**1yr**) safety of **varenicline** for smoking cessation. Curr Med Res Opin. 2007 Apr;23(4):793-801.
Wilson SR, Farber HJ, et al. A Randomized Trial of Parental Behavioral Counseling and Cotinine Feedback for Lowering Environmental Tobacco Smoke Exposure in Children With Asthma: Results of the LET'S Manage Asthma Trial. Chest. 2011 Mar;139(3):581-90.
Winkels RM, Botma A, Van Duijnhoven FJ et al. Smoking Increases the Risk for **Colorectal Adenomas** in Patients With Lynch Syndrome. Gastroenterology. 2011 Nov 4.
Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. **Nicotine patches for pregnant** smokers: a randomized controlled study. Obstet Gynecol. 2000 Dec;96(6):967-71.
Woloshin S, Schwartz LM, Welch HG. The risk of **death** by age, sex, and smoking status in the United States: putting health risks in context. J Natl Cancer Inst. 2008 Jun 18;100(12):845-53. Epub 2008 Jun 10. Cigarettes rob 5 to 10 years of life from smokers. Get a copy of this paper because it has several tables that might be useful to help motivate patients to quit smoking. An earlier paper by this team also has useful tables that can be found at http://www.aafp.org/afp/20070315/poc.html. (LOE = 2c)
Xu, Xiaohui, Cook, Robert L., Ilacqua, Vito A., et al. Racial Differences in the Effects of Postnatal Environmental Tobacco Smoke on Neurodevelopment (a **ADHD** risk). Pediatrics 2010 0: peds.2009-3589
Xue Fei; Willett Walter C.; Rosner Bernard A.; et al. Cigarette Smoking and the Incidence of **Breast Cancer**. Arch Intern Med. 2011;171(2):125-133.
Yadav Dhiraj; Hawes Robert H.; et al. for the North American Pancreatic Study Group. Alcohol Consumption, Cigarette Smoking, and the Risk of Recurrent Acute and **Chronic Pancreatitis.** Arch Intern Med. 2009;169(11):1035-1045.
Yamin Cyrus K., Bitton Asaf, Bates David W.. **E-Cigarettes**: A Rapidly Growing Internet Phenomenon. *Ann Intern Med* November 2, 2010 153:607-609.
Yeh Hsin-Chieh, Duncan Bruce B., Schmidt Maria Inês, et al. Smoking, Smoking Cessation, and **Risk for Type 2 Diabetes** Mellitus: A Cohort Study. Ann Intern Med January 5, 2010 152:10-17.
Zammit, Stanley, Thomas, Kate, Thompson, Andrew, et al. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent **psychotic symptoms** in offspring. The British Journal of Psychiatry 2009 195: 294-300
Zesiewicz TA, Greenstein PE, Sullivan KL, et al. A randomized trial of **varenicline** (Chantix) for the treatment of **spinocerebellar ataxia type 3**. Neurology. 2012 Feb 21;78(8):545-50.
Zivadinov R, Weinstock-Guttman B, Hashmi K, Abdelrahman N, Stosic M, Dwyer M, Hussein S, Durfee J, Ramanathan M. Smoking is associated with increased lesion volumes and brain atrophy in **multiple sclerosis**. Neurology. 2009 Aug 18;73(7):504-10.

[xlviii] Critchley J, Capewell S. Mortality Risk Reduction Associated with Smoking Cessation in Patients with Coronary Heart Disease. JAMA 2003; 290(1):86-97.
[xlix] http://heartdisease.about.com/cs/riskfactors/a/rimonabant_p.htm; http://www.docguide.com/news/content.nsf; http://www.uc.edu/news/NR.asp?id=1417; http://psychiatriymmc.com/displayArticle.cfm?article.cfm?articleID=article105
[l] Acomplia (rimonabant) and OTC orlistat for weight loss. Pharmacist's Letter 2006;22(3):220313.

TOP

References Cannabinoids:

Prepared by: Brent Jensen BSP, Loren Regier BSP BA for www.RxFiles.ca

Link to – Health Canada - Medical Marihuana: How to Apply: http://www.hc-sc.gc.ca/dhp-mps/marihuana/how-comment/applicant-demandeur/index-eng.php

1. Williamson EM, Evans FJ. Cannabinoids in clinical practice. Drugs. 2000 Dec;60(6):1303-14.
2. Use of Cannabis or Cannabinoids for Non-Malignant Chronic Pain Feb 2004. Alberta Heritage Foundation for Medical Research http://www.ahfmr.ab.ca/publications
3. Beal JE, Olson R, Laubenstein L, et al. **Dronabinol** as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage. 1995 Feb;10(2):89-97. n-139
4. Natural Medicines Comprehensive Database 2011
   May/09 CNN: The average potency of marijuana, which has risen steadily for three decades, has exceeded 10 percent for the first time, the U.S. government will report on Thursday. Scientists working for the government predict that potency, as measured by the drug's concentration of the psychoactive ingredient THC, will continue to rise. At the University of Mississippi's Potency Monitoring Project, where thousands of samples of seized marijuana are tested every year, project director Mahmoud ElSohly said some samples have THC levels exceeding 30 percent. Average THC concentrations will continue to climb before leveling off at 15 percent or 16 percent in five to 10 years, ElSohly predicted. The average THC for tested marijuana during 2008 was 10.1 percent, according to the government, compared to 1983 when it was reportedly under 4 percent. Even drugs seized at the United States' southwest border are showing increasing potency, the Office of National Drug Control Policy says. The median potency increased from 4.8 percent in 2003 to 7.3 percent in 2007. Marijuana from Mexico and other southern sources traditionally had lower THC content than other sources. http://www.whitehousedrugpolicy.gov/drugfact/marijuana/index.html
5. Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ. 2001 Jul 7;323(7303):13-6. Conclusion: Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for **pain management** is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed.
6. Tramer MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ. 2001 Jul 7;323(7303):16-21. CONCLUSIONS: In selected patients, the cannabinoids tested in these trials **may be** useful as mood enhancing adjuvants for controlling **chemotherapy** related sickness. Potentially serious adverse effects, even when taken short term orally or intramuscularly, are likely to limit their widespread use.
7. Zajicek J, Fox P, et al.; UK MS Research Group. Cannabinoids for treatment of spasticity & other symptoms related to **multiple sclerosis** (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 2003 Nov 8;362(9395):1517-26.n=630 15wk INTERPRETATION: Treatment with cannabinoids did **not** have a beneficial effect on **spasticity** when assessed with the Ashworth scale. However, though there was a degree of unmasking among the patients in the active treatment groups, objective improvement in mobility and patients' **opinion of an improvement in pain** suggest cannabinoids might be clinically useful.
8. Fox P, Bain PG, Glickman S, et al. The effect of cannabis on **tremor** in patients with **multiple sclerosis**. Neurology. 2004 Apr 13;62(7):1105-9. n=14 Cannabis extract does **not** produce a functionally significant improvement in MS-associated **tremor**.
9. Smith PF. The safety of cannabinoids for the treatment of **multiple sclerosis**. Expert Opin Drug Saf. 2005 May;4(3):443-56. Conclusion: given the modest therapeutic effects of cannabinoids demonstrated so far, & the risk of long-term adverse side effects, there is reason to be **cautious about their use** in the treatment of MS.
10. Marijuana Medical Access Division, Drug Strategy & Controlled Substances Program, AL: 3503B, Ottawa, On K1A 1B9 **1-866-337-7705**) or the **website** www.hc-sc.gc.ca/dhp-mps/marihuana/index_e.html -Forms **B1** & **B2** & **Daily** Amount Fact Sheet Info for Health care professionals: www.hc-sc.gc.ca/dhp-mps/marihuana/how-comment/medpract/infoprof/information_e.html
    Marijuana Stakeholder statistics from Health Canada: http://www.hc-sc.gc.ca/dhp-mps/marihuana/stat/index-eng.php
11. Sativex Fact sheet Health Canada http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/sativex_factsheet_e.pdf Trial Info at www.gwpharm.com & **www.ccohta.ca**
12. Zajicek JP, et al.. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005 Dec;76(12):1664-9.
13. Laumon B, Gadegbeku B, Martin JL, Biecheler MB. Cannabis intoxication and fatal road crashes in France: population based case-control study. BMJ. 2005 Dec 10;331(7529):1371. Epub 2005 Dec 1.
14. London Royal Collage of Physicians Report Cannabis and cannabis-based medicines. Potential benefits and risks to health. Report of a Working Party 2005 Summary & Conclusions: http://www.rcplondon.ac.uk/pubs/books/cannabis/cannabis_summary.pdf
15. Arendt M, Rosenberg R, Foldager L, Perto G, Munk-Jorgensen P. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. Br J Psychiatry. 2005 Dec;187:510-5. (Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002 Nov 23;325(7374):1212-3.)
16. Fergusson DM, Poulton R, Smith PF, Boden JM. Cannabis and psychosis. BMJ. 2006 Jan 21;332(7534):172-5.
17. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. Ann Pharmacother. 2006 Feb;40(2):251-60. Epub 2006 Jan 31.
18 Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9.
19. Fergusson DM, Poulton R, Smith PF, Boden JM. Cannabis and psychosis. BMJ. 2006 Jan 21;332(7534):172-5.
20. Muller-Vahl KR. Cannabinoids reduce symptoms of Tourette's syndrome. Expert Opin Pharmacother. 2003 Oct;4(10):1717-25.
21. Mehra R, Moore BA, Crothers K, Tetrault J, Fiellin DA. The association between marijuana smoking and lung cancer: a systematic review. Arch Intern Med. 2006 Jul 10;166(13):1359-67.
22. Nabilone for Chemotherapy induced nausea & vomiting. Medical Letter Dec 4/18, 2006.
23. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. J Pain Symptom Manage. 2006 Nov;32(5):497-501. n=30 Doses of marihuana ranged from less than 1 to 5g per day via the smoked or oral route of administration. Ninety-three percent of patients reported moderate or greater pain relief. Side effects were reported by 76% of patients, the most common of which were increased appetite and a sense of well-being, weight gain, and slowed thoughts. (Ave dose = 2.5g/day).
24. Collin C, Davies P, Mutiboko IK, Ratcliffe S; Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol. 2007 Mar;14(3):290-6. (n=189 6 weeks) The primary efficacy analysis on the intention to treat (ITT) population (n = 184) showed the active preparation to be significantly superior (P = 0.048). Secondary efficacy measures were all in favour of active preparation but did not achieve statistical significance. The responder analysis favoured active preparation, 40% of subjects achieved >30% benefit (P = 0.014). Eight withdrawals were attributed to adverse events (AEs); six were on active preparation and two on placebo. We conclude that this CBM may represent a useful new agent for treatment of the symptomatic relief of spasticity in MS.
25. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007 Feb 13;68(7):515-21. n=50 Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.
26. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med. 2007 Feb 12;167(3):221-8.
27. Moore TH, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007 Jul28;370(9584):319-28. The evidence is consistent with the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong. The uncertainty about whether cannabis causes psychosis is unlikely to be resolved by further longitudinal studies such as those reviewed here. However, we conclude that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.
28. Pharmacist's Letter. Sativex for Advanced Cancer Pain. Sept 2007.
29. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A,Robinson G, Beasley R. THE EFFECTS OF CANNABIS ON PULMONARY STRUCTURE, FUNCTION AND SYMPTOMS. Thorax. 2007 Jul 31; [Epub ahead of print] Smoking cannabis was associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. In contrast, cannabis smoking was seldom associated with macroscopic emphysema. The 1:2.5 to 5 dose equivalence between cannabis joints and tobacco cigarettes for adverse effects on lung function is of major public health significance.
30. Narang S, Gibson D, Wasan AD, et al. Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy. J Pain. 2007 Dec 12; [Epub ahead of print]
31. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008 Feb;9(2):164-73. n=40 4weeks Epub 2007 Nov 5. As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia.
32. Wissel J, Haydn T, Müller J, Brenneis C, Berger T, Poewe W, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. J Neurol 2006;253(10):1337-41.
33. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone 2mg and dihydrocodeine 240mg for chronic neuropathic pain: randomised, crossover, double blind study. BMJ. 2008 Jan 8; [Epub ahead of print] Dihydrocodeine provided better pain relief than the synthetic cannabinoid nabilone and had slightly fewer side effects, although no major adverse events occurred for either drug.
34. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004 Jul 31;329(7460):253. Epub 2004 Jul 16. Dronabinol has a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis. Adverse events, including dizziness, were more frequent with dronabinol than with placebo during the first week of treatment.
35. Thomson WM, Poulton R, et al. Cannabis smoking and periodontal disease among young adults. JAMA. 2008 Feb 6;299(5):525-31. Cannabis smoking may be a risk factor for periodontal disease that is independent of the use of tobacco.
36. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J. 2008 Mar;155(3):465-70. These preliminary results suggest possible hazards of marijuana for patients who survive acute myocardial infarction.
37. Hézode C, Zafrani ES, Roudot-Thoraval F, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. Gastroenterology. 2008 Feb;134(2):432-9. Epub 2007 Nov 28.
38. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008 Jun 17;178(13):1669-78. Short-term use of existing medical cannabinoids appeared to increase the risk of nonserious adverse events. The risks associated with long-term use were poorly characterized in published clinical trials and observational studies. High-quality trials of long-term exposure are required to further characterize safety issues related to the use of medical cannabinoids.
39. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007 Dec 15;133(1-3):210-20. Epub 2007 Nov 7.
40. Ghaffar O, Feinstein A. Multiple sclerosis and cannabis: a cognitive and psychiatric study. Neurology. 2008 Jul 15;71(3):164-9. Epub 2008 Feb 13. Inhaled cannabis is associated with impaired mentation in patients with multiple sclerosis, particularly with respect to cognition.
41. Busse F, Omidi L, Timper K, Leichtle A, Windgassen M, Kluge E, Stumvoll M. Lead poisoning due to adulterated marijuana. N Engl J Med. 2008 Apr 10;358(15):1641-2.
42. Vandrey RG, Budney AJ, Hughes JR, Liguori A. A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. Drug Alcohol Depend. 2008 Jan 1;92(1-3):48-54. Epub 2007 Jul 23.
43. Arendt M, Mortensen PB, Rosenberg R, et al. Familial predisposition for psychiatric disorder: comparison of subjects treated for cannabis-induced psychosis and schizophrenia. Arch Gen Psychiatry. 2008 Nov;65(11):1269-74. Predisposition to both psychiatric disorders in general and psychotic disorders specifically contributes equally to the risk of later treatment because of schizophrenia and cannabis-induced psychoses. Cannabis-induced psychosis could be an early sign of schizophrenia rather than a distinct clinical entity.
44. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. A Randomised Placebo Controlled Double Blind Clinical Trial of Cannabis Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy: Depression is a Major Confounding Factor. Diabetes Care. 2009 Oct 6. [Epub ahead of print] n=30. This first ever, trial assessing the efficacy of cannabis has shown it to be no more efficacious than placebo in painful-DPN. Depression was a major confounder and may have important implications for future painful-DPN trials.
45. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet. 2009 Oct 17;374(9698):1383-91.
46. Di Forti M, Morgan C, Dazzan P, et al. High-potency cannabis and the risk of psychosis. Br J Psychiatry. 2009 Dec;195(6):488-91.
47. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg. 2010 Feb;110(2):604-10. Epub 2009 Dec 10.
    (CADTH Rapid Response: Limited evidence suggests that nabilone may be better than placebo in relieving chronic pain but its relative benefits compared to other analgesics have not been proven. Current guidelines recommend the dosage of nabilone for treating neuropathic pain be titrated gradually until target relief is obtained.)
48. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). CNS Neurosci Ther. 2009;15(1):84-8.
49. Medical Letter. Medical Marijuana. Jan 25,2010.
50. Moulin DE, Clark AJ, Gilron I, et al. Canadian Pain Society. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag. 2007 Spring;12(1):13-21.
51. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med. 2009 Nov;10(8):1353-68. Epub 2009 Sep 1.
52. Yamreudeewong W, Wong HK, Brausch LM, et al. Probable interaction between warfarin and marijuana smoking. Ann Pharmacother. 2009;43:1347-1353.
53. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9:506-521.
54. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy. Diabetes Care 2010; 33(10):128-130.

TOP

55. Regier L. RxFiles Substance Abuse Chart, from RxFiles Drug Comparison Charts. Accessed online at 23 Mar, 2010: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Substance-Abuse.pdf
56. Winstock Adam R, Ford Chris, Witton John. Assessment and management of cannabis use disorders in primary care. BMJ 2010;340:c1571, doi: 10.1136/bmj.c1571 (1 April 2010).
57. Hoffmann, Diane E., Weber, Ellen. Medical Marijuana and the Law. N Engl J Med 2010 362: 1453-1457.
58. Goldman RD. Drug-induced gynecomastia in children and adolescents. Can Fam Physician. 2010 Apr;56(4):344-5.
59. Ware, Mark A., Wang, Tongtong, Shapiro, Stan, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010 0: cmaj.091414
60. Room R. Prohibition of cannabis. BMJ. 2010 Oct 6;341:c5492. doi:10.1136/bmj.c5492.
61. Nguyen LT, Picard-Bernard V, Perriot J. Legionnaires disease in cannabis smokers. Chest. 2010 Oct;138(4):989-91.
62 Large Matthew; Sharma Swapnil; Compton Michael T.; et al. Cannabis Use and Earlier Onset of Psychosis: A Systematic Meta-analysis. Arch Gen Psychiatry. 2011;0(2011):archgenpsychiatry.2011.5.
63. Kuepper R, van Os J, Lieb R, Wittchen H, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study BMJ 342:doi:10.1136/bmj.d738 (Published 1 March 2011)Accessed online at: http://www.bmj.com/content/342/bmj.d738.full.
64. Wells Daina L, Ott Carol A. The "New" Marijuana. Articles Ahead of Print published on 1 March 2011, DOI 10.1345/aph.1P580. Ann Pharmacother ;45:414-417. (JWH-018 powder, K2, spice)
65. Honarmand Kimia, Tierney Mary C., O'Connor Paul, et al. Effects of cannabis on cognitive function in patients with multiple sclerosis. Neurology March 29, 2011 76:1153-1160.
66. Robbins MS, Tarshish S, Solomon S, Grosberg BM. Cluster attacks responsive to recreational cannabis and dronabinol. Headache. 2009 Jun;49(6):914-6. Epub 2009 Feb 11.
67. Fontes, Maria Alice, Bolla, Karen I., Cunha, Paulo Jannuzzi, et al. Cannabis use before age 15 and subsequent executive functioning. The British Journal of Psychiatry 2011 198: 442-447.
68. Mir Arshid, Obafemi Adebisi, Young Amy, et al. Myocardial Infarction Associated With Use of the Synthetic Cannabinoid K2. Pediatrics 2011; peds.2010-3823; published ahead of print November 7, 2011
69. Zajicek JP, Apostu VI. Role of cannabinoids in multiple sclerosis. CNS Drugs. 2011;25(3):187-201.
70. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol. 2011;72(5):735-44
71. Drugs in Pregnancy and Lactation. 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Philadelphia, PA: 2011.
72. Klumpers LE, Beumer TL, van Hasselt JG, et al. Novel Δ(9) –tetrahydrocannabinol formulation Namisol table has beneficial pharmacokinetics and promising pharmacodynamic effects. Br J Clin Pharmacol. 2011 Dec 28.
73. Bhattacharyya S, Crippa JA, Allen P, et al. Induction of psychosis by {delta}9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012 Jan;69(1):27-36.
74. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012 Jan 11;307(2):173-81.
75. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ 2012;344:e536.
76. Cohen J, Morrison S, Greenberg J et al. Clinical Presentation of Intoxication Due to Synthetic Cannabinoids. Pediatrics. 2012 Mar 19.
77. Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc. 2012 Feb;87(2):114-9.
78. Fitzcharles MA, McDougall J, Ste-Marie PA, Padjen I. Clinical implications for cannabinoid use in the rheumatic diseases: Potential for help or harm? Arthritis Rheum. 2012 May 17.
79. Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ. 2012 May 14.
80. Jerry J, Collins G, Streem D. Synthetic legal intoxicating drugs: The emerging 'incense' and 'bath salt' phenomenon. Cleve Clin J Med. 2012 Apr;79(4):258-64. (cannabinoids, mephedrone)
81. Health Canada June/12: Q & N Omega Tree The Singapore Health Sciences Authority informed of a recall after this product was found to contain controlled drug substances (cannabinol and tetrahydrocannabinol (THC)).

Canadian Medical Association (CMA): Statement: http://www.cma.ca/index.cfm/ci_id/3396/la_id/1.htm accessed 19Jun06.

TOP

References: Anemia - Hemoglobin Control: Landmark Outcome Trials – Summary (www.RxFiles.ca)

1 Anemia Guidelines for Family Medicine; **Anemia Review Panel**, 2008 Edition.
2 White CT, Barrett BJ, Madore F, Moist LM, Klarenbach SW, Foley RN, Culleton BF, et al. Canadian Society of Nephrology. Clinical practice guidelines for **evaluation of anemia**. Kidney Int Suppl. 2008 Aug;(110):S4-6.
3 Charytan C, Qunibi W, Bailie GR, Venofer Clinical Studies G. Comparison of intravenous **iron sucrose to oral** iron in the treatment of anemic patients with chronic kidney disease not on dialysis. Nephron 2005;100(3):55-62.
4 Van Wyck DB. Roppolo M. Martinez CO. Mazey RM. McMurray S. for the United States **Iron Sucrose** (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. Kidney Int. 2005 Dec;68(6):2846-2856.
5 DeVita MV, Frumkin D, Mittal S, Kamran A, Fishbane S, et al. Targeting higher ferritin concentrations with intravenous **iron dextran** lowers erythropoietin requirement in hemodialysis patients. Clin.Nephrol. 2003 Nov;60(5):335-340.
6 Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S, et al. Optimization of epoetin therapy with **intravenous iron therapy in hemodialysis** patients. J.Am.Soc.Nephrol. 2000 Mar;11(3):530-538.
7 Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE. A randomized controlled study of **iron supplementation** in patients treated **with erythropoietin**. Kidney Int. 1996 Nov;50(5):1694-1699.
8 Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic **intravenous iron** supplementation. Am.J.Kidney Dis. 1995 Jul;26(1):41-46.
9 Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV, et al. **Ferric gluconate** is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. J.Am.Soc.Nephrol. 2007 Mar;18(3):975-984.
10 Kapoian T, O'Mara NB, Singh AK, Moran J, Rizkala AR, Geronemus R, et al. **Ferric gluconate** reduces epoetin requirements in hemodialysis patients with elevated ferritin. J.Am.Soc.Nephrol. 2008 Feb;19(2):372-379.
11 Revicki DA, Brown RE, Feeny DH, Henry D, et al. Health-related **quality of life** associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. Am.J.Kidney Dis. 1995 Apr;25(4):548-554.
12 Roth D, Smith RD, Schulman G et al. Effects of recombinant human erythropoietin on **renal function** in chronic renal failure predialysis patients. Am J Kidney Dis 1994; 24: 777–784.
13 Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay **left ventricular mass** growth in patients with CKD. Am.J.Kidney Dis. 2005 Nov;46(5):799-811.
14 Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. **Normalization of hemoglobin level** in patients with chronic kidney disease and anemia. N.Engl.J.Med. 2006 Nov 16;355(20):2071-2084. (**CREATE**)
15 Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of **anemia with epoetin** alfa in chronic kidney disease. N.Engl.J.Med. 2006 Nov 16;355(20):2085-2098. (**CHOIR**)
16 Association between recombinant human erythropoietin and **quality of life** and exercise capacity of patients receiving haemodialysis. Canadian Erythropoietin Study Group. BMJ 1990 Mar 3;300(6724):573-578.
Muirhead N, Keown PA, Churchill DN, et al. Dialysis patients treated with Epoetin α show improved exercise tolerance and physical function: A new analysis of the Canadian Erythropoietin Study Group trial. Hemodial Int. 2010 Dec 7. doi: 10.1111/j.1542-4758.2010.00508.x.
17 Parfrey PS, Foley RN, Wittreich BH, et al. Double-blind comparison of **full and partial anemia correction** in incident hemodialysis patients without symptomatic heart disease. J.Am.Soc.Nephrol. 2005 Jul;16(7):2180-2189.
18 Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic **cardiomyopathy**. Kidney Int. 2000 Sep;58(3):1325-1335.
19 Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N.Engl.J.Med. 1998 Aug 27;339(9):584-590. (**Normal Hematocrit Study**)
Coyne DW. The health-related quality of life was not improved by targeting higher hemoglobin in the normal hematocrit trial. Kidney Int , doi:10.1038/ki.2012.76.
20 Tonelli M, Winkelmayer WC, Jindal KK, Owen WF, Manns BJ. The **cost-effectiveness** of maintaining higher hemoglobin targets with erythropoietin in hemodialysis patients. Kidney Int. 2003 Jul;64(1):295-304.
21 Mix TC, et al. Rationale--Trial to Reduce Cardiovascular Events with Aranesp Therapy (**TREAT**): evolving the management of cardiovascular risk in patients with chronic kidney disease. Am.Heart J. 2005 Mar;149(3):408-413.
Pfeffer, Marc A., Burdmann, Emmanuel A., Chen, Chao-Yin, et al. the **TREAT** Investigators, A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. N Engl J Med 2009 0: NEJMoa0907845.
Solomon Scott D, Lewis Eldrin F., Eckardt Kai-Uwe, et al. for the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators. Erythropoietic Response and Outcomes in Kidney Disease and Type 2 Diabetes. N Engl J Med 2010; 363:1146-1155.
Skali H, Parving HH, Parfrey PS, et al. Stroke in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia treated with darboetin alfa: the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) experience. Circulation. 2011;124:2903–2908.
22 Braden J Manns, Colin T White, Francois Madore, et al. **Canadian** Society of Nephrology Clinical Practice Guidelines for the management of **anemia** associated with chronic kidney disease. 2008 Kidney Int 74: S1-S24.
23 KDOQI. **KDOQI** clinical practice guideline and clinical practice recommendations for **anemia** in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis 2007 Sep;50(3):471-530.
24 Locatelli F. Aljama P. Barany P. et al. **European** Best Practice Guidelines Working Group. Revised European best practice guidelines for the management of **anaemia** in patients with chronic renal failure. Nephrology Dialysis Transplantation. 19 Suppl 2:ii1-47, 2004 May.
25 National Collaborating Centre for Chronic Conditions. **Anaemia** management in chronic kidney disease. National clinical guideline for management in adults and children. London (UK): Royal College of Physicians; 2006. 172 p.
26 **CARI**. The CARI Guidelines Biochemical and Haematological Targets NEPHROLOGY 2008; 13, S44–S56.
27 Tonelli M, Klarenbach S, Wiebe N, et al. Erythropoiesis-Stimulating Agents for Anemia of Chronic Kidney Disease: Systematic Review and Economic Evaluation [Technology report number 106]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008. (**CADTH**)
28 Locatelli F, Nissenson AR, Barrett BJ, Walker RG, et al. Clinical Practice Guidelines for Anemia in Chronic Kidney Disease: Problems and Solutions. A Position Statement From **KDIGO**. Kidney Int. 2008;74(10):1237-1240.
29. Foley RN, Curtis BM, Parfrey PS. Erythropoietin therapy, hemoglobin targets, & quality of life in healthy **hemodialysis** patients: a randomized trial. Clin J Am Soc Nephrol. 2009 Apr;4(4):726-33. Epub 2009 Apr 1. (n=596 96 weeks) In relatively healthy hemodialysis pts, normal hemoglobin targets may have beneficial effects on fatigue. Improvement in multiple domains of quality of life is associated with higher body mass index & lower erythropoietin requirements.
30. Uprichard James, Bain Barbara J. **Investigating** suspected anaemia. BMJ 2009;338:b1644, doi: 10.1136/bmj.b1644 (Published 22 May 2009)
31. Moreno Chulilla JA, Romero Colás MS, Gutiérrez Martín M. **Classification of anemia** for gastroenterologists. World J Gastroenterol. 2009 Oct 7;15(37):4627-37.
32. Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C, Mayne TJ. Systematic Review and Meta-analysis of **Exercise Tolerance and Physical Functioning** in Dialysis Patients Treated With Erythropoiesis-Stimulating Agents. Am J Kidney Dis. 2010 Feb 2.
33. Mehrotra Rajnish; Chiu Yi-Wen; Kalantar-Zadeh Kamyar; et al. Similar Outcomes With **Hemodialysis and Peritoneal Dialysis** in Patients With End-Stage Renal Disease. Arch Intern Med. 2010;0(2010):archinternmed.2010.352.
34. Sood, Manish M., Komenda, Paul, Sood, Amy R., et al. Adverse outcomes among **Aboriginal** patients receiving **peritoneal dialysis**. CMAJ 2010 182: 1433-1439.
35. Bross MH, Soch K, Smith-Knuppel T. **Anemia in older persons**. Am Fam Physician. 2010 Sep 1;82(5):480-7.
36. Himmelfarb J, Ikizler TA. **Hemodialysis**. N Engl J Med. 2010 Nov 4;363(19):1833-45.
37. Fellstrom BC, Jardine AG, Schmeider RE, et al. **Rosuvastatin** and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407.
38. Wanner C, Krane V, M.rz W, et al. **Atorvastatin** in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238-48.
39. Jamison RL, Hartigan P, Kaufman JS, et al. Effect of **homocysteine lowering** on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. JAMA 2007;298:1163-70.
40. Suki WN, Zabaneh R, Cangiano JL, et al. Effects of **sevelamer and calciumbased phosphate binders** on mortality in hemodialysis patients. Kidney Int 2007; 72:1130-7.
41. Besarab A, Bolton WK, Browne JK, et al. The effects of **normal as compared with low hematocrit** values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339:584-90.
42. Rosansky Steven J.; Eggers Paul; Jackson Kirby; et al. **Early Start of Hemodialysis May Be Harmful**. Arch Intern Med. 2010;0(2010):archinternmed.2010.415.
43. **FHN** Trial Group. In-Center **Hemodialysis** Six Times per Week versus Three Times per Week. November 20, 2010 (10.1056/NEJMoa1001593)
44. Cooper BA, Branley P, Bulfone L, et al.; the **IDEAL** Study. A Randomized, Controlled Trial of **Early versus Late Initiation of Dialysis**. N Engl J Med. 2010 Jun 27.
45. Manns B, Hemmelgarn B, Tonelli M, et al; Alberta Kidney Disease Network. **Population based screening** for chronic kidney disease: cost effectiveness study. BMJ. 2010 Nov 8;341:c5869. doi: 10.1136/bmj.c5869.
46. Tonelli Marcello, Muntner Paul, Lloyd Anita, Manns Braden J., et al., for the Alberta Kidney Disease Network. Using **Proteinuria and Estimated Glomerular Filtration Rate** to Classify Risk in Patients With Chronic Kidney Disease: A Cohort Study. Ann Intern Med Jan 4, 2011 154:12-21.
47. Clark, William F., Na, Yingbo, Rosansky, Steven J., et al. Association between **estimated glomerular filtration rate at initiation of dialysis and mortality**. CMAJ 2011 183: 47-53.
48. Mehrotra Rajnish; Chiu Yi-Wen; Kalantar-Zadeh Kamyar; et al. **Similar** Outcomes With **Hemodialysis and Peritoneal Dialysis** in Patients With End-Stage Renal Disease. Arch Intern Med. 2011;171(2):110-118. In the most recent cohorts, patients who began treatment with HD or PD have similar outcomes.
49. Kutner Nancy G.; Zhang Rebecca; Huang Yijian; et al. **Patient Awareness and Initiation of Peritoneal Dialysis**. Arch Intern Med. 2011;171(2):119-124.
50. Hemmelgarn BR, Moist LM, Lok CE, et al. the Prevention of Dialysis Catheter **Lumen Occlusion with rt-PA versus Heparin** (**PreCLOT**) Study Group. Prevention of Dialysis Catheter Malfunction with Recombinant Tissue Plasminogen Activator. N Engl J Med. 2011 Jan 27;364(4):303-312.
51. Tonelli Marcello, Manns Braden. **Supplementing Creatinine-Based Estimates** of Risk in Chronic Kidney Disease: Is It Time? *JAMA*. 2011;Published online April 11, 2011. doi:10.1001/jama.2011.502.
52. Peralta Carmen A., Shlipak Michael G., Judd Suzanne, et al. Detection of Chronic Kidney Disease With **Creatinine, Cystatin C, and Urine Albumin-to-Creatinine** Ratio and Association With Progression to End-Stage Renal Disease and Mortality. *JAMA*. 2011;Published online April 11, 2011.
53. Tangri Navdeep, Stevens Lesley A., Griffith John, et al. A Predictive **Model for Progression of Chronic Kidney Disease** to Kidney Failure. *JAMA*. 2011;Published online April 11, 2011. doi:10.1001/jama.2011.451
54. **FDA** June/11 notified healthcare professionals that new, modified recommendations for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) have been approved to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The new dosing recommendations are based on clinical trials showing that using **ESAs to target a hemoglobin level of greater than 11 g/dL in patients with CKD provides no additional benefit** than lower target levels, and increases the risk of experiencing ser adverse cardiovascular events, such as heart attack or stroke. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm260641.htm
55. Pergola Pablo E., Raskin Philip, Toto Robert D., et al. for the BEAM Study Investigators. **Bardoxolone Methyl** and Kidney Function in CKD with Type 2 Diabetes. June 24, 2011 (10.1056/NEJMoa1105351)

TOP

56. Hilton R. **Defining acute renal failure**. CMAJ. 2011 Jul 2;183(10):1167-9.
57. Salisbury AC, Reid KJ, Alexander KP, et al. Diagnostic Blood Loss From **Phlebotomy and Hospital-Acquired Anemia** During Acute Myocardial Infarction. Arch Intern Med. 2011 Aug 8.
58. Vivante A, Afek A, Frenkel-Nir Y, et al. Persistent asymptomatic isolated **microscopic hematuria** in Israeli adolescents and young adults and risk for end-stage renal disease. JAMA. 2011 Aug 17;306(7):729-36.
59. Zhang Y, Thamer M, Kaufman JS et al. **High doses of epoetin** do not lower mortality and cardiovascular risk among elderly **hemodialysis patients with diabetes**. Kidney Int 2011;80:663 – 669.
60. Levey AS, Coresh J. **Chronic kidney disease**. Lancet. 2011 Aug 12.
61. Foley RN, Gilbertson DT, Murray T et al. **Long Interdialytic Interval** and Mortality among Patients Receiving Hemodialysis. N Engl J Med 2011;365:1099-107.
62. Kucirka LM, Grams ME, Lessler J, et al. Association of **race and age** with survival among patients undergoing dialysis. JAMA. 2011 Aug 10;306(6):620-6.
63. Heiwe S, Jacobson SH. **Exercise training for adults** with chronic kidney disease. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD003236. DOI: 10.1002/14651858.CD003236.pub2. There is evidence for significant beneficial effects of regular exercise on physical fitness, walking capacity, cardiovascular dimensions (e.g. blood pressure and heart rate), health-related quality of life and some nutritional parameters in adults with CKD.
64. Winkelmayer WC, Liu J, Chertow GM, Tamura MK. **Predialysis nephrology care of older patients** approaching end-stage renal disease. Arch Intern Med. 2011 Aug 8;171(15):1371-8.
65. Kiaii M, Djurdjev O, Farah M, Levin A, Jung B, MacRae J. Use of **electronbeam sterilized hemodialysis** membranes and risk of thrombocytopenia. JAMA. 2011;306(15):1679-1687.
66. O'Hare AM, Choi AI, Boscardin WJ, et al. **Trends in timing of initiation of chronic dialysis** in the United States. Arch Intern Med. 2011 Oct 10;171(18):1663-9.
67. Isakova T, Xie H, Yang W, et al. Chronic Renal Insufficiency Cohort (CRIC) Study Group. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA. 2011 Jun 15;305(23):2432-9.
68. Marti-Carvajal AJ, Sola I, Pena-Marti GE, et al. Treatment for anemia in people with **AIDS**. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004776.
69. Weinhandl ED, Liu J, Gilbertson DT, Arneson TJ, Collins AJ. Survival in **Daily Home Hemodialysis** and Matched Thrice-Weekly In-Center Hemodialysis Patients. J Am Soc Nephrol. 2012 Feb 23.
70. Nesrallah GE, Lindsay RM, Cuerden MS, et al. **Intensive Hemodialysis** Associates with Improved Survival Compared with Conventional Hemodialysis. J Am Soc Nephrol. 2012 Feb 23.
71. Lacson E Jr, Xu J, Suri R, et al. Survival with **Three-Times Weekly In-Center Nocturnal** Versus Conventional Hemodialysis. J Am Soc Nephrol. 2012 Feb 23.
72. Daugirdas JT, Chertow GM, Larive B, et al Effects of **Frequent Hemodialysis** on Measures of CKD Mineral and Bone Disorder. J Am Soc Nephrol. 2012 Feb 23. (control of hyperphosphatemia)
73. Carson JL, Grossman BJ, Kleinman S, et al., for the Clinical Transfusion Medicine Committee of the AABB. **Red Blood Cell Transfusion**: A Clinical Practice Guideline From the AABB. Ann Intern Med ahead of print Mar 26,12.
74. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum **creatinine and cystatin C**. N Engl J Med 2012;367:20-9.
75. Bao Y, Dalrymple L, Chertow GM, et al. **Frailty, Dialysis Initiation, and Mortality** in End-Stage Renal Disease Frailty, Dialysis Initiation, & Mortality in ESRD. Arch Intern Med. 2012 Jun 25:1-7.

TOP

Addional information about Mircera (Web-only)

Methoxy polyethylene glycol-epoetin beta **MIRCERA** [11] Single-dose **vials** (solution): 50, 100, 200, 300, 400, 600, 1000 µg/mL Single-dose **pre-filled syringes:** 50µg/0.3mL, 75µg/0.3mL, 100µg/0.3mL, 150µg/0.3mL, 200µg/0.3mL, 250µg/0.3mL, 400µg/0.6mL, 600µg/0.6mL	✓ **Tx of anemia with CKD** Pre-filled syringes: sterile & do not contain preservatives. Store in fridge at 2-8°. (Do not freeze) Keep in original package to protect from light. Stable at room temperature ≤ 25° C for up to 1 month Allow to reach room temp. before inj.		SubQ in ND-CKD & PD-CKD; **IV** or SubQ in HD-CKD Not currently on ESA tx: 0.6 mcg/kg every 2 weeks as a single IV or SQ inj Pts on ESA: can convert to MIRCERA given once a month as a single IV or SQ inj. Monthly Mircera starting IV or SQ dose mcg/monthly: 120 if <40 Aranesp or <8,000 Eprex; 200 if <40-80 Aranesp or 8-16,000 Eprex; 360 if >80 Aranesp or >16,000 Eprex (Aranesp in mcg/week, Eprex in IU/week) Equivalent with IV or SQ. If Hgb target is reached, may give once monthly using a dose equal to twice the previous every two week dose.	✗ ⊗ Not on formulary. Not yet avail. in Canada, but NOC received Mar 2008

Erythropoiesis Stimulating Agents (ESA) in Anemia of Chronic Kidney Disease (CKD): Therapeutic Alternatives

References

1 eCPS Monographs, Lexi-Drugs, Micromedex 2010
2 Clinical Practice Guidelines for evidence-based use of ESAs (CSN)
3 uptodate.com – EPO for the anemia of CKD among predialysis and peritoneal dialysis pts (accessed nov 19)
4 Continuous Erythropoietin Receptor Activator (Mircera®) for Renal Anemia Issues in Emerging Health Technologies – CADATH Report
5 Health Canada - Drugs and Health Products – Public Communication - Black Box Warning 2007
http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2007/aranesp_eprex_hpc-cps-eng.php
6 Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomized trials. Lancet. 2009 May 2;373(9674):1532-42. Treatment with erythropoiesis-stimulating agents in patients with cancer increased mortality during active study periods and worsened overall survival. The increased risk of death associated with treatment with these drugs should be balanced against their benefits.
7 Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ. 2009 Apr 30. Use of erythropoiesis-stimulating agents in patients with cancer-related anemia improved some disease-specific measures of quality of life and decreased the use of blood transfusions. However, it increased the risk of death and serious adverse events. Our findings suggest that such therapy not be used routinely as an alternative to blood transfusion in patients with anemia related to cancer.
8 Canadian Society of Nephrology (CSN) 2008
9 Kidney Disease Outcomes Quality Initiative (National Kidney Foundation) (KDOQI) 2007 NKF KDOQI Guidelines: 2007 Update of Hemoglobin Target
10 Kidney Disease: Improving Global Outcomes (KDIGO) 2008
11 Continuous Erythropoietin Receptor Activator (Mircera®) for Renal Anemia Issues in Emerging Health Technologies – CADATH Report
12. Anemia Guidelines for Family Medicine; Anemia Review Panel, 2008 Edition.

Additional references:

Abboud, Hanna, Henrich, William L. **Stage IV** Chronic Kidney Disease.N Engl J Med 2010 362: 56-65.
Bennett CL, Silver SM, Djulbegovic B, et al. Venous **thromboembolism and mortality** associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA. 2008 Feb 27;299(8):914-24.
Bennett CL, Luminari S, Nissenson AR, et al. **Pure red-cell aplasia** and epoetin therapy. N Engl J Med 2004;351:1403-1408.
Berger A, Lord C, Corey-Lisle PK, et al. Utilization and Cost in Clinical Practice of **Darbepoetin Alfa and Epoetin Alfa for Anemia Concomitant With Chemotherapy**. Clin Ther. 2012 May 14.
Besarab A, Frinak S, Yee J. What is so bad about a **hemoglobin level of 12 to 13** g/dL for chronic kidney disease patients anyway? Adv Chronic Kidney Dis 2009;16:131-142.
Besarab A, Bolton WK, Browne JK, Egrie JC, et al. The effects of normal as compared with low **hematocrit** values in patients with cardiac disease who are receiving hemodialysis and epoetin. (**Normal Hematocrit Study**) N Engl J Med. 1998 Aug 27;339(9):584-90.
Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and **cancer patients**: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006;98:708-714.
Bohlius J, Schmidlin K, Brillant C, et al. Erythropoietin or Darbepoetin for **patients with cancer**--meta-analysis based on individual patient data. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007303. ESA treatment in cancer patients increased on study mortality and worsened overall survival. For patients undergoing chemotherapy the increase was less pronounced, but an adverse effect could not be excluded.
Brines M, Cerami A. Erythropoietin-mediated tissue protection: reducing collateral damage from the primary injury response. J Intern Med 2008;264:405-432.
Carson JL, Grossman BJ, Kleinman S, et al., for the Clinical Transfusion Medicine Committee of the AABB. **Red Blood Cell Transfusion**: A Clinical Practice Guideline From the AABB. Ann Intern Med ahead of print Mar 26,12.
Choukroun G, Kamar N, Dussol B, et al.; **CAPRIT** study Investigators: Correction of **postkidney transplant** anemia reduces progression of allograft nephropathy. J Am Soc Nephrol 23: 360–368, 2012.
Clement Fiona M.; Klarenbach Scott; Tonelli Marcello; Johnson Jeffrey A.; Manns Braden J. The Impact of Selecting a High Hemoglobin Target Level on Health-Related **Quality of Life** for Patients With Chronic Kidney Disease: A Systematic Review and Meta-analysis. Arch Intern Med. 2009;169(12):1104-1112.
Cooper BA, Branley P, Bulfone L, et al.; the IDEAL Study. A Randomized, Controlled Trial of **Early versus Late Initiation of Dialysis**. N Engl J Med. 2010 Jun 27.
Coyne DW. The health-related **quality of life was not** improved by targeting higher hemoglobin in the **normal hematocrit trial**. Kidney Int , doi:10.1038/ki.2012.76.
den Elzen, Wendy P.J., Willems, Jorien M., Westendorp, Rudi G.J., et al. Effect of **erythropoietin levels** on mortality in old age: the Leiden 85-plus Study. CMAJ 2010 0: cmaj.100347.
Dharmarajan TS, Widjaja D. Erythropoiesis-stimulating agents in **anemia**. Geriatrics. 2008 Jun;63(6):13-29.
Drüeke TB, Locatelli F, Clyne N, et al. Normalization of haemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071-84. (**Choir**)
Drugs in Pregnancy and Lactation. 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Philadelphia, PA: 2011.
Ehrenreich H, Weissenborn K, Prange H, Schneider D, Weimar C, et al.; for the **EPO Stroke** Trial Group. Recombinant Human Erythropoietin in the Treatment of Acute Ischemic Stroke. Stroke. 2009 Oct 15.
Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and II clinical trial. N Engl J Med **1987**;316:73-78.
FDA Feb/10 and Amgen notified healthcare professionals and patients that all ESAs must be used under a REMS risk management program. As part of the risk management program, a Medication Guide explaining the risks and benefits of ESAs must be provided to all patients receiving an ESA. Under the ESA APPRISE Oncology program, Amgen will ensure that only those hospitals and healthcare professionals who have enrolled and completed training in the program will prescribe and dispense ESAs to patients with cancer. Amgen is also required to oversee and monitor the program to ensure that hospitals and healthcare professionals are fully compliant with all aspects of the program. FDA is requiring a REMS because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions.
FDA June/11 notified healthcare professionals that new, modified recommendations for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) have been approved to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The new dosing recommendations are based on clinical trials showing that using **ESAs to target a hemoglobin level of greater than 11 g/dL in patients with CKD provides no additional benefit** than lower target levels, and increases the risk of experiencing serious adverse cardiovascular events, such as heart attack or stroke.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm260641.htm

TOP

Ferraris V, Brown J, Despotis G, et al. 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists **Blood Conservation Clinical Practice Guidelines**. Ann Thorac Surg 2011; 91:944-82.
Fontaine C, Cevallos L, Léké A, Krim G, Tourneux P. [Assessment of erythropoietin treatment in **preterm newborns** older than 30 weeks of gestation]. Arch Pediatr. 2009 Apr;16(4):331-6. Epub 2009 Feb 20. This study did not find any benefit using rhEPO in 30 to 32 WG preterm infants in terms of the number of transfusions or hemoglobin levels.
Hayden SJ, Albert TJ, Watkins TR, Swenson ER. **Anemia in Critical Illness**: Insights into Etiology, Consequences and Management. Am J Respir Crit Care Med. 2012 Jan 26.
Heinze G, Kainz A, Hörl WH, Oberbauer R. **Mortality** in renal transplant recipients given erythropoietins to increase haemoglobin concentration: cohort study. BMJ. 2009 Oct 23;339:b4018. doi: 10.1136/bmj.b4018. Increasing haemoglobin concentrations to above 125 g/l with erythropoietins in renal transplant recipients is associated with an increase in mortality. This increase was significant at concentrations above 140 g/l.
Hershman DL, Buono DL, Malin J, McBride R, Tsai WY, Neugut AI. Patterns of Use and Risks Associated With **Erythropoiesis-Stimulating Agents Among Medicare Patients With Cancer**. J Natl Cancer Inst. 2009 Nov 10. Use of erythropoiesis-stimulating agent increased rapidly after its approval in 1991, but the blood transfusion rate did not change. Use of erythropoiesis-stimulating agents was associated with an increased risk of **venous thromboembolism** but not of mortality.
Himmelfarb J, Ikizler TA. **Hemodialysis**. N Engl J Med. 2010 Nov 4;363(19):1833-45.
Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C, Mayne TJ. Systematic Review and Meta-analysis of **Exercise Tolerance and Physical Functioning** in Dialysis Patients Treated With Erythropoiesis-Stimulating Agents. Am J Kidney Dis. 2010 Feb 2.
Khuri FR. Weighing the hazards of erythropoiesis stimulation in patients with cancer. N Engl J Med 2007;356:2445-2448.
Kulnigg S, Teischinger L, Dejaco C, Waldhör T, Gasche C. Rapid recurrence of **IBD-associated** anemia and iron deficiency after intravenous iron sucrose and erythropoietin treatment. Am J Gastroenterol. 2009 Jun;104(6):1460-7. Epub 2009 Apr 21.
Levey AS, Coresh J. **Chronic kidney disease**. Lancet. 2011 Aug 12.
Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, Burns K, Manns B, White C, Madore F, Moist L, Klarenbach S, Barrett B, Foley R, Jindal K, Senior P, Pannu N, Shurraw S, Akbari A, Cohn A, Reslerova M, Deved V, Mendelssohn D, Nesrallah G, Kappel J, Tonelli M; **Canadian** Society of Nephrology. Guidelines for the management of **chronic kidney disease**. CMAJ. 2008 Nov 18;179(11):1154-62. http://www.cmaj.ca/cgi/data/179/11/1154/DC1/1

Macdougall, Iain C., Rossert, Jerome, Casadevall, Nicole, et al. A Peptide-Based Erythropoietin-Receptor Agonist (Hematide) for **Pure Red-Cell Aplasia**. N Engl J Med 2009 361: 1848-1855.
McFarlane PA, Pisoni RL, Eichleay MA, Wald R, Port FK, Mendelssohn D. **International trends in erythropoietin use** and hemoglobin levels in hemodialysis patients. Kidney Int. 2010 Apr 28.
McMurray JJ, Anand IS, et al.; on behalf of the **RED-HF** Committees and Investigators. Design of the Reduction of Events with Darbepoetin alfa in **Heart Failure** (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Fail. 2009 Aug;11(8):795-801.
Moist LM, Foley RN, Barrett BJ, Madore F, White CT, Klarenbach SW, Culleton BF, Tonelli M, Manns BJ; **Canadian** Society of Nephrology. Clinical practice guidelines for evidence-based use of erythropoietic-stimulating agents. Kidney Int Suppl. 2008 Aug;(110):S12-8.
Muirhead N, Keown PA, Churchill DN, et al. Dialysis patients treated with Epoetin α show **improved exercise tolerance and physical function**: A new analysis of the Canadian Erythropoietin Study Group trial. Hemodial Int. 2010 Dec 7. doi: 10.1111/j.1542-4758.2010.00508.x.
Najjar SS, Rao SV, Melloni C, et al. **REVEAL** Investigators. Intravenous **erythropoietin** in patients with **ST-segment elevation myocardial infarction** (STEMI): REVEAL: a randomized controlled trial. JAMA. 2011 May 11;305(18):1863-72.
National Institute for Health and Clinical Excellence (**NICE**). Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia [Internet]. London (UK): NICE; 2008 May. (Technology appraisal guidance; no. 142). [cited 2009 Nov 23]. Available from: http://www.nice.org.uk/nicemedia/pdf/TA142Guidance.pdf
Ngo K, Kotecha D, Walters JA, Manzano L, Palazzuoli A, van Veldhuisen DJ, Flather M. Erythropoiesis-stimulating agents for anaemia in **chronic heart failure** patients. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007613.
NICE: Clinical Guideline 114- Feb 2011. **Anaemia management** in people with chronic kidney disease. http://www.nice.org.uk/nicemedia/live/13329/52857/52857.pdf
Palmer Suetonia C., Navaneethan Sankar D., Craig Jonathan C., Et al. Systematic Review: **Erythropoiesis-Stimulating Agents** in Patients With Chronic Kidney Disease. *Ann Intern Med* published ahead of print May 3, 2010, doi:10.1059/0003-4819-153-1-201007060-00252.
Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: **erythropoiesis-stimulating agents** in patients with chronic kidney disease. Ann Intern Med. 2010 Jul 6;153(1):23-33.
Pfeffer, Marc A., Burdmann, Emmanuel A., Chen, Chao-Yin, et al. the **TREAT** Investigators, A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. N Engl J Med 2009 0: NEJMoa0907845.
Phrommintikul A, Haas SJ, Elsik M, Krum H. **Mortality** and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 2007;369:381-388.
Rizzo JD, Somerfield MR, Hagerty KL, et al.; **American** Society of Clinical Oncology **(ASCO)**; American Society of Hematology. Use of epoetin and darbepoetin in patients with **cancer**: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. J Clin Oncol. **2008** Jan 1;26(1):132-49. Epub 2007 Oct 22. Erratum in: J Clin Oncol. 2008 Mar 1;26(7):1192.
Rizzo JD, Brouwers M, Hurley P, et al. **American** Society of Clinical Oncology **(ASCO)** / American Society of Hematology Clinical Practice Guideline Update on the Use of **Epoetin and Darbepoetin in Adult Patients With Cancer**. *JCO* JCO.2010.29.2201; online on Oct 25, **2010**. http://jco.ascopubs.org/content/early/2010/10/25/JCO.2010.29.2201.full.pdf+html
Singh AK, Szczech L, Tang KL, et al. Correction of **anemia** with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355:2085-98.
Singh AK, Himmelfarb J, Szczech LA. Resolved: targeting a **higher hemoglobin** is associated with greater risk in patients with CKD anemia. J Am Soc Nephrol 2009;20:1436-1443.
Skali H, Parving HH, Parfrey PS, et al. **Stroke** in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia treated with **darboetin alfa**: the Trial to Reduce Cardiovascular Events With Aranesp Therapy (**TREAT**) experience. Circulation. 2011;124:2903–2908.
Solomon Scott D, Lewis Eldrin F., Eckardt Kai-Uwe, et al. for the Trial to Reduce Cardiovascular Events with Aranesp Therapy (**TREAT**) Investigators. Erythropoietic Response and Outcomes in Kidney Disease and Type 2 Diabetes. N Engl J Med 2010; 363:1146-1155.
Steensma DP, Sloan JA, Dakhil SR, et al. Phase III, Randomized Study of the Effects of **Parenteral Iron, Oral Iron, or No Iron** Supplementation on the Erythropoietic Response to **Darbepoetin** Alfa for Patients With Chemotherapy-Associated Anemia. J Clin Oncol. 2010 Nov.
Sühs K, Hein K, Sättler M. A randomized, double-blind, phase II study on erythropoietin in **optic neuritis**. Annals of Neurology Accepted manuscript online: 28 FEB 2012.
Tehrani F, Dhesi P, Daneshvar D, Phan A, Rafique A, Siegel RJ, Cercek B. Erythropoiesis Stimulating Agents in **Heart Failure** Patients with Anemia: A Meta-Analysis. Cardiovasc Drugs Ther. 2009 Oct 28.
Tseng KC, Chen LH, Chen CY, et al. Low dose erythropoietin-beta improves anemia and maintains ribavirin dose in chronic **hepatitis C** patients receiving combination therapy with ribavirin plus pegylated interferon Alfa-2b.Hepatol Res. 2009 Feb 25. [Epub ahead of print]
Tonelli M, Lloyd A, Lee H, et al. Erythropoiesis-stimulating agents for **anemia of cancer or of chemotherapy**: systematic review and economic evaluation [Technology report number 119]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
Van der Meer P, Groenveld H, Januzzi JL, Van Veldhuisen DJ. Erythropoietin Treatment in Patients with Chronic **Heart Failure**: a meta-analysis. Heart. 2009 Jan 23. [Epub ahead of print]
van der Putten K, Braam B, Gaillard CA. Epoetin alfa in **critically ill** patients. N Engl J Med. 2007 Dec 13;357(24):2515-6
Vanrenterghem Y. Anemia after **kidney transplantation**. Transplantation. 2009 May 15;87(9):1265-7.
Voors AA, Belonje AM, Zijlstra F, et al. A single dose of erythropoietin in **ST-elevation myocardial infarction**. Eur Heart J 2010; DOI:10.1093/eurheartj/ehq304.
Weiner Daniel E. , Miskulin Dana C. Anemia Management in Chronic Kidney Disease: **Bursting the Hemoglobin Bubble**. Ann Intern Med published ahead of print May 3, 2010.
Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet **1986**;2:1175-1178.
Zhang Y, Thamer M, Kaufman JS et al. **High doses of epoetin** do not lower mortality and cardiovascular risk among elderly **hemodialysis patients with diabetes**. Kidney Int 2011;80:663 – 669.

TOP

Extras:

Oct/11 The FDA has granted accelerated approval for **deferiprone (Ferriprox)** to treat transfusion-related iron overload in patients with thalassemia who do not respond to prior chelation therapy. The drug, an oral iron chelator, is the first new treatment approved for this disorder since 2005, according to the agency. Agranulocytosis was noted in about 2% of patients in clinical studies. Other adverse effects included nausea, arthralgia, vomiting, neutropenia, and increased alanine aminotransferase levels.

References: Iron Management: Chronic Kidney Disease – Iron Deficiency Anemia (CKD-IDA)

1. Best Practice Guidelines for Management of Renal Anaemia. *Indian J Nephrol* 2005;15(Suppl 1):S32-S41. Available: http://medind.nic.in/iav/t05/s1/iavt05s1p32.pdf (accessed 2009 Feb 18).
2. Comparison of Oral Iron Supplements. Pharmacist's Letter/Prescriber's Letter 2008 ;24(8):240811.
3. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV, et al. Ferric Gluconate is Highly Efficacious in Anemic Hemodialysis Patients with High Serum Ferritin and Low Transferrin Saturation: Results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol* 2007;18:975-984.
4. Coyne DW, Singh AK, Kapoian T, Pizzi LT. A road map for intravenous iron and anemia management: Preparing for the future. *Am J Kidney Dis* 2008;52(6):S1-S33.
5. Drugdex Drug Evaluations - Micromedex 2010, Iron. Dec 2002.
6. e-CPS [database on the Internet]. Ottawa (ON): Canadian Pharmacists Association. c2009 - [cited 2009 Feb 22]. Infufer [product monograph]. Available from: https://www.e-therapeutics.ca/wps/portal/!ut/p/.scr/Login.
7. e-CPS [database on the Internet]. Ottawa (ON): Canadian Pharmacists Association. c2009 - [cited 2009 Feb 22]. Venofer [product monograph]. Available from: https://www.e-therapeutics.ca/wps/portal/!ut/p/.scr/Login.
8. Ferrlecit product monograph. Toronto (ON): Janssen-Ortho Inc. Available from: www.janssen-ortho.com/JOI/pdf_files/FERRLECIT_E.pdf.
9. Hunt J, Roughead Z. Adaptation of iron absorption in men consuming diets with high or low iron bioavailability. *Am J Clin Nutr* 2000;71:94-102.
10. Killip S, Bennett J, Chambers M. Iron deficiency anemia. *Am Fam Physician* 2007;75:671-8.
11. Madore F, White CT, Folet RN, Barrett BJ, Moist LM, Klarenbach SW, et al. **Canadian** Clinical Practice Guidelines for assessment and management of iron deficiency. *Kidney Int* 2008;74(Suppl 110):S7-S11.
    National Kidney Foundation. **KDOQI** clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006;47(5 Suppl 3):S1-S145. Available from: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/pdf/AnemiaInCKD.pdf.
    KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target; 2007 Sep
12. White CT, Barrett BJ, Madore F, Moist LM, Klarenbach SW, Foley RN, et al. Clinical Practice Guidelines for evaluation of anemia. *Kidney Int* 2008;74(Suppl 110):S4-S6.
13. Anemia Guidelines for Family Medicine; Anemia Review Panel, 2008 Edition.
14. Weiss G, Goodnough LT. Anemia of chronic disease. NEJM 2005; 352:1011-23.
16. American College of Obstetricians and Gynecologists (ACOG). Anemia in pregnancy. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 Jul. 7 p. (ACOG practice bulletin; no. 95).
17. Singh A, Patel T, Hertel J, Bernardo M, Kausz A, Brenner L. Safety of ferumoxytol in patients with anemia and CKD. Am J Kidney Dis. 2008 Nov;52(5):907-15. Epub 2008 Sep 27.
18. Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, Burns K, Manns B, White C, Madore F, Moist L, Klarenbach S, Barrett B, Foley R, Jindal K, Senior P, Pannu N, Shurraw S, Akbari A, Cohn A, Reslerova M, Deved V, Mendelssohn D, Nesrallah G, Kappel J, Tonelli M; Canadian Society of Nephrology. Guidelines for the management of chronic kidney disease. CMAJ. 2008 Nov 18;179(11):1154-62. http://www.cmaj.ca/cgi/data/179/11/1154/DC1/1
19. Crowe E, Halpin D, Stevens P; Guideline Development Group. Early identification and management of chronic kidney disease: summary of NICE guidance. BMJ. 2008 Sep 29;337:a1530. doi: 10.1136/bmj.a1530.
20. Reveiz L, Gyte GM, Cuervo LG. Treatments for iron-deficiency **anaemia in pregnancy**. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003094.
21. Auerbach M, Rodgers GM. Intravenous iron. N Engl J Med. 2007 Jul 5;357(1):93-4.
22. Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. Am Fam Physician. 2007 Mar 1;75(5):671-8.
23. Uprichard James, Bain Barbara J. Investigating suspected anaemia. BMJ 2009;338:b1644, doi: 10.1136/bmj.b1644 (Published 22 May 2009)
24. Kulnigg S, et al. Rapid recurrence of **IBD-associated** anemia and iron deficiency after intravenous iron sucrose and erythropoietin treatment. Am J Gastroenterol. 2009 Jun;104(6):1460-7. Epub 2009 Apr 21.
25. den Elzen WP, Willems JM, et al. Effect of anemia and comorbidity on functional status and **mortality in old age**: results from the Leiden 85-plus Study. CMAJ. 2009 Aug 4;181(3-4):151-7. Epub 2009 Jul 27.
26. Pfeffer, Marc A., Burdmann, Emmanuel A., Chen, Chao-Yin, et al. the **TREAT** Investigators, A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. N Engl J Med 2009 0: NEJMoa0907845.
27. Vanrenterghem Y. Anemia after kidney transplantation. Transplantation. 2009 May 15;87(9):1265-7.
28. Anker SD, Comin Colet J, Filippatos G, et al. the **FAIR-HF** Trial Investigators. **Ferric Carboxymaltose** in Patients with **Heart Failure** and Iron Deficiency. N Engl J Med. 2009 Nov 17. Treatment with intravenous ferric carboxymaltose (200mg IV weekly until iron stores repleted then q4wks up to week 24, n=459) in patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life; the side-effect profile is acceptable.
29. Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency **FERRIC-HF**: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol. 2008 Jan 15;51(2):103-12. (n=35)
30. Deved V, Poyah P, James MT, Tonelli M, Manns BJ, Walsh M, Hemmelgarn BR; Alberta Kidney Disease Network. Ascorbic Acid for Anemia Management in Hemodialysis Patients: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2009 Sep 22.
31. Chandler G, Harchowal J, Macdougall IC. Intravenous **iron sucrose**: establishing a safe dose. Am J Kidney Dis. 2001 Nov;38(5):988-91.
32. Parker MJ. Iron supplementation for anemia after **hip fracture surgery**: a randomized trial of 300 patients. J Bone Joint Surg Am. 2010 Feb;92(2):265-9.
    Patients treated with iron for anemia after hip fracture surgery have no clinically meaningful differences in hemoglobin response or outcomes compared with patients not treated with iron.
33. Zehetner AA, Orr N, Buckmaster A, Williams K, Wheeler DM. Iron supplementation for **breath-holding attacks** in children. Cochrane Database Syst Rev. 2010 May 12;5:CD008132. Iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to be useful in reducing the frequency and severity of breath-holding attacks.
34. Bross MH, Soch K, Smith-Knuppel T. **Anemia in older persons**. Am Fam Physician. 2010 Sep 1;82(5):480-7.
35. Hajjar LA, Vincent JL, Galas FR, et al. **Transfusion requirements** after **cardiac surgery**: the **TRACS** randomized controlled trial. JAMA. 2010 Oct 13;304(14):1559-67.
36. Van Vranken Michele. Evaluation of **Microcytosis**. Am Fam Physician. 2010 Nov 1;82(9):1117-1122.
37. Himmelfarb J, Ikizler TA. **Hemodialysis**. N Engl J Med. 2010 Nov 4;363(19):1833-45.
38. Berglund S, Westrup B, Domellof M. Iron supplements reduce the risk of iron deficiency anemia in **marginally low birth weight infants**. Pediatrics. 2010 Oct;126(4):e874-83.
39. Baker RD, Greer FR, Committee on Nutrition, Clinical Report--Diagnosis and Prevention of Iron Deficiency and **Iron-Deficiency Anemia in Infants and Young Children (0-3 Years of Age)**. Pediatrics 2010 0: peds.2010-2576.
40. Steensma DP, Sloan JA, Dakhil SR, et al. Phase III, Randomized Study of the Effects of **Parenteral Iron, Oral Iron, or No Iron** Supplementation on the Erythropoietic Response to **Darbepoetin** Alfa for Patients With Chemotherapy-Associated Anemia. J Clin Oncol. 2010 Nov.
41. Chi AC, Neville BW, Krayer JW, Gonsalves WC. **Oral manifestations** of systemic disease. Am Fam Physician. 2010 Dec 1;82(11):1381-8.
42. Christian P, Murray-Kolb LE., Khatry SK., et al. **Prenatal Micronutrient Supplementation (iron/folic)** and Intellectual and Motor Function in Early School-aged Children in Nepal. JAMA. 2010;304(24):2716-72
43. Rimon E, Kagansky N, Kagansky M, et al. Are we giving too much iron? **Low-dose iron therapy is effective in octogenarians**. *Am J Med* 2005;118:1142-7.

TOP

44. Walsh TS, Wyncoll DL, Stanworth SJ. Managing **anaemia in critically ill** adults. BMJ. 2010 Sep 3;341:c4408. doi: 10.1136/bmj.c4408.
45. Coppol E, Shelly J, Cheng S, et al. A Comparative Look at the Safety Profiles of **Intravenous Iron Products Used in the Hemodialysis** Population. 1 Feb 2011, DOI 10.1345/aph.1P466. Ann Pharmacother ;45:241-247.
46. Daoud E, Nakhla E, Sharma R. Q: Is **iron therapy for anemia harmful in the setting of infection**? Cleveland Clinic Journal of Medicine 2011; 78(3):168-170; doi:10.3949/ccjm.78a.10156
47. Ferraris V, Brown J, Despotis G, et al. 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists **Blood Conservation** Clinical Practice Guidelines. Ann Thorac Surg 2011; 91:944-82.
48. **NICE**: Clinical Guideline 114- Feb 2011. Anaemia management in people with chronic kidney disease. http://www.nice.org.uk/nicemedia/live/13329/52857/52857.pdf
49. Lachance K, Savoie M, Bernard M, et al. **Oral Ferrous Sulfate** Does Not Increase Preoperative Hemoglobin in Patients **Scheduled for Hip or Knee Arthroplasty**. 1 June 2011. Ann Pharmacother ;45:764-770.
50. Salisbury AC, Reid KJ, Alexander KP, et al. Diagnostic Blood Loss From **Phlebotomy and Hospital-Acquired Anemia** During Acute Myocardial Infarction. Arch Intern Med. 2011 Aug 8.
51. Levey AS, Coresh J. **Chronic kidney disease**. Lancet. 2011 Aug 12.
52. Musallam KM, Tamim HM, Richards T, et al. **Preoperative anaemia and postoperative outcomes** in non-cardiac surgery: a retrospective cohort study. Lancet 2011; published online Oct 6.
53. Krayenbuehl P-A et al. **Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women** with low serum ferritin concentration. Blood 2011 Sep 22; 118:3222.
54. Andersson O, Hellström-Westas L, Andersson D, Domellöf M. Effect of **delayed versus early umbilical cord clamping** on neonatal outcomes and iron status at 4 months: a randomised controlled trial. BMJ 2011;343:d7156.
55. Drugs in Pregnancy and Lactation. 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Philadelphia, PA: 2011.
56. Lozoff B et al. Iron-fortified vs low-**iron infant formula: Developmental outcome at 10 years**. Arch Pediatr Adolesc Med2011 Nov 7; [e-pub ahead of print],
57. Carson JL, Terrin ML, Noveck H, et al. **Liberal or restrictive transfusion** in high-risk patients after **hip surgery**. (**Focus**) N Engl J Med 2011. DOI: 10.1056/NEJMoa1012452.
58. De-Regil LM, Jefferds ME, Sylvetsky AC, et al. **Intermittent iron** supplementation for improving nutrition and development in children under 12 years of age. Cochrane Database Syst Rev. 2011 Dec 7;12:CD009085.
Intermittent iron supplementation is efficacious to improve haemoglobin concentrations and reduce the risk of having anaemia or iron deficiency in children younger than 12 years of age when compared with a placebo or no intervention, but it is less effective than daily supplementation to prevent or control anaemia.
59. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian S. **Anaemia in low-income and middle-income countries**. Lancet. 2011 Aug 1.
60. Carson JL, Grossman BJ, Kleinman S, et al., for the Clinical Transfusion Medicine Committee of the AABB. **Red Blood Cell Transfusion**: A Clinical Practice Guideline From the AABB. Ann Intern Med ahead of print Mar 26,12.
61. Hayden SJ, Albert TJ, Watkins TR, Swenson ER. **Anemia in Critical Illness**: Insights into Etiology, Consequences and Management. Am J Respir Crit Care Med. 2012 Jan 26.
62. Müller KF, Lorenz L, Poets CF, et al **Hepcidin** Concentrations in Serum and Urine Correlate with Iron Homeostasis in Preterm Infants. J Pediatr. 2012 Jan 26.
63. Pattakos G, Koch CG, Brizzio ME, et al. Outcome of patients who **refuse transfusion {Jehovah's Witness** patients (Witnesses)} after cardiac surgery. A natural experiment with severe blood conservation. Arch Intern Med 2012

TOP

Red Flags for calciphylaxis?

Natural Products Database Search on phosphate-containing products:

Enemol Sodium Phosphate Enema (Dominion Pharmacal): Each 60 ml serving contains: Sodium Phosphate dibasic, heptahydrate 6 g. • Sodium Phosphate monobasic, anhydrous 16 g. Other Ingredients: Benzalkonium Chloride, Edetate Disodium, Purified Water. NPN 02096900.

Enema (HJ Sutton): Each 30 mL serving contains: Dibasic Sodium Phosphate 7 g (118 mL) • Monobasic Sodium Phosphate 19 g (118 mL). Other Ingredients: Benzalkonium Chloride, Disodium EDTA, Purified Water. NPN 02231170.

Kali Phosphoricum 6x (Thompson's Homeopathic Supplies Ltd): For 'stress and tension'. Potassium Phosphate 6X. Other Ingredients: Ground Corn Starch, Lactose. DIN-HM 00190101
Magnesia Phosphorica 6x tabs (Thompson's Homeopathic Supplies Ltd): Oral Laxative. Magnesium Phosphate 6X. Other Ingredients: Ground Corn Starch, Lactose. DIN-HM 00189995.

Natrum Phosphoricum 6x tabs (Thompson's Homeopathic Supplies Ltd.): Oral laxative. Each tablet contains: Sodium Phosphate 6X. Other Ingredients: Corn Starch, Lactose. DIN-HM 00190160

Naturally Sourced Calcium from Milk with Vit D and Magnesium (Immunotec Inc): Oral Laxative. Two tablets contain: Calcium Phosphate 250 mg • Magnesium 15 mg • Vitamin D (D3) 100 IU. Other Ingredients: Acacia Gum, Carnauba Wax, Croscarmellose Sodium, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Purified Water. NPN 02243453
New Era Biochemic Tissue Salt 10, 2, 6, 8 (Seven Seas Limited): Each tablet contains: Sodium Phosphate 6x 0.07 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 0016935.

New Era Combination F Biochemic Tissue Salts (Seven Seas Limited): Each tablet contains: Magnesium Phosphate 6x 0.0175 mcg • Potassium Phosphate 6x 0.0175 mcg • Silicon Dioxide 6x 0.0175 mcg • Sodium Chloride 6x 0.0175 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 00147028

New Era Combination G Biochemic Tissue Salts (Seven Seas Limited): Each tablet contains: Calcium Fluoride 6x 0.0175 mcg • Calcium Phosphate 6x 0.0175 mcg • Potassium Phosphate 6x 0.0175 mcg • Sodium Chloride 6x 0.0175 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 00147036

New Era Combination N Biochemic Tissue Salts (Seven Seas Limited): Oral Laxative. Each tablet contains: Calcium Phosphate 6x 0.0175 mcg • Magnesium Phosphate 6x 0.0175 mcg • Potassium Chloride 6x 0.0175 mcg • Potassium Phosphate 6x 0.0175 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 00534862
Oral Laxative (HJ Sutton Industries): Each 1 tsp serving contains: Dibasic Sodium Phosphate 0.9 g. Other Ingredients: Glycerin, Sodium Saccharin, Sodium Benzoate, Purified Water. NPN 80003212

Phoslax: Oral Laxative (Odan Laboratories Ltd): Each one tsp serving contains: Dibasic Sodium Phosphate 0.9 g. • Monobasic Sodium Phosphate 2.4 g. Other Ingredients: Glycerin, Natural Ginger Flavour, Natural Lemon Flavour, Sodium Benzoate, Purified Water. NPN 80000689

Schuessler Tissue Salts General Debility Comb B (Martin & Pleasance): Oral Laxative. Each tablet contains: Calcium Phosphate 6.0 X • Ferrum Phosphoricum 6.0 X • Kali Phosphoricum 6.0 X. Other Ingredients: Anhydrous Calcium Hydrogen Phosphate, Lactose, Magnesium Stearate. DIN-HM 80003543

Thanks to Contributors and Reviewers: Dr. J. Kappel (SHR neph), Dr. B. Manns (Calgary neph), Marianne Gulka (SHR Pharm), Patty Chorneyko (SHR Pharm), Sandy Knezacek (SHR Pharm), Angie Mckinnon (SHR Pharm), Poppy Lowe (SHR Dietician), Andrea Woodland (Newfoundland Pharm), Peter Ricci (Regina Pharm), Michael Chan (Regina Dietician)

References: PHOSPHATE BINDERS in HYPERPHOSPHATEMIA of CKD

1 National Kidney Foundation. **K/DOQI** clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:S1-201. Available from http://www.kidney.org/professionals/kdoqi/guidelines_bone/index.htm. Accessed May 1st, 2010.

2 Kidney Disease Improving Global Outcomes. **KDIGO** Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney International 2009; 76:(Suppl 113), S1–S130.

3 Guidelines for the Management of Chronic Kidney Disease. Canadian Society of Nephrology (**CSN**). CMAJ. Nov. 2008; 179:(11), 1154-1162.

4 Tonelli M, Pannu N, Manns B. Oral **Phosphate Binders** in Patients with Kidney Failure. N Engl J Med. 2010. 362:1312-24.

5 Tentori F, Blayney MJ, Albert JM et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (**DOPPS**). Am J Kidney Dis 2008; 52: 519–530.

6 Savica V, A. Calo`, Monardo P et al. Phosphate binders and management of hyperphosphataemia in end-stage renal disease Nephrol Dial Transplant (2006) 21: 2065–2068

7 Burke SK. Phosphate is a uremic toxin. Journal of Renal Nutrition, Vol 18, No 1 (January), 2008: pp 27–32

8 National Collaborating Centre for Chronic Conditions (NHS, NICE- UK). Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians, September 2008. Available at: http://guidance.nice.org.uk/CG73

9 The Merck Manual Medical Library. Available online at: http://www.merck.com/mmpe/sec12.html?WT.z_section=Endocrine and Metabolic Disorders

10 Selva O'Callaghan A, San Jose A, Simeon CP et al. M. Fatal hypocalcemia from sodium phosphate enemas. J Am Geriatr Soc. 1995 Dec;43(12):1447-8

11 Kirschbaum B. The acidosis of exogenous phosphate intoxication. Review. Arch Intern Med. 1998 Feb 23;158(4):405-8.

12 Blayney M.J., Tentori F. (2009). Trends and consequences of mineral bone disorder in haemodialysis patients: Lessons from the dialysis outcomes and practice patterns study (DOPPS). Journal of Renal Care 35(s1), 7–13.

13 Floege J. 2008 Calcium-containing phosphate binders in dialysis patients with cardiovascular calcifications: should we CARE-2 avoid them? Nephrol Dial Transplant (2008) 23: 3050–3052

14 Plantinga, L. C., Fink, N. E., Melamed, M. L., and others (2008). Serum phosphate levels and risk of infection in incident dialysis patients. Clin Journal of the American Society of Nephrology 3, pp. 1398-1406.

15 Hutchison AJ. Oral Phosphate Binders. Kidney International (2009) 75, 906–914

16 Health Canada. Food and Nutrition. Dietary Reference Intakes. http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/ref_elements_tbl-eng.php

17 Sullivan C, Sayre S; Leon JB et al. Effect of Food Additives on Hyperphosphatemia Among Patients With End-stage Renal Disease A Randomized Controlled Trial. JAMA. 2009;301(6):629-635

18 Milas NC, Nowalk MP, Akpele L et al. Factors associated with adherence to the dietary protein intervention in the Modification of Diet in Renal Disease Study. J Am Diet Assoc 1995;95:1295- 300

19 Ford JC, Pope JF, Hunt AE et al. The effect of diet education on the laboratory values and knowledge of hemodialysis patients with hyperphosphatemia. J Ren Nutr 2004; 14: 36–44.

20 Silver J. The details bedevil DCOR. Kidney International 2007;72:1041-1043.

21 Salusky IB. A new era in phosphate binding: What are the options? Kidney International (2006) 70, S10–S15.

22 Barna MM, Kapoian T, O'Mara NB. Sevelamer Carbonate. The Annals of Pharmacotherapy. 2010 January, Volume 44. 127 – 134.

23 AlBaaj F, Hutchison AJ. Hyperphosphatemia in Renal Failure. Causes, Consequences and Current Management. Drugs 2003; 63 (6): 577-596

24 European Best Practice Guideline on Nutrition in CKD. 2007. Available at: http://www.ndt-educational.org/guidelines.asp

25 Pierratos A, McFarlane P, Chan CT. Quotidian dialysis–update 2005. Curr Opin Nephrol Hypertens 2005; 14: 119–124.

26 Lindsay RM, Al-Hejaili F, Nesrallah G. Calcium and phosphate balance with quotidian hemodialysis. Am J Kidney Dis 2003; 42 [Suppl 1]: S24–S29

27 Musci I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A. Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. Kidney Int 1998; 53: 1399–1404

28 Micromedex® online. 2010. Monographs – Calcium Salts, Amphojel®, Basaljel®, Magnesium Hydroxide, Renagel®, Renvela®, Fosrenol®. Accessed May 2nd, 2010.

29 e-CPS. Ottawa (ON): Canadian Pharmacists Association. c2009. Monographs – Calcium Salts, Amphojel®, Basaljel®, Magnesium Hydroxide, Renagel®, Fosrenol®. Available from: https://www.e-therapeutics.ca/wps/portal/!ut/p/.scr/Login.

30 AHFS-DI online. 2010. Monographs – Calcium Salts, Amphojel®, Basaljel®, Magnesium Hydroxide, Renagel®, Renvela®, Fosrenol®. Accessed May 2nd, 2010.

31 Briggs G, Freeman, Roger, Yaffe, Sumner, ed. Drugs in Pregnancy and Lactation. 9th ed: TechBooks

32 McGuinnes B, Logan JI. Milk alkali syndrome. Ulster Med J. 2002 November; 71(2): 132–135

33 Ross EA, Szabo NJ, Tebbett IR. Lead Content of Calcium Supplements. JAMA. 2000;284:1425-1429.

34 Navaneethan SD, Palmer SC, Craig JC et al. Benefits and Harms of Phosphate Binders in CKD: A **Systematic Review** of Randomized Controlled Trials. Am J Kidney Dis 54:619-637.

35 Schaefer K, Scheer J, Asmus G et al: The treatment of uraemic hyperphosphataemia with calcium acetate and calcium carbonate: A comparative study. Nephrol Dial Transplant.1991. 6:170-175.

36 Cannata-Andia, JB, Fernandez-Martin, JL. The clinical impact of aluminium overload in renal failure. Nephrol Dial Transplant 2002; 17 Suppl 2:9.

37 Llanyee L, Hershman JM.Conditions and Drugs interfering with thyroxine absorption.Best Practice & Research Clinical Endocrinology & Metabolism. 2009. 23:781–792

38 Friedman EA: Calcium-based phosphate binders are appropriate in chronic renal failure. Systematic Review. Clin J Am Soc Nephrol.2006. 1:704-709.

39 Almirall J, Veciana L, Llibre J: Calcium acetate versus calcium carbonate for the control of serum phosphorus in hemodialysis patients. Am J Nephrol 1994. 14:192-196

40 Micromedex 2010. Sucralfate.

41Massey L Magnesium therapy for nephrolithiasis. Magnes Res. 2005 Jun;18(2):123-6.

42 Guillot AP, Hood VL, Runge CF, Gennari FJ: The use of magnesium-containing phosphate binders in patients with endstage renal disease on maintenance hemodialysis. Nephron 30: 114-117, 1982

43 Delmez JA, Kelber J, Norward KY et al. Magnesium carbonate as a phosphorus binder: A prospective, controlled, crossover study. Kidney International 1996 (49): 163-167.

44Spiegel DM, Farmer B, Smits G et al. Magnesium Carbonate is an effective Phosphate binder for Chronic Hemodialysis Patients: A pilot study. J Renal Nutrition. 2007. 17(6); 416-422.

45 Suki WN et al. Effects of sevelamer and calcium-based phosphate binder on mortality in hemodialysis patients (DCOR). Kidney International. 2007;72:1130-1137.

46 Manns B, Klarenbach S, Lee H, Culleton B, Shrive F, Tonelli M. Economic evaluation of sevelamer in patients with end-stage renal disease. Nephrol Dial Transplant 2007;22:2867-78.

47 Sturtevant J, Hawley CM, Reiger K et al. Efficacy and side-effect profile of sevelamer hydrochloride used in combination with conventional phosphate binders. Nephrology. 2004. 9. 406-413.

48 9 studies: CADTH Health Technology Inquire Service. Sevelamer Hydrochloride for the Treatment of Patients with Chronic Kidney Disease : A Review of the Clinical Effectiveness. September 8th 2009. Available at: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/665

49 Chertow GM, Dillon M, Burke SK, et al: A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. Clin Nephrol. 1999. 51:18-26.

50 Koiwa F, Onoda N, Kato H, et al: Prospective randomized multicenter trial of sevelamer hydrochloride and calcium carbonate for the treatment of hyperphosphatemia in hemodialysis patients in Japan. Ther Apher Dial :340-346, 2005

51 Medical Letter. Phosphate Binders. Feb. 13, 2006.

52 Pai AB, Shepler BM. Comparison of Sevelamer hydrochloride and Sevelamer Carbonate: Risk of Metabolic Acidosis and Clinical Implications. Pharmacotherapy. 2009. 29(5):554-561.

53 Namagondlu G, Main N, Yates L et al. Lanthanum associated abnormal liver function tests in two patients on dialysis: a case report. J Med Case Reports. 2009 Dec 9;3:9321.

54 Weitzman S, Ginsburg KC, Carlson HE. Colesevelam hydrochloride and lanthanum carbonate Interfere with the absorption of Levothyroxine. Thyroid. 2009. 19 (1)77-79.

55 E-cps; Product Monograph, Fosrenol®

56 How PP, Mason DL, Lau AH. Current Approaches in the treatment of Chronic Kidney Disease Mineral and Bone Disorder. J Pharmacy Practice. 2008. 21(3)196-213.

TOP

57CADTH-CEDAC final recommendations on reconsideration and reasons for recommendation: Lanthanum carbonate hydrate.2008. (http://wwwcadth.ca/media/cdr/complete/cdr_complete_Fosrenol_February-29-2008.pdf)

58 Davis RL, Abraham JL. Lanthanum deposition in a dialysis patient. Nephrol Dial Transplant. 2009. 24:3247-3250.

59 Fosrenol (lanthanum carbonate). Pharmacist's Letter/Prescriber's Letter 2007;23(4):230419.

60Jaffe, JA, Liftman, C, Glickman, JD. Frequency of elevated serum aluminum levels in adult dialysis patients. Am J Kidney Dis 2005; 46:316

61Goldsmith DR et al. Sevelamer hydrochloride: a review of its use for hyperphosphataemia in pts with end-stage renal disease on haemodialysis. Drugs 2008;68:85-104

62 Poulouse J, Medscape Clinical Meetings 2010, Abstract Poster 180. Presented April 14, 2010

63 Bellasi A, Kooienga L, Block GA. Phosphate Binders: New products and challenges. Hemodialysis International.2006:10-225-234.

64 Savica V, Calò LA, Monardo P et al. (2009) Salivary phosphate-binding chewing gum reduces hyperphosphatemia in dialysis patients. J Am Soc Nephrol.2009. 20:639–644.

Additional References: **PHOSPHATE BINDERS in HYPERPHOSPHATEMIA of CKD**

1. Abboud H, Henrich WL. Stage IV Chronic Kidney Disease. N Engl J Med. 2010. 32; 56-65.
2. Block GA, Spiegel DM, Ehrlich J et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to dialysis. Kidney International. 2005. 68:1815-1824.- New HD pts with no evidence of coronary calcification compared to pts with evidence of at least mild coronary calcification who had SIG progression. Use of Ca-containing binders resulted in more rapid progression than did use of sevelamer in such pts.
3. Brewster UC, Ciampi MA, Abu-Alfa AK et al. Long-term comparison of sevelamer hydrochloride to calcium-containing phoshate binders. Nephrology.2006. 11:142-146. -N=30 HD pts, Pts on sevelamer for >1 yr compared to those on calcium binders had a lower serum bicarb conc, a higher serum phosphorus and a higher CaXP product.
4. Braun J, Asmus HG, Holzer H et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate- phosphorus metabolism and cardiovascular calcification. Clin Nephrol. 2004; 62(2):104-115.
5. Block GA, Klassen PS, Lazarus JM et al. Mineral metabolism, mortality and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004. 15(8):2208-18.
6. Block GA et al. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney International. 2007;71:438-441.
7. CKD-MBD as a systemic disorder. Editorial. Bone. 2009. 45:S1. – describes term CKD-MBD, discusses spectrum of bone disease in CKD (high turnover bone disease (osteitis fibrosa, renal osteodystrophy) to low turnover bone disease (osteomalacia, adynamic bone disease), vascular calcification.
8. Coladonato JA. Control of Hyperphosphatemia among Patients with ESRD. J Am Soc Nephrol. 2005. 16:S107-S114.
9. CSN Hemodialysis Clinical Practice Guidelines. J Am Soc Nephrol 2006. 17: S1-S27.
10. Curran MP, Robinson DM. Lanthanum Carbonate. A review of its use in lowering Serum phosphate in pts with ESRD. Drugs. 2009. 69(16):2329-2349.
11. Geary DF, Hodson EM, Craig JC. Interventions for bone disease in children with CKD. Cochrane Review. Jan. 2010. Issue 1.
12. Ganesh SK, Stack AG, Levin NW et al. Associationof Elevated Serum PO4, Ca x PO4 Product and Parathyroid Hormone with Cardiac Mortality Risk in Chronic Hemodialysis Patients. J Am Soc Nephrol. 2001. 12: 2131-2138. – Study Identifies relationships between elevated serum PO4, CaxPO4 product & PTH and cardiac causes of death in HD pts, especially deaths resulting from CAD & sudden death.
13. Jamal SA, Fitchett D, Lok CE et al. The effects of calcium-based versus non-calcium based phosphate binders on mortality among pts with CKD : a meta-analysis. Nephrol Dial Transplant. 2009. 24:3168-3174. – Did not find a statistically SIG difference in cardiovascular mortality and coronary artery calcification in pts receiving calcium-based phosphate binders compared to non-calcium-based binders. However the data are limited! by the small number of studies and the confidence intervals do not exclude a potentially important beneficial effect. Further RCTs are needed.
14. Kazama JJ. Oral Phosphate binders: History and Prospects. Bone. 2009. 45:S8-S12.
15. Martin KJ, Gonzalez EA. Metabolic Bone disease in CKD. J Am Soc Nephrol. 2007.18:875-885.
16. Mohammed I, Hutchison AJ. Oral Phosphate Binders for the management of serum phosphate levels in dialysis patients. J of Renal Care. 35(21).65-70.
17. Moe SM. Disorders Involving Calcium, Phosphorus and Magnesium. Prim Care. 2008. June; 35(2):215-vi.
18. Persy VP, Behets GJ, Bervoets AR et al. Lanthanum a safe phosphate binder.Seminars in Dialysis. 19(3):195-199.
19. Qunibi W, M Moustafa, Muenz LR et al. A 1 yr Randomized trial of Calcium Acetate vs Sevelamer on Progression of Coronary Artery Calcification in Hemodialysis Patients with Comparable Lipid Control: The Calcium Acetate Renagel Evaluation-2 (CARE-2) Study. Am J Kidney Dis.2008. 51:952-965.
20. Qunibi WY. Consequences of hyperphosphatemia in pts with ESRD. Kidney International. 2004. 66:S8-S12.
21. Rees L, Shroff R. Phosphate binders in CKD: chalking out the differences. Pediatr Nephrol. 2010. 25:385-394.
22. Ring T et al. Calcium acetate versus calcium carbonate as phosphorus binders in patients on chronic haemodialysis: a controlled study. Nephrology Dialysis Transplantation. 1993;8:341-346.
23. Ruffino M, De Bonis E, Martin M et al. Is it possible to control hyperphosphatemia with diet, without inducing protein malnutrition? Nephrol Dial Transplant. 1998. 12 (Supp 3):65-67.- In chronic HD pts, a neutral phosphate balance is hard to achieve despite binder therapy, when protein intake is >50g. Additional protein restriction may impose risk of protein malnutrition.
24. Sprague SM, Abboud H, Qiu P et al. Lanthanum Carbonate Reduces Phosphorus Burden in Patients with CKD Stages 3 and 4: An RCT. Clin J Am Soc Nephrol. 2009. 4:178-185.
25. St Peter W, Liu J, Weinhandl E et al. A Comparison of Sevelamer and Calcium-based Phosphate Binders on Mortality, Hospitalization and Morbidity in Hemodialysis: A Secondary Analysis of the Dialysis Clinical Outcoes Revisited (DCOR) Randomized Trial Using Claims Data. Am J Kidney Dis. 2008. 51:445-454.
26. Add in: O'Donovan R. Lancet 1986. MgCO3 as a binder. 0.5 – 1.5g/d.
27. Matro R, Shnitser A, Spodik M, et al. Efficacy of Morning-Only Compared With Split-Dose Polyethylene Glycol Electrolyte Solution for Afternoon Colonoscopy: A Randomized Controlled Single-Blind Study. Am J Gastroenterol. 2010 Apr 20
28. Prie, Dominique, Friedlander, Gerard. Genetic Disorders of Renal Phosphate Transport. N Engl J Med 2010 362: 2399-2409.
29. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. **Vitamin D compounds** for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD008175.
30. Gutierrez, Orlando M., Anderson, Cheryl, Isakova, Tamara, et al. on behalf of the CRIC Study Group, **Low Socioeconomic Status** Associates with Higher Serum Phosphate Irrespective of Race. J Am Soc Nephrol 2010 0: ASN.2010020221.
31. Mehrotra Rajnish; Chiu Yi-Wen; Kalantar-Zadeh Kamyar; et al. Similar Outcomes With **Hemodialysis and Peritoneal Dialysis** in Patients With End-Stage Renal Disease. Arch Intern Med. 2010;0(2010):archinternmed.2010.352.
32. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998 Apr;31(4):607-17.
33. **FHN** Trial Group. In-Center **Hemodialysis Six Times** per Week versus Three Times per Week. November 20, 2010 (10.1056/NEJMoa1001593)
34. Moe SM, Zidehsarai MP, Chambers MA, et al. **Vegetarian** Compared with Meat Dietary Protein Source and Phosphorus Homeostasis in Chronic Kidney Disease. Clin J Am Soc Nephrol. 2010 Dec 23.
35. Pallan S, Khan A. **Primary hyperparathyroidism**: Update on presentation, diagnosis, and management in primary care. Can Fam Physician. 2011 Feb;57(2):184-9.
36. Palmer Suetonia C., Hayen Andrew, Macaskill Petra, et al. Serum Levels of **Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease** in Individuals With Chronic Kidney Disease: A Systematic Review and Meta-analysis. JAMA. 2011;305(11):1119-1127.doi:10.1001/jama.2011.308
37. Levey AS, Coresh J. **Chronic kidney disease**. Lancet. 2011 Aug 12.
38. Marcocci C, Cetani F. Clinical practice. **Primary hyperparathyroidism**. N Engl J Med. 2011 Dec 22;365(25):2389-97
39. Thadhani R; Appelbaum E; Pritchett Y, et al. Vitamin D therapy (**paricalcitol**) and **cardiac** structure and function in patients with chronic kidney disease: The PRIMO randomized controlled trial. JAMA 2012; 307:674-684.
40. Daugirdas JT, Chertow GM, Larive B, et al Effects of **Frequent Hemodialysis** on Measures of CKD Mineral and Bone Disorder. J Am Soc Nephrol. 2012 Feb 23. (control of hyperphosphatemia)
41. Vondracek SF, Hoody DW. Combination vitamin D therapy in stage 5 chronic kidney disease. Ann Pharmacother. 2011 Jul;45(7-8):1011-5.
42.

TOP

REFERENCES:

General References:

1. Fraser Health Hospice Palliative Care Symptom Guidelines. Available at: http://www.fraserhealth.ca/professionals/hospice_palliative_care/
2. Hospital Pharmacists' Special Interest Group in Palliative Care. Care Beyond Cure: Management of Pain and Other Symptoms, 4th ed. APES Quebec, Canada; 2009.
3. Pereia JL, Associates. The Pallium Palliative Pocketbook: a peer-reviewed, referenced resource. 1st Canadian ed. Edmonton, Canada: The Pallium Project; 2008.
4. Downing M, ed. Medical Care of the Dying, 4th ed. Victoria Hospice Society. Victoria, BC; 2006.

Anorexia-Cachexia:

5. Berenstein G, Ortiz Z. Megestrol acetate for treatment of anorexia-cachexia syndrome. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD004310. DOI: 10.1002/14651858.CD004310.pub2
6. Loprinzi CL et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. J Clin Oncol. 1999 Oct;17(10):3299-306.
7. Jatoi A et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol. 2002 Jan 15;20(2):567-73.
8. Dewey A, Baughan C, Dean TP, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD004597. DOI: 10.1002/14651858.CD004597.pub2.

Dyspnea:

9. Jennings AL et al. Opioids for the palliation of breathlessness in advanced disease and terminal illness. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No.: CD002066. DOI: 10.1002/14651858.CD002066.
10. Polosa R, Simidchiev A, Walters EH. Nebulised morphine for severe interstitial lung disease. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD002872. DOI: 10.1002/14651858.CD002872.
11. Penson RT, Joel SP, Roberts M, Gloyne A, Beckwith S, Slevin ML. The bioavailability and pharmacokinetics of subcutaneous, nebulized and oral morphine-6-glucuronide. Br J Clin Pharmacol. 2002 Apr;53(4):347-54.
12. Abernethy AP et al. Randomised,double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ. 2003 Sep 6;327(7414):523-8.
13. Currow DC et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. J Pain Symptom Manage. 2011 Sep;42(3):388-99.
14. Simon ST et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007354. DOI: 10.1002/14651858.CD007354.pub2.
15. Cranston JM, Crockett A, Currow D. Oxygen therapy for dyspnoea in adults. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004769. DOI: 10.1002/14651858.CD004769.pub2.

Delirium:

16. Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill adult patients. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD004770. DOI: 10.1002/14651858.CD004770.

Myoclonus:

17. Stone P, Minton O. European Palliative Care Research collaborative pain guidelines. Central side-effects management: what is the evidence to support best practice in the management of sedation, cognitive impairment and myoclonus? Palliat Med. 2011 Jul;25(5):431-41.

Hypercalcemia:

18. Major P et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol. 2001 Jan 15;19(2):558-67.
18. Wong RKS,Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD002068. DOI: 10.1002/14651858.CD002068.

Respiratory Congestion:

19. Wildiers H et al; Flemish Federation of Palliative Care. Atropine, hyoscine butylbromide, or scopolamine are equally effective for the treatment of death rattle in terminal care. J Pain Symptom Manage. 2009 Jul;38(1):124-33.

TOP

TOP

PATIENT SAFETY – DRUG CONSIDERATIONS

[1] Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, Etchells E, Ghali WA, Hebert P, Majumdar SR, O'Beirne M, Palacios-Derflingher L, Reid RJ, Sheps S, Tamblyn R. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ. 2004 May 25;170(11):1678-86.

[2] Finchem JE. An overview of adverse drug reactions. *American Pharmacy*. 1991;NS31 (6):47-52.

[3] Martys CR. Adverse reactions to drugs in general practice. *BMJ*. 1997;2:1194-97.

[4] Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348:1556-64.

[5] Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. 2006 Oct 18;296(15):1858-66.

[6] David Flockhart: Important DI cytochrome p450 information http://medicine.iupui.edu/flockhart/

[7] The Institute for Safe Medication Practices – website accessede at www.ismp.org

[8] ISMP Medication Safety Alert – Acute Care, May 31, 2012.

Agency for Healthcare Research and Quality (**AHRQ**) www.ahrq.gov

American Academy of Pediatrics, Steering Committee on Quality Improvement and Management and Committee on **Hospital Care**. Principles of **pediatric patient safety**: reducing harm due to medical care. Pediatrics. 2011;127(6):1199 –1210.

Andrews LB, Stocking C, Krizek T, Gottlieb L, Krizek C, Vargish T, et al. An **alternative strategy** for studying adverse events in medical care. *Lancet* 1997;349:309-13.

Avery AJ, Rodgers S, Cantrill JA, et al. A **pharmacist-led information technology intervention** for medication errors (**PINCER**): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. Lancet. 2012 Feb 20.

Avorn J. Learning about the **Safety of Drugs** — A Half-Century of Evolution. N Engl J Med 2011; 365:2151-2153.

Bartlett G, Blais R, Tamblyn R, Clermont RJ, MacGibbon B. Impact of patient communication problems on the risk of preventable adverse events in acute care settings. CMAJ. 2008 Jun 3;178(12):1555-62. Patients with communication problems appeared to be at highest risk for preventable adverse events.

Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA, et al.; Adverse Drug Events Prevention Study Group. The costs of adverse events in hospitalized patients. JAMA 1997;277(4):307-311.

Bell CM, Brener SS, Gunraj N, et al. Association of ICU or hospital admission with **unintentional discontinuation** of medications for chronic diseases. JAMA. 2011; 306(8):840-847.

Benning Amirta, Ghaleb M, Suokas A, et al. **Large scale organizational intervention** to improve patient safety in four UK hospitals: mixed method evaluation. BMJ 2011;342:doi:10.1136/bmj.d195 (3 Feb 2011)

Benning Amirta, Dixon-Woods M, Nwulu U, et al. **Multiple component patient safety intervention** in English hospitals: controlled evaluation of second phase. BMJ 2011;342:doi:10.1136/bmj.d199 (3 Feb 2011)

Berwick DM. Errors today and errors tomorrow. *N Engl J Med* 2003;348:2570-2.

Bishop TF, Ryan AM, Casalino LP. **Paid malpractice claims** for adverse events in inpatient and outpatient settings. JAMA. 2011;305(23):2427-2431.

Blendon RJ, DesRoches CM, Brodie M, Benson JM, Rosen AB, Schneider E, et al. **Views of practicing physicians** and the public on medical errors. *N Engl J Med* 2002;347:1933-40.

Blossom DB, Kallen AJ, Patel PR, Elward A, Robinson L, Gao G, et al. Outbreak of Adverse Reactions Associated with **Contaminated Heparin**. N Engl J Med. 2008 Dec 3. [Epub ahead of print]

Bourgeois, Florence T., Mandl, Kenneth D., Valim, Clarissa, et al. **Pediatric Adverse Drug Events** in the Outpatient Setting: An 11-Year National Analysis. Pediatrics 2009 124: e744-e750.

Brennan TA, Leape LL, Laird NM, Hebert L, et al. Incidence of **adverse events** and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med* 1991;324:370-6.

Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to **emergency department visits** for adverse drug events in older adults. Ann Intern Med. 2007;147:755-65.

Budnitz DS et al. **Emergency hospitalizations for adverse drug events** in older Americans. N Engl J Med 2011 Nov 24; 365:2002. A few medications — including **warfarin, insulins, oral antiplatelet agents, and oral hypoglycemic agents** — cause most of the problems that lead to emergency hospitalization in older patients.

Camiré E, Moyen E, Stelfox HT. Medication errors in **critical care**: risk factors, prevention and disclosure. CMAJ. 2009 Apr 28;180(9):936-43.

CDC MMWR Oct/10 QuickStats: Rates of **Drug-Induced Deaths**,* by Race/Ethnicity† --- United States, 1999—2007 Weekly October 29, 2010 / 59(42);1376 http://www.cdc.gov/mmwr/pdf/other/su6001.pdf

Chan PS, Jain R, Nallmothu BK, Berg RA, Sasson C. **Rapid response** teams: a systematic review and meta-analysis. *Arch Intern Med* 2010;170:18-26.

Chassin MR, Loeb JM, Schmaltz SP, Wachter RM. **Accountability measures** — using measurement to promote quality improvement. N Engl J Med 2010;363:683-8.

Cousins D, Gerrett D, Warner B. A review of medication incidents reported to the **National Reporting and Learning System in England and Wales** over six years (2005 - 2010). Br J Clin Pharmacol. 2011 Dec 22.

Daniels JP, Hunc K, Cochrane D, et al. **Identiication by families** of **pediatric adverse events** and near misses overlooked by health care providers CMAJ 2012;184:29-34.

Dart RC, Paul IM, Bond GR, et al. Pediatric fatalities associated with over the counter (nonprescription) **cough and cold medications**. Ann Emerg Med. 2009 Apr;53(4):411-7. Epub 2008 Dec 19.

De Bruijn, H. Managing professionals. Chapter 3. Routledge, 2010. 15 Wu AW, Folkman S, McPhee SJ, Lo B. Do **house officers learn from their mistakes**? *JAMA* 1991;265:2089-94.

De Vries EN, Prins HA, Crolla RM, den Outer AJ, van Andel G, van Helden SH, et al. Effect of a comprehensive **surgical safety system** on patient outcomes. *N Engl J Med* 2010;363:1928-37.

Delaney JAM, Opatrny LMDM, Brophy JMMDP, Suissa SP. **Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding**. Can Med Assoc J 2007;177:347-51.

Doherty C, Mc Donnell C. **Tenfold Medication Errors**: 5 Years' Experience at a University-Affiliated Pediatric Hospital. Pediatrics. 2012 Apr 2.

Dudas RA, Bundy DG, Miller MR, Barone M. Can **teaching medical students** to investigate medication errors change their attitudes towards patient safety? Qual Saf Health Care. 2011 Jan 12.

Duke J, Friedlin J, Ryan P. A quantitative analysis of adverse events and **"overwarning" in drug labeling.** Arch Intern Med. 2011 May 23;171(10):944-6.

Eggertson Laura. New network (**cNODES**) created to assess drug safety. CMAJ December 13, 2011 183:E1293-E1294; ahead of print Nov 7, 2011, doi:10.1503/cmaj.109-4045.

Epstein AM, Jha AK, Orav JE. The relationship between **hospital readmission rates and rehospitalizations**. N Engl J Med 2011; 365:2287-2295.

FDA November 5, 2009 — The US Food and Drug Administration (FDA) has launched a new program called the **Safe Use Initiative** to reduce drug-related injuries from preventable sources of harm.

FDA Mar/10 In late April, Takeda Pharmaceuticals will begin marketing its proton pump inhibitor **Kapidex** (dexlansoprazole) under the new name **Dexilant**, owing to dispensing errors that have occurred from mix-ups with the prostate cancer drug Casodex (bicalutamide) and the analgesic Kadian (morphine).FDA news release

Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. **Updating the Beers criteria for potentially inappropriate medication use in older adults**: results of a US consensus panel of experts. Arch Intern Med. 2003 Dec 8-22;163(22):2716-24. Erratum in: Arch Intern Med. 2004 Feb 9;164(3):298. http://www.hqc.sk.ca/download.jsp?Tnpy1RKzAkMsCVz+LX1gQTBIzBf0QfLQkUwK4QBZaJst2U9rf2NOdQ==

Forster AJ, Clark HD, Menard A, Dupuis N, Chernish R, Chandok N, et al. Adverse events among medical patients after discharge from hospital. CMAJ 2004;170(3):345-349. Erratum in: CMAJ 2004;170(5):771.

Frankovich J, Longhurst CA, Sutherland SM. Evidence-based medicine in the **EMR** era. N Engl J Med 2011;365:1758-9.

Gallagher P, O'Mahony D. **STOPP** (Screening Tool of Older Persons' potentially **inappropriate Prescriptions**): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008;37:673-9.

Gandhi TK, Lee TH. **Patient safety beyond the hospital**. N Engl J Med. 2010; 363(11):1001-1003.

Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of **nonsteroidal anti-inflammatory drugs in chronic heart failure**. Arch Intern Med 2009;169:141-9.

TOP

Guthrie Bruce, McCowan Colin, Davey Peter, et al. **High risk prescribing in primary care** patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice. BMJ 2011

Guttmann A, Schull MJ, Vermeulen MJ, et al. Association between waiting times and short term mortality and hospital admission **after departure from emergency department**: population based cohort study from Ontario, Canada. BMJ 2011;342:d2983.

Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, Crosby AE, Paulozzi LJ. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008 Dec 10;300(22):2613-20. The majority of overdose deaths in West Virginia in 2006 were associated with nonmedical use and diversion of pharmaceuticals, primarily **opioid** analgesics.

Hamilton Hilary; Gallagher Paul; Ryan Cristin; et al. **Potentially Inappropriate Medications** Defined by **STOPP** Criteria and the Risk of Adverse Drug Events in **Older Hospitalized Patients**. Arch Intern Med. 2011;171(11):1013-1019.

Handler SM, Hanlon JT, Perera S, et al. Castle NG, Studenski SA. Consensus list of **signals** to detect potential adverse drug reactions in nursing homes. J Am Geriatr Soc. 2008 May;56(5):808-15. Epub 2008 Mar 21.

Haynes AB, Weiser TG, et al. Safe Surgery Saves Lives Study. A **surgical safety checklist** to reduce morbidity and mortality in a global population. N Engl J Med. 2009 Jan 29;360(5):491-9. Epub 2009 Jan 14.

Hébert PC, Stanbrook MB, Macdonald N, et al. Can **Health Canada** protect Canadians from unsafe drugs? CMAJ. 2011 Jul 12;183(10):1125-6.

Health Canada: Sound alike, Look alike. http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/lasa-pspcs_factsheet-faitsaillant_e.html

Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of **warfarin and its drug and food interactions**. Arch Intern Med. 2005;165: 1095-106.

Howard R, Avery A, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which **drugs cause preventable admissions** to hospital? A systematic review. Br J Clin Pharmacol 2007;63:136-47.

Institute of Medicine. **Health IT** and patient safety: building safer systems for better care. 2011. www.iom.edu/Reports/2011/Health-IT-and-Patient-Safety-Building-Safer-Systemsfor-Better-Care.aspx.

ISMP: **Anticoagulants the Leading Reported Drug Risk** in 2011. QuarterWatch 2012. http://www.ismp.org/quarterwatch/pdfs/2011Q4.pdf (suspect drugs list: 1) dabigatran, 2) Warfarin)

Jefferson T, Doshi P, Thompson M, et al. **Ensuring safe and effective drugs**: who can do what it takes? BMJ. 2011 Jan 11;342:c7258. doi:10.1136/bmj.c7258.

Joint Commission on Accreditation of Healthcare Organizations (JCAHO) www.jointcommission.org

Kachalia Allen, Kaufman Samuel R., Boothman Richard, Et al. Liability Claims and Costs Before and After Implementation of a **Medical Error Disclosure Program**. *Ann Intern Med* August 17, 2010 153:213-221.

Kaldjian LC, Jones EW, Wu BJ, Forman-Hoffman VL, et al. **Reporting medical errors** to improve patient safety: a survey of physicians in teaching hospitals.Arch Intern Med. 2008 Jan 14;168(1):40-6.

Kiekkas P, Karga M, Lemonidou C, Aretha D, Karanikolas M. Medication **errors in critically ill adults**: a review of direct observation evidence. Am J Crit Care. 2011 Jan;20(1):36-44.

Kohn LT, Corrigan JM, Donaldson MS, eds. **To Err Is Human: Building a Safer Health System**. Washington, DC: Institute of Medicine; 2000.

Lamont T, Beaumont C, Fayaz A, et al. Checking placement of **nasogastric feeding tubes** in adults (interpretation of x ray images): summary of a safety report from the National Patient Safety Agency. BMJ. 2011 May 5;342:d2586. doi:10.1136/bmj.d2586

Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA, Sharek PJ. **Temporal trends** in rates of patient harm resulting from medical care. *N Engl J Med* 2010;363:2124-34.

Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998 Apr 15;279(15):1200-5. The overall incidence of serious ADRs was **6.7%** (95% confidence interval [CI], 5.2%-8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%) of hospitalized patients. We estimated that in 1994 overall **2,216,000** (1721000-2711000) hospitalized patients had serious ADRs and **106,000** (76000-137000) had **fatal** ADRs, making these reactions between the fourth and sixth leading cause of death.

Leape LL, Berwick DM. **Five years after To Err Is Human**: what have we learned? *JAMA* 2005;293:2384-90.

Lipitz-Snyderman Allison, Steinwachs Donald, Needham Dale M, et al. Impact of a **statewide intensive care unit quality improvement initiative** on hospital mortality and length of stay: retrospective comparative analysis. BMJ 2011;342:doi:10.1136/bmj.d219 (Published 31 January 2011)

Loboz K, Shenfield G. **Drug combinations and impaired renal function—the "triple whammy**". Br J Clin Pharmacol 2005;59:239-43.

Longhurst CA, Parast L, Sandborg CI, Widen E, Sullivan J, Hahn JS, Dawes CG, Sharek PJ. Decrease in Hospital-wide Mortality Rate After Implementation of a Commercially Sold **Computerized Physician Order Entry System**. Pediatrics. 2010 May 3.

Longhurst CA, Landa HM. **Health information technology** and patient safety. BMJ. 2012 Feb 20;344:e1096.

Lopez Lenny; Weissman Joel S.; Schneider Eric C.; et al. **Disclosure of Hospital Adverse Events** and Its Association With Patients' Ratings of the Quality of Care. Arch Intern Med. 2009;169(20):1888-1894.

Lyons M. Do classical origins of **medical terms** endanger patients? Lancet. 2008 Apr 19;371(9621):1321-2.

Madlon-Kay DJ,Mosch FS. Liquid medication dosing errors. J Fam Pract. 2000; 49(8):741-744.

Mattison MLP; Afonso KA; Ngo LH. et al. Preventing Potentially Inappropriate Medication Use in Hospitalized Older Patients With a **Computerized Provider Order Entry** Warning System. Arch Intern Med. 2010;170(15):1331-1336.

McBride WG. **Thalidomide** and congenital abnormalities. Lancet 1961;2:1358.

McCannon J, Berwick DM. A **new frontier in patient safety**. JAMA. 2011 Jun 1;305(21):2221-2.

McCulloch P, Kreckler S, New S, et al. Effect of a **"Lean" intervention** to improve safety processes and outcomes on a surgical emergency unit. BMJ. 2010 Nov 2;341:c5469. doi: 10.1136/bmj.c5469.

Merry AF, Webster CS, et al. Multimodal system designed to **reduce errors** in recording and administration of drugs in **anaesthesia**: prospective randomised clinical evaluation. BMJ. 2011 Sep 22;343:d5543.

Moore TJ, Glenmullen J, Furberg CD (2010) Prescription **Drugs Associated with Reports of Violence** Towards Others. PLoS ONE 5(12): e15337. doi:10.1371/journal.pone.0015337

MyMedRec: Jun/12 launched to include a free new iPhone and iPad app, **MyMedRec,** and website www.knowledgeisthebestmedicine.org which have been developed by the Institute for Safe Medication Practices Canada with input from Canadian patient groups and health care provider organizations.

Murray MD, Ritchey ME, Wu J, Tu W. Effect of a **pharmacist** on adverse drug events and medication errors in outpatients with cardiovascular disease. Arch Intern Med. 2009 Apr 27;169(8):757-63.

National Patient Safety Agency Alerts (**NHS**) http://www.nrls.npsa.nhs.uk/resources/type/alerts/

Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004 May 18;140(10):795-801.

O'Connor NR. **FDA boxed warnings**: how to prescribe drugs safely. Am Fam Physician. 2010 Feb 1;81(3):298-303.

O'Leary Kevin J.; Buck Ryan; Fligiel Helene M.; et al. **Structured Interdisciplinary Rounds** in a Medical Teaching Unit: Improving Patient Safety.*Arch Intern Med*. 2011;171(7):678-684.

Onder Graziano; Petrovic Mirko; Tangiisuran Balamurugan; et al. Development and Validation of a Score to Assess Risk of Adverse Drug Reactions Among In-Hospital Patients 65 Years or Older: The **GerontoNet ADR Risk Score**. Arch Intern Med. 2010;170(13):1142-1148.

Perras C, Jacobs P, Boucher M, Murphy G, et al. **Technologies to Reduce Errors** in Dispensing and Administration of Medication in Hospitals: Clinical and Economic Analyses [Technology report number 121].
In particular, the use of barcoding for medication dispensing and administration systems, and the simultaneous use of technologies and ward-based automatic dispensing devices could reduce the risk of medication errors in hospitals.

Pharmacist's Letter. May 2007. Medication Errors and Patient Safety Resources.

Pharmacist's Letter. June 2008. Preventing Pediatric Medication Errors. See also Joint Commission: http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_39.htm

Pierluissi E, Fischer MA, Campbell AR, Landefeld CS. **Discussion of medical errors** in morbidity and mortality conferences. *JAMA* 2003;290:2838-42.

Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. **Adverse drug reactions as cause of admission** to hospital: prospective analysis of 18 820 patients. BMJ 2004;329:15-9.

Pitrou Isabelle; Boutron Isabelle; Ahmad Nizar; et al. **Reporting of Safety** Results in Published Reports of Randomized Controlled Trials. *Arch Intern Med*. 2009;169(19):1756-1761.

Poon EG et al. Effect of **bar-code technology** on the safety of medication administration. N Engl J Med 2010 May 6; 362:1698.

TOP

Powers A, Cook GE. Potential **safety signals** and their significance [published online November 14, 2011]. Arch Intern Med. doi:10.1001/archinternmed .2011.525.
Pronovost Peter J.; Faden Ruth R. **Setting Priorities** for Patient Safety: Ethics, Accountability, and Public Engagement. JAMA. 2009;302(8):890-891.
Qato DM, Alexander GC, Conti RM, et al. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA. 2008 Dec 24;300(24):2867-78. In this sample of community-dwelling older adults, prescription and nonprescription medications were commonly used together, with nearly **1 in 25 individuals potentially at risk for a major drug-drug interaction**.
Quach C, McArthur M, McGeer A, et al. Risk of **infection following a visit to the emergency department**: a cohort study. CMAJ. 2012 Mar 6;184(4):E232-9.
Rothschild JM et al. Risks of complications by attending physicians after performing **nighttime procedures**. JAMA 2009 Oct 14; 302:1565.
Samoy LJ, Zed PJ, Wilbur K, et al. Drug-related hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study. Pharmacotherapy 2006;26(11): 1578-1586.
Schneider EL, Campese VM. Adverse drug responses: an increasing threat to the well-being of older patients: Comment on "Development and **validation of a score to assess risk of adverse drug reactions** among in-hospital patients 65 years or older." Arch Intern Med. 2010;170:1148-9.
Schiff Gordon D.; Hasan Omar; Kim Seijeoung; et al. **Diagnostic Error** in Medicine: Analysis of 583 Physician-Reported Errors. Arch Intern Med. 2009;169(20):1881-1887.
Schiff Gordon D.; Galanter William L.; Duhig Jay; et al. **Principles of Conservative Prescribing**. Arch Intern Med. 2011;0(2011):archinternmed.2011.256.
Schwartz LM, Woloshin S. Communicating **uncertainties about prescription drugs to the public**: a national randomized trial. Arch Intern Med. 2011;171 (16):1463-1468.
Sharek PJ, McClead RE Jr, Taketomo C, Luria JW, Takata GS, Walti B, Tanski M, Nelson C, Logsdon TR, Thurm C, Federico F. An intervention to decrease **narcotic**-related adverse drug events in children's hospitals. Pediatrics. 2008 Oct;122(4):e861-6.
Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis. 2008 Sep 15;47(6):735-43. On the basis of 6614 cases, an estimated 142,505 visits (95% confidence interval [CI], 116,506-168,504 visits) annually were made to US EDs for drug-related adverse events attributable to systemic antibiotics. Antibiotics were implicated in 19.3% of all ED visits for drug-related adverse events. Most ED visits for antibiotic-associated adverse events were for allergic reactions (78.7% of visits; 95% CI, 75.3%-82.1% of visits). One-half of the estimated ED visits were attributable to penicillins (36.9% of visits; 95% CI, 34.7%-39.2% of visits) and cephalosporins (12.2%; 95% CI, 10.9%-13.5%). Among commonly prescribed antibiotics, sulfonamides and clindamycin were associated with the highest rate of ED visits (18.9 ED visits per 10,000 outpatient prescription visits [95% CI, 13.1-24.7 ED visits per 10,000 outpatient prescription visits] and 18.5 ED visits per 10,000 outpatient prescription visits [95% CI, 12.1-25.0 ED visits per 10,000 outpatient prescription visits], respectively). Compared with all other antibiotic classes, sulfonamides were associated with a significantly higher rate of moderate-to-severe allergic reactions (4.3% [95% CI, 2.9%-5.8%] vs. 1.9 % [95% CI, 1.5%-2.3%]), and sulfonamides and fluoroquinolones were associated with a significantly higher rate of neurologic or psychiatric disturbances (1.4% [95% CI, 1.0%-1.7%] vs. 0.5% [95% CI, 0.4%-0.6%]). CONCLUSIONS: Antibiotic-associated adverse events lead to many ED visits, and allergic reactions are the most common events. Minimizing unnecessary antibiotic use by even a small percentage could significantly reduce the immediate and direct risks of drug-related adverse events in individual patients.
Shekelle Paul G., Pronovost Peter J., Wachter Robert M., et al. Advancing the **Science of Patient Safety**. Ann Intern Med May 17, 2011 154:693-696.
Shepherd G, Mohorn P, Yacoub K, Williams May D. **Adverse Drug Reaction Deaths** Reported in United States Vital Statistics, 1999-2006 (February). Ann Pharmacother. 2012 Jan 17.
Sikdar KC, Alaghehbandan R, MacDonald D, Barrett B, Collins KD, Donnan J, Gadag V. Adverse drug events in adult patients leading to **emergency department visits**. Ann Pharmacother. 2010 Apr;44(4):641-9.
Singh H, Graber M. **Reducing diagnostic error** through medical home-based primary care reform. JAMA. 2010;304(4):463-464.
Smyth RMD et al. Adverse drug reactions in children—a systematic review. PLoS ONE 2012; 7: e24061.
Soar J, Peyton J, Leonard M, Pullyblank AM. **Surgical safety checklists**. BMJ. 2009 Jan 21;338:b220. doi: 10.1136/bmj.b220.
Stefanacci RG, Cavallaro E, Beers MH, Fick DM. Developing explicit positive **beers criteria** for preferred central nervous system medications in older adults. Consult Pharm. 2009 Aug;24(8):601-10.
Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in **ambulatory care**: a systematic review. Ann Pharmacother 2011;45(7-8): 977-989.
Takata GS, Mason W, Taketomo C, et al. Development, testing, and findings of a **pediatric-focused trigger tool** to identify medication-related harm in US children's hospitals. Pediatrics. 2008 Apr;121(4):e927-35.
Valentin A, Capuzzo M, Guidet B, et al. Research Group on Quality Improvement of the European Society of Intensive Care Medicine (ESICM); Sentinel Events Evaluation (SEE) Study Investigators. Errors in administration of **parenteral drugs in intensive care units**: multinational prospective study. BMJ. 2009 Mar 12;338:b814. doi: 10.1136/bmj.b814.
van Walraven, Carl, Bennett, Carol, Jennings, Alison, Austin, Peter C., Forster, Alan J. Proportion of **hospital readmissions deemed avoidable**: a systematic review CMAJ 2011 183: E391-402
Vincent C, Aylin P, Franklin BD, Holmes A, Iskander S, Jacklin A, Moorthy K. Is health care getting safer? BMJ. 2008 Nov 13;337:a2426. doi: 10.1136/bmj.a2426.
Volpp KG, Grande D. Residents' suggestions for **reducing errors** in teaching hospitals. *N Engl J Med* 2003;348:851-5.
Weingart Saul N.; Simchowitz Brett; Padolsky Harper; et al. An Empirical Model to Estimate the Potential Impact of **Medication Safety Alerts** on Patient Safety, Health Care Utilization, and Cost in Ambulatory Care. Arch Intern Med. 2009;169(16):1465-1473.
West Colin P.; Tan Angelina D.; Habermann Thomas M.; et al. Association of **Resident Fatigue** and Distress With Perceived Medical Errors. JAMA. 2009;302(12):1294-1300.
Westbrook Johanna I.; Woods Amanda; Rob Marilyn I.; et al. Association of **Interruptions** With an Increased Risk and Severity of Medication Administration Errors. Arch Intern Med. 2010;170(8):683-690.
Weiss-Smith S, Deshpande G, Chung S, et al. The **FDA drug safety surveillance program**: adverse event reporting trends. Arch Intern Med 2011;171:591-3. In the FDA database, when an outcome was reported, patients were hospitalized in 42% and the patient died in 15% of cases. Overall, women were represented in 55% of reports. One-third of reports were among adults aged 30–64 years of age. The drugs most frequently cited were biologic agents etanercept, adalimumab and infliximab (the first, third and fourth most frequently reported suspect drugs). Others in the top 10 suspect list were rofecoxib, quetiapine, exenatide (Byetta, to be marketed in Canada in June), teriparatide, interferon beta-1a (Avonex), norelgestromin–ethinyl estradiol transdermal system (Ortho Evra) and levonorgestrel-releasing intrauterine system (Mirena).
WHO Collaborating Centre for Patient Safety Releases **Nine Life-Saving Patient Safety Solutions** http://www.jointcommissioninternational.org/24839/
Wilson RM, Michel P, Olsen S, et al; for the WHO Patient Safety EMRO/AFRO Working group. **Patient safety in developing countries**: retrospective estimation of scale and nature of harm to patients in hospital. BMJ. 2012 Mar 13;344:e832.
Wolf MS, Curtis LM, Waite K, et al. Helping patients simplify and **safely use complex prescription regimens**. Arch Intern Med. 2011 Feb 28;171(4):300-5.
Wysowski DK, Swartz L. **Adverse drug event surveillance and drug withdrawals** in the United States, 1969-2002: the importance of reporting suspected reactions. Arch Intern Med. 2005;165(12):1363-1369.
Yin H. Shonna; Wolf Michael S.; Dreyer Benard P.; et al. Evaluation of Consistency in **Dosing Directions and Measuring Devices** for Pediatric Nonprescription Liquid Medications. JAMA. 2010;0(2010):jama.2010.1797.
Zandieh SO, Goldmann DA, Keohane CA, Yoon C, Bates DW, Kaushal R. Risk factors in preventable adverse drug events in pediatric outpatients. J Pediatr. 2008 Feb;152(2):225-31. Epub 2007 Nov 19.
Zed PJ, Abu-Laban RB, Balen RM, Loewen PS, et al. Incidence, severity and preventability of medication-related visits to the emergency department: a prospective study. CMAJ. 2008 Jun 3;178(12):1563-9. More than **1 in 9 emergency department visits** are due to drug-related adverse events, a potentially preventable problem in our health care system.
Zhang M, Holman CD, Price SD, et al. **Comorbidity** and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. BMJ. 2009 Jan 7;338:a2752. doi: 10.1136/bmj.a2752. Comorbidity, but not advancing age, predicts repeat admission for ADRs in older adults, especially those with comorbidities often managed in the community. Awareness of these predictors can help clinicians to identify which older adults are at greater risk of admission for ADRs and, therefore, who might benefit from closer monitoring.

TOP

Academic Detailing:

- **BC CDUP: http://www.cdup.org/**
- **Dalhousie: http://cme.medicine.dal.ca/ADS.htm**
- **Pennsylvania (RxFacts.org): http://www.rxfacts.org/detailing.php**

Select Bibliography

- **Academic Detailing - Canada**

  Margaret Jin (*2012*) A brief overview of academic detailing in Canada: Another role for pharmacists. Canadian Pharmacists Journal: May 2012, Vol. 145, No. 3, pp. 142-146.e2. http://www.cpjournal.ca/doi/abs/10.3821/145.3.cpj142

References: RxFiles Academic Detailing & Those One of a Kind Drug Charts

[i] Groves KE, Sketris I, Tett SE. Prescription drug samples--does this marketing strategy counteract policies for quality use of medicines? J Clin Pharm Ther. 2003 Aug;28(4):259-71.
[ii] Gourlay DL, Heit HA. Universal precautions revisited: managing the inherited pain patient. Pain Med. 2009 Jul;10 Suppl 2:S115-23.

TOP

Extras Continued:

Quotes

- "it takes more than 2½ minutes to assess a patient for a possible opioid prescription" ; a challenge, especially for busy walk-in and minor emergency types of practice
- "it takes only 30 minutes to argue, but only 30 seconds to write a Rx"; reflecting the realities and frustrations of everyday practice.
- "Its OK to say 'No'"
- "I didn't realize how big a problem Rx opioids were on the street"

UK Study Ranking - most harmful drugs: overall, to individual and to society.

- Nutt DJ, King LA, Phillips LD; on behalf of the Independent Scientific Committee on Drugs. Lancet. 2010 Oct 29. Drug harms in the UK: a multicriteria decision analysis.
- BACKGROUND: Proper assessment of the harms caused by the misuse of drugs can inform policy makers in health, policing, and social care. We aimed to apply multicriteria decision analysis (MCDA) modelling to a range of drug harms in the UK. METHODS: Members of the Independent Scientific Committee on Drugs, including two invited specialists, met in a 1-day interactive workshop to score 20 drugs on 16 criteria: nine related to the harms that a drug produces in the individual and seven to the harms to others. Drugs were scored out of 100 points, and the criteria were weighted to indicate their relative importance. FINDINGS: MCDA modelling showed that heroin, crack cocaine, and metamfetamine were the most harmful drugs to individuals (part scores 34, 37, and 32, respectively), whereas alcohol, heroin, and crack cocaine were the most harmful to others (46, 21, and 17, respectively). Overall, alcohol was the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places. INTERPRETATION: These findings lend support to previous work assessing drug harms, and show how the improved scoring and weighting approach of MCDA increases the differentiation between the most and least harmful drugs. However, the findings correlate poorly with present UK drug classification, which is not based simply on considerations of harm. FUNDING: Centre for Crime and Justice Studies (UK).

Salvia leaves (magic mint, diviner's sage, sally D, purple sticky)

- Member of mint family, smoked or chewed. Contains salvinorin A, a selective kappa opioid receptor antagonist; does not bind to $5HT_{2A}$ receptors like other hallucinogens. Halucinogen effects rapid & last <30min. SE: dysphoria, diuresis, chills, headache, insomnia, exhaustion, loss of control, impaired coordination & judgement (= DANGEROUS!). Sensationalized in SK by Saskatoon media DJ who smoked herb on live broadcast in Dec 2010.

Angel's Trumpet: (Angel's tears, Apple of Peru, Green Dragon, Devil's trumpet)

- Alkaloid (atropine, scopolamine) containing flowers & stem. Each flower contains 0.2mg atropine & 0.65mg scopolamine; 3-6 flowers causes hallucinations; 9+ flowers can be life-threatening. Commonly ingested by making a tea. Effects in 1-4hrs; duration 24+hrs. SE: mydriasis, dry mouth, tachycardia, fever, erythema, constipation, ↑↑ thirst, retrograde amnesia & anxiety; arrhythmias & CV collapse / respiratory failure in high doses. (= DANGEROUS!)

"Bath Salts" PABS for abuse: are actually designer stimulants (e.g. methylenedioxypyrovalerone-MDPV, NRG-1; mephedrone-M-Cat, Meow, 4-MMC, Bubbles; methylone-methylenedioxymethcathinone, bk-MDMA,M1, Explosion) being sold in shops & online. *Cloud 9, Ivory Wave, Vanilla Sky, Purple Wave, Blizzard, Blue Silk*, etc.
Common in UK, now USA via New Orleans, India, China.
Similar effects (↑HR, paranoia, psychosis) & tx as stimulants. May/11 CDC: MMWR- Emergency Department Visits After Use of a Drug Sold as "Bath Salts" --- Michigan, November 13, 2010--March 31, 2011 http://www.cdc.gov/mmwr/pdf/wk/mm60e0518.pdf
Two common ingredients: MDPV (a dopamine & norepinephrine (NE) reuptake inhibitor ➔ stimulant); mephedporone: MAOI effects that ↑ 5HT, NE, & DA at neuronal synapses (AEs: agitation, aggression, anxiety, bruxism, chest pain, confusion, diaphoresis, headache, hyperreflexia, ↑BP, N&V, palpitations, periopheral vasoconstriction, pareshtesia, psychosis, seizure, ↑HR.)
Sep/11: DEA invoked its emergency authority necessary to protect the public & will make Schedule 1 substances in 30 days from now.
Ross EA, Watson M, Goldberger B. Bath Salts Intoxication. NEJM. 2011 Sep 8;365(10):967-8.
Aboujaoude E. Psychology Today, Apr 2012: Accessed 09 May, 2012 http://www.psychologytoday.com/blog/compulsive-acts/201204/bath-salts.

Synthetic Cannabinoids – common in herbal incense products

- Full agonists of CB1 & therefore ↑potential for overdose & toxicity
- ↑ association with seeking medical attention. AEs: agitation, altered time perception, anxiety, dysphoria, ↑BP, listlessness, hallucinations/psychosis, nausea, paranoia, seizures, tachycardia.

Videos – informational related to teen drug recreational drug use (for teens, by teens) - Canada

- **Unwasted - 4 videos by teens regarding gambling, alcohol, marijuana, opioids/oxycontin: http://unwasted.ca/; or http://unwasted.ca/the-pressures (★★★★★)**
- **Mixing prescription drugs and alcohol. http://itdoesntmix.ca/**
- **Your when moment (videos from Nova Scotians): http://changingtheculture.ns.ca/**

Videos – other

- **Addressing the risk of diversion of Rx drugs; secure storage of medications. Powerful.** http://www.youtube.com/watch?v=-sunbJDZe1whttp://www.youtube.com/watch?v=-sunbJDZe1w

Guidelines of interest:

Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline CAMH: http://www.cpso.on.ca/uploadedFiles/policies/guidelines/office/buprenorphine_naloxone_gdlns2011.pdf

Additional refs:

Achar S, Rostamian A, Narayan SM. Cardiac and metabolic effects of anabolic-androgenic steroid abuse on lipids, blood pressure, left ventricular dimensions, and rhythm. Am J Cardiol. 2010 Sep 15;106(6):893-901.
Alcohol Use and Pregnancy Consensus Clinical Guidelines. SOGC 2010. http://www.sogc.org/guidelines/documents/gui245cpg1008e.pdf
Alford Daniel P.; LaBelle Colleen T.; Kretsch Natalie; et al. Collaborative Care of Opioid-Addicted Patients in Primary Care Using Buprenorphine: Five-Year Experience. Arch Intern Med. 2011;171(5):425-431.
Ali WM, Al Habib KF, Al-Motarreh A, et al. Acute coronary syndrome use and khat herbal amphetamine use (Catha edulis). An observational report.Circulation 2011
Altice FL, Kamarulzaman A, Soriano VV, et al. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet. 2010 Jul 31;376(9738):367-87.
Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev. 2010 Mar 17;3:CD005063. Benzodiazepines showed a protective benefit against alcohol withdrawal symptoms, in particular seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with other drugs. Nevertheless, no definite conclusions about the effectiveness and safety of benzodiazepines was possible, because of the heterogeneity of the trials both in interventions and the assessment of outcomes.
Amato L, Minozzi S, Pani PP, et al. Dopamine agonists for the treatment of cocaine dependence. Cochrane Database Syst Rev. 2011 Dec 7;12:CD003352. Current evidence from randomised controlled trials does not support the use of dopamine agonists for treating cocaine dependence.
American Psychiatric Association Brochures: http://www.healthyminds.org/Functional-Library/brochures.aspx
Anton RF, Myrick H, Wright TM, et al. Gabapentin Combined With Naltrexone for the Treatment of Alcohol Dependence. Am J Psychiatry. 2011 Mar 31.
Aquaro GD, Gabutti A, Meini M, Prontera C, Pasanisi E, Passino C, Emdin M, Lombardi M. Silent myocardial damage in cocaine addicts. Heart. 2011 Jun 20.
Barrowclough Christine, Haddock Gillian, Wykes Til, et al. Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. BMJ 341:doi:10.1136/bmj.c6325 (Published 24 Nov 2010).
Berkey, Catherine S., Willett, Walter C., Frazier, A. Lindsay, et al. Prospective Study of Adolescent Alcohol Consumption and Risk of Benign Breast Disease in Young Women. Pediatrics 2010 125: e1081-e1087.
Bohnert Amy S. B., Valenstein Marcia, Bair Matthew J., et al. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. JAMA. 2011;305(13):1315-1321.doi:10.1001/jama.2011.370.
Boshuisen K, Arends JE, Rutgers DR, Frijns CJ. A young man with hemiplegia after inhaling the bath salt "Ivory Wave". Neurology. 2012 May 8;78(19):1533-4.
Bradley KA, Rubinsky AD, Sun H, et al. Alcohol screening and risk of postoperative complications in male VA patients undergoing major non-cardiac surgery. J Gen Intern Med. 2011 Feb;26(2):162-9.
Brahm NC, Yeager LL, Fox MD, Farmer KC, Palmer TA. Commonly prescribed medications and potential false-positive urine drug screens. Am J Health Syst Pharm. 2010 Aug 15;67(16):1344-50.
Brands Bruna, Paglia-Boak Angela, Sproule Beth A., et al. Nonmedical use of opioid analgesics among Ontario students. Can Fam Physician 2010 56: 256 -262.
Brière FN, Fallu JS, Janosz M, Pagani LS. Prospective associations between meth/amphetamine (speed) and MDMA (ecstasy) use and depressive symptoms in secondary school students. J Epidemiol Community Health. 2012 Apr 19.
Brody GH, Chen YF, Kogan SM et al. Family-centered Program Deters Substance Use, Conduct Problems, and Depressive Symptoms in Black Adolescents. Pediatrics. 2012 Jan;129(1):108-15.
Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:x.ex-x.ex. PII: S0002-9378(10)02524-X doi:10.1016/j.ajog.2010.12.039.
Callaghan RC, Cunningham JK, Sajeev G, Kish SJ. Incidence of Parkinson's disease among hospital patients with methamphetamine-use disorders. Mov Disord. 2010 Aug 24.
CDC: Centers for Disease Control and Prevention. Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. MMWR Morb Mortal Wkly Rep. 2010 Jun 18;59(23):705-9. This report describes the results of that review, which showed that the esti
for nonmedical use of opioid analgesics increased 111% during 2004-2008 (from 144,600 to 305,900 visits) and increased 29% during 2007-2008. The highest numbers of ED visits were recorded for oxycodone, hydrocodone, and methadone, all of which showed statistically significant increases during the 5-year peri

TOP

ED visits involving nonmedical use of benzodiazepines increased 89% during 2004-2008 (from 143,500 to 271,700 visits) and 24% during 2007-2008.
CDC July/11 Drug Overdose Deaths --- Florida, 2003—2009 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6026a1.htm?s_cid=mm6026a1_x
CDC Feb/12 Severe Methemoglobinemia and Hemolytic Anemia from Aniline Purchased as 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), a Recreational Drug, on the Internet — Oregon, 2011. Weekly. February 10, 2012 / 61(05);85-88.
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6105a1.htm?s_cid=mm6105a1_x
CDC: Centers for Disease Control and Prevention. Severe methemoglobinemia and hemolytic anemia from aniline purchased as 2C-E(4-ethyl-2,5-dimethoxyphenethylamine), a recreational drug, on the Internet - Oregon, 2011. MMWR Morb Mortal Wkly Rep. 2012 Feb 10;61(5):85-8.
Chapman E, Leipsic J, Satkunam N, Churg A. Pulmonary alveolar proteinosis as a reaction to fentanyl patch smoke. Chest. 2012 May;141(5):1321-3.
Chen WY, Rosner B, Hankinson SE, et al. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA. 2011;306(17): 1884-1890.
Chung T, Smith GT, Donovan JE, et al. Drinking Frequency as a Brief Screen for Adolescent Alcohol Problems. Pediatrics. 2012 Jan 4.
Cimolai N. Zopiclone: is it a pharmacologic agent for abuse? Can Fam Physician. 2007 Dec;53(12):2124-9.
Cohen J, Morrison S, Greenberg J et al. Clinical Presentation of Intoxication Due to Synthetic Cannabinoids. Pediatrics. 2012 Mar 19.
Colfax GN, Santos GM, Das M, et al. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. Arch Gen Psychiatry. 2011 Nov;68(11):1168-75.
Committee on Substance Abuse. Substance use screening, brief intervention, and referral to treatment for pediatricians. Pediatrics. 2011 Nov;128(5):e1330-40.
Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010 Oct 26;341:c5475. doi: 10.1136/bmj.c5475.
Darrell Hulisz. Is Hookah Harmful? Medscape: accessed at http://www.medscape.com/viewarticle/727687. {Hookah is a waterpipe used for smoking tobacco (often with additional flavours). Hookah smoking, also known as narghile, shisha, and goza. Less studied but similar concerns (CV, cancer, addiction) to tobacco.}
Davis LL, Pilkinton P, Wisniewski SR, et al. Effect of concurrent substance use disorder on the effectiveness of single and combination antidepressant medications for the treatment of major depression: an exploratory analysis of a single-blind randomized trial. Depress Anxiety. 2012 Feb;29(2):111-22.
Department of Veteran Affairs, Department of Defense. VA/DoD clinical practice guideline for management of substance use disorders (SUD). Washington (DC): Department of Veteran Affairs, Department of Defense; 2009 Aug. 158 p. http://www.healthquality.va.gov/sud/sud_full_601f.pdf
Di Iorio CR, Watkins TJ, Dietrich MS, et al. Evidence for Chronically Altered Serotonin Function in the Cerebral Cortex of Female 3,4-Methylenedioxymethamphetamine Polydrug Users. Arch Gen Psychiatry. 2011 Dec 5.
Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist (ketamine) in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010 Aug;67(8):793-802.
Dubow JS, Singer S, Segal AZ. Rhomboencephalitis due to cocaine-induced bony erosion of skull base. Neurology. 2011 Sep 27;77(13):1313
Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine-naloxone: In opioid-related disorders. Can Fam Physician. 2012 Jan;58(1):37-41.
Elton-Marshall, Tara, Leatherdale, Scott T., Burkhalter, Robin. Tobacco, alcohol and illicit drug use among Aboriginal youth living off-reserve: results from the Youth Smoking Survey. CMAJ 2011 183: E480-486
Fagbemi K. Q: What is the best questionnaire to screen for alcohol use disorder in an office practice? Cleve Clin J Med. 2011 Oct;78(10):649-51.
Fahmy V, Hatch SL, Hotopf M, Stewart R. Prevalences of illicit drug use in people aged 50 years and over from two surveys. Age Ageing. 2012 Apr 5.
Fass JA, Fass AD, Garcia AS. Synthetic cathinones (bath salts): legal status and patterns of abuse. Ann Pharmacother. 2012 Mar;46(3):436-41.
Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. Cochrane Database Syst Rev. 2010 Aug 4;8:CD003410. The available evidence suggests a small added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment-refractory opioid users, considering a decrease in the use of street heroin and other illicit substances, and in the probability of being imprisoned; and an increase in retention in treatment. Due to the higher rate of serious adverse events, heroin prescription should remain a treatment of last resort for people who are currently or have in the past failed maintenance treatment.
Ferrell M, Wodak A, Gowing L. Maintenance drugs to treat opioid dependence. BMJ 2012;344:e2823. Accessed online 15 May 2012 at: http://www.bmj.com/content/344/bmj.e2823?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+bmj%2Feducation+(Latest+BMJ+Education)
Flegel K, Macdonald N, Hébert PC. Binge drinking: all too prevalent and hazardous. CMAJ. 2011 Jan 17. Accessed online at: http://www.cmaj.ca/cgi/content/full/183/4/411?etoc
Foxcroft DR, Tsertsvadze A. Universal school-based prevention programs for alcohol misuse in young people. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD009113. DOI: 10.1002/14651858.CD009113.
Freedman Neal D, Murray Liam J, Kamangar Farin, et al. Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON Consortium. Gut gut.2010.233866Published Online First: 14 March 2011 doi:10.1136/gut.2010.233866
French DD, Margo CE, Harman LE. Substance Use Disorder (cocaine) and the Risk of Open-angle Glaucoma. J Glaucoma. 2011 Sep;20(7):452-7.
Furlan AD, Reardon R, Weppler C; National Opioid Use Guideline Group. Opioids for chronic noncancer pain: a new Canadian practice guideline. (NOUGG) CMAJ. 2010 Jun 15;182(9):923-30. Links: http://nationalpaincentre.mcmaster.ca/opioid/documents.html
Part A Executive summary & background: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_a_v4_5.pdf
Part B Recommendations for practice: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf
Gapstur Susan M.; Jacobs Eric J.; Deka Anusila; et al. Association of Alcohol Intake With Pancreatic Cancer Mortality in Never Smokers. Arch Intern Med. 2011;171(5):444-451.
Gardy JL, Johnston JC, Sui SJ, et al. Whole-genome sequencing and social-network analysis (crack cocaine) of a tuberculosis outbreak. N Engl J Med. 2011 Feb 24;364(8):730-9.
Goldman RD. Drug-induced gynecomastia in children and adolescents. Can Fam Physician. 2010 Apr;56(4):344-5. Adolescents who use anabolic steroids, or who abuse alcohol, marijuana, heroin, or amphetamines, should be alerted to the fact that gynecomastia might develop.
Graf J, Lynch K, Yeh CL et al. Purpura, cutaneous necrosis, and antineutrophil cytoplasmic antibodies associated with levamisole-adulterated cocaine. Arthritis Rheum. 2011 Dec;63(12):3998-4001.
Gregston M. Alcohol abuse and teens. Parenting Today's Teens. Accessed online 04 Aug at: http://www.heartlightministries.org/blogs/markgregston/2011/06/03/alcohol-abuse-teens/
Han C, Sreenivasan G, Dutz JP. Reversible retiform purpura: a sign of cocaine use. CMAJ. 2011 Jun 14;183(9):E597-600. (contamination with levamisole)
Handford C. Buprenorphine/naloxone for opioid dependence: clinical practice guideline. Toronto: Centre for Addiction and Mental Health; 2011. http://knowledgex.camh.net/primary_care/guidelines_materials/Documents/buprenorphine_naloxone_gdlns2011.pdf (accessed November 14, 2011).
Harris SK, Csémy L, Sherritt L, et al. Computer-Facilitated Substance Use Screening and Brief Advice for Teens in Primary Care: An International Trial. Pediatrics. 2012 May 7.
Health Canada Mar/11 Salvia divinorum (S. divinorum) is a species of sage belonging to the mint family. Some street names for S. divinorum include: Sally D, Lady Sally, Maria pastora, ska Maria pastora, ska pastora, diviner's sage, magic mint, puff, incense special, and salvia. Canadians are cautioned against the use of products containing S. divinorum and/or salvinorin A because these products are known to cause hallucinations and little is known about the long-term effects of these substances on the brain and body.
Hellinger WC, Bacalis LP, Kay RS, et al. Health care-associated hepatitis C virus infections attributed to narcotic diversion. Ann Intern Med. 2012 Apr 3;156(7):477-82.
Hudak ML, Tan RC et al. Neonatal Drug Withdrawal. Pediatrics. 2012 Jan 30.
Jerry J, Collins G, Streem D. Synthetic legal intoxicating drugs: The emerging 'incense' and 'bath salt' phenomenon. Cleve Clin J Med. 2012 Apr;79(4):258-64.
Johnson BA. Medication treatment of different types of alcoholism. Am J Psychiatry. 2010 Jun;167(6):630-9.
Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010 Dec 9;363(24):2320-31.
Kahan, Meldon, Srivastava, Anita, Ordean, Alice, Cirone, Sharon. Buprenorphine: New treatment of opioid addiction in primary care. Can Fam Physician 2011 57: 281-289.
Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran. BMJ 2012;344:e2502.
Krokodil (desomorphine): roughly same effect as heroin but is at least three times cheaper & extremely easy to make. The active component is codeine, & addicts mix it with ingredients including gasoline, paint thinner, hydrochloric acid, iodine and red phosphorous, which they scrape from the striking pads on matchboxes.
Krupitsky E, Nunes EV, Ling W, Illeperuma A, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet 2011; published online April 28. DOI:10.1016/S0140-6736(11)60358-9.
Kuepper R, van Os J, Lieb R, Wittchen H, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study BMJ 342:doi:10.1136/bmj.d738 (Published 1 March 2011)Accessed online at: http://www.bmj.com/content/342/bmj.d738.full
Kimber J, Copeland L, Hickman M, et al. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. BMJ. 2010 Jul 1;341:c3172. doi: 10.1136/bmj.c3172.
Lagasse LL, Derauf C, Smith LM et al. Prenatal Methamphetamine Exposure and Childhood Behavior Problems at 3 and 5 Years of Age. Pediatrics. 2012 Mar 19.
Latino-Martel P, Arwidson P, Ancellin R, et al. Alcohol consumption and cancer risk: revisiting guidelines for sensible drinking. CMAJ. 2011 Nov 8;183(16):1861-5.
Ling Walter; Casadonte Paul; Bigelow George; et al. Buprenorphine Implants for Treatment of Opioid Dependence: A Randomized Controlled Trial. JAMA. 2010;304(14):1576-1583.
Lyon JE, Khan RA, Gessert CE, et al. Treating alcohol withdrawal with oral baclofen: a randomized, double-blind, placebo-controlled trial. J Hosp Med. 2011 Oct;6(8):469-74.
March 11, 2010 (Savannah, Georgia) — Barbiturates are still the drugs of first choice among adults 60 years and older who commit suicide by overdose, despite a significant decrease in their use since 1990. In a study presented here at the American Association for Geriatric Psychiatry 2010 Annual Meeting, Robert C. Abrams, MD, Weill Cornell Medical College, New York City, found that 27.2% of adults 60 years and older living in New York City who overdosed fatally between 1990 and 2006 used barbiturates.
Marshall BD, Milloy MJ, Wood E, et al. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. Lancet. 2011 Apr 15.
Marsolek, Melinda R., White, Nicole C., Litovitz, Toby L. Inhalant Abuse: Monitoring Trends by Using Poison Control Data, 1993-2008. Pediatrics 2010 0: peds.2009-2080.
McCann UD, Sgambati FP, Schwartz AR, Ricaurte GA. Sleep apnea in young abstinent recreational MDMA ("ecstasy") consumers. Neurology. 2009 Dec 8;73(23):2011-7.
McLarnon ME, Monaghan TL, Stewart SH, Barrett SP. Drug misuse and diversion in adults prescribed anxiolytics and sedatives. Pharmacotherapy. 2011;31: 262-272.
McCord J, Jneid H, et al. Management of Cocaine-Associated Chest Pain and Myocardial Infarction. A Scientific Statement From the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation online Mar 17,2008.
Melotti, Roberto, Heron, Jon, Hickman, Matthew, et al. Adolescent Alcohol and Tobacco Use and Early Socioeconomic Position: The ALSPAC Birth Cohort. Pediatrics 2011 127: e948-e955
Miller CL, Pearce ME, Moniruzzaman A, et al; for the Cedar Project Partnership. The Cedar Project: risk factors for transition to injection drug use among young, urban Aboriginal people. CMAJ. 2011 Jul 12;183(10):1147-1154.
Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev. 2010 Mar 17;3:CD005064.
MMWR: Emergency Department Visits Involving Nonmedical Use of Selected Prescription Drugs — United States, 2004–2008. MMWR Morbidity and Mortality Weekly Report June2010. http://www.cdc.gov/mmwr/pdf/wk/mm5923.pdf
Montastruc F, Montastruc G, Vigreux P et al. Valvular Heart Disease in a patient taking 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"). Br J Clin Pharmacol. 2012 Feb 24.
Muzyk AJ, Fowler JA, Norwood DK, Chilipko A. Role of {alpha}2-Agonists (clonidine, dexmedetomidine) in the Treatment of Acute Alcohol Withdrawal. Ann Pharmacother. 2011 May;45(5):649-57.
NICE:Methadone and buprenorphine for the management of opioid dependence. NICE technology appraisal guidance 114 (2007). www.nice.org.uk/guidance/TA114
NICE:Naltrexone for the management of opioid dependence. NICE technology appraisal guidance 115 (2007). www.nice.org.uk/guidance/TA115
NICE: Drug misuse: opioid detoxification. NICE clinical guideline 52 (2007). www.nice.org.uk/guidance/CG52
NICE: Guidance for methadone & buprenorphine in addiction managment. Evidence link: http://guidance.nice.org.uk/TA114/Guidance/Evidence_1
NICE: Clinical Guideline 120. Mar 2011. Psychosis with coexisting substance misuse. http://www.nice.org.uk/nicemedia/live/13414/53691/53691.pdf Guick Guide http://www.nice.org.uk/nicemedia/live/13414/53731/53731.pdf
NICE: Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. NICE clinical guideline 115 (2011). www.nice.org.uk/guidance/CG115
Nielsen SF, Hjorthøj CR, Erlangsen A, Nordentoft M. Psychiatric disorders and mortality among people in homeless shelters in Denmark: a nationwide register-based cohort study. Lancet 2011; published online June 14. DOI:10.1016/S0140-6736(11)60747-2.

TOP

Nosyk B, Guh DP, Bansback NJ, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. (NAOMI) CMAJ. 2012 Mar 12.
Nutt DJ, King LA, Phillips LD; on behalf of the Independent Scientific Committee on Drugs. Drug harms in the UK: a multicriteria decision analysis. Lancet. 2010 Oct 29. Overall, alcohol was the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places.
Okie, Susan. A Flood of Opioids, a Rising Tide of Deaths. N Engl J Med 2010; 363:1981-1985
O'Mara K, Gal P, Davanzo C. Treatment of neonatal withdrawal with clonidine after long-term, high-dose maternal use of tramadol. Ann Pharmacother. 2010 Jul-Aug;44(7-8):1342-4.
Oral R et al. Illicit drug exposure in patients evaluated for alleged child abuse and neglect. Pediatr Emerg Care 2011 Jun; 27:490.
Ordean Alice, Kahan Meldon. Comprehensive treatment program for pregnant substance users in a family medicine clinic. Can Fam Physician November 2011 57: e430-e435.
O'Shea RS, Dasarathy S, McCullough AJ; Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. Hepatology. 2010 Jan;51(1):307-28.
Patel RA, Gallagher JC. Drug Fever. Pharmacotherapy. 2010 Jan;30(1):57-69.
Patra J, Bakker R, Irving H, et al. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. BJOG. 2011 Nov;118(12):1411-1421.
Patrick SW, Schumacher RE, Benneyworth BD, et al. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009 [published online April 30, 2012]. JAMA.
Pettinati HM et al. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. Am J Psychiatry 2010 Mar 15
Pharmacist's Letter. Clonidine abuse. Mar,2010.
Pharmacist's Letter. OTC and Rx Drugs of Abuse. Nov,2010.
Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012 Jan 11;307(2):173-81.
Purshouse RC, Meier PS, Brennan A, Taylor KB, Rafia R. Estimated effect of alcohol pricing policies on health and health economic outcomes in England: an epidemiological model. Lancet. 2010 Apr 17;375(9723):1355-64.
Rangel Carlos; Shu Richard G.; Lazar Lawrence D. et al; {beta}-Blockers for Chest Pain Associated With Recent Cocaine Use Arch Intern Med. 2010;170(10):874-879.
Reddy RG, Aung T, Karavitaki N, Wass JA. Opioid induced hypogonadism. BMJ. 2010 Aug 31;341:c4462. doi: 10.1136/bmj.c4462.
Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2. {In pts with EtOH dependence: ↓ return to drinking & ↑ abstinence vs Pl NNY=10; 8wk-12mo; ↑diarrhea;NS vs naltrexone.}
Rosenquist J. Niels, Murabito Joanne, Fowler James H., et al. The Spread of Alcohol Consumption Behavior in a Large Social Network. *Ann Intern Med* April 6, 2010 152:426-433; doi:10.1059/0003-4819-152-7-201004060-00007.
Ross EA, Watson M, Goldberger B. Bath Salts Intoxication. NEJM. 2011 Sep 8;365(10):967-8.
Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. Drugs. 2010 Sep 10;70(13):1657-75. doi: 10.2165/11537940-000000000-00000.
Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ* 2011; DOI:10.1136/bmj.d671.
Schneider JP, Matthews M, Jamison RN. Abuse-deterrent and tamper-resistant opioid formulations: what is their role in addressing prescription opioid abuse? CNS Drugs. 2010 Oct 1;24(10):805-10. doi: 10.2165/11584260-000000000-00000.
Schulze-Döbold C, Ben Denoun M, Dupas B, Paques M, Massin P. Retinal toxicity in users of "poppers". Ann Intern Med. 2012 May 1;156(9):670-2.
Schütze Madlen, Boeing Heiner, Pischon Tobias, et al. Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. BMJ 2011;342:doi:10.1136/bmj.d1584 (Published 7 April 2011)
Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. Circulation. 2010 Dec 14;122(24):2558-69.
Smedslund G, Berg RC, Hammerstrom KT, et al. Motivational interviewing for substance abuse. Cochrane Database Syst Rev. 2011 May 11;5:CD008063.
Smith Peter C.; Schmidt Susan M.; Allensworth-Davies Donald; et al. A Single-Question Screening Test for Drug Use in Primary Care. Arch Intern Med. 2010;170(13):1155-1160. How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?"
SOGC Clinical Practice Guideline: Substance Use in Pregnancy No. 256, April 2011 http://www.sogc.org/guidelines/documents/gui256CPG1104E.pdf
Stein Steinhausen HC, Blattmann B, Pfund F. Developmental outcome in children with intrauterine exposure to substances (heroin or methadone). Eur Addict Res. 2007;13(2):94-100.
Strang J, Metrebian N, Lintzeris N, et al. Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial. Lancet. 2010 May 29;375(9729):1885-95.
Substance Abuse and Mental Health Services Administration SAMHSA, Center for Behavioral Health Quality and Statistics. (Nov 3, 2011). The DAWN Report: Drug-Related Emergency Department Visits Attributed to Intentional Poisoning. Rockville, MD. http://oas.samhsa.gov/2k11/DAWN040/WEB_DAWN_040.htm
Swendsen J, Burstein M, Case B et al. Use and Abuse of Alcohol and Illicit Drugs in US Adolescents: Results of the National Comorbidity Survey-Adolescent Supplement. Arch Gen Psychiatry. 2012 Apr;69(4):390-8.
Taffe MA et al. Long-lasting reduction in hippocampal neurogenesis by alcohol consumption in adolescent nonhuman primates. Proc Natl Acad Sci U S A 2010 Jun 15; 107:11104.
Tiihonen J et al. Naltrexone implant for the treatment of polydrug dependence: A randomized controlled trial. Am J Psychiatry 2012 Feb 17
Vinson, Daniel C., Manning, Brian K., Galliher, James M., et al. Alcohol and Sleep Problems in Primary Care Patients: A Report from the AAFP National Research Network. Ann Fam Med 2010 8: 484-492.
Walton MA, Chermack ST, Shope JT, et al. Effects of a brief intervention for reducing violence and alcohol misuse among adolescents: a randomized controlled trial. JAMA. 2010 Aug 4;304(5):527-35.
Wells Daina L, Ott Carol A. The "New" Marijuana. Articles Ahead of Print published on 1 March 2011, DOI 10.1345/aph.1P580. Ann Pharmacother ;45:414-417. (JWH-018 powder, K2, spice, Mr. Smiley, Red X Dawn, and Blaze)
Westover AN, Nakonezny PA. Aortic dissection in young adults who abuse amphetamines. Am Heart J 2010; 160:315-321.
World Drug Report 2011 (UNODC) is at http://www.unodc.org/unodc/en/data-and-analysis/WDR-2011.html This year's edition starts with an overview of the illicit drug situation worldwide and regionally, followed by more comprehensive discussions and statistical trends for the key transnational drug markets, namely opium/heroin, coca/cocaine, amphetamine-type stimulants and cannabis.

References:

eMedicine from WebMD. Alcohol and Substance Abuse Evaluation: http://emedicine.medscape.com/article/805084-print
Saskatoon Health Region – Addictions Services: http://www.saskatoonhealthregion.ca/your_health/ps_addic_profresources.htm
NY - HIV - Substance Abuse: http://www.guideline.gov/summary/summary.aspx?view_id=1&doc_id=15098

---

[1] Centre for Addiction and Mental Health (CAMH): Defining addiction, dependence and abuse. Accessed online at Jan 19, 2010 at http://www.camh.net/Publications/Resources_for_Professionals/Pregnancy_Lactation/defining_addiction.html . [Also see CSAM definitions at http://www.csam.org/non_member/definitions/]
[2] Jovey RD, Ennis J, Gardner-Nix J, Goldman B, Hays H, Lynch M, Moulin D. Use of opioid analgesics for the treatment of chronic noncancer pain--a consensus statement and guidelines from the Canadian Pain Society, 2002. Pain Res Manag. 2003 Spring;8 Suppl A:3A-28A.
[3] Canadian Alcohol and Drug Use Monitoring Survey (CADUMS). Accessed online Jan 05, 2010 at http://www.hc-sc.gc.ca/hc-ps/drugs-drogues/stat/index-eng.php {definition of harm: respondents having experienced at least one of 8 harms during the past year as a result of their drug use. The eight harms that were examined in the CADUMS include respondents feeling that their drug use had a harmful effect on their friendships of social life; physical health; work, studies, or employment opportunities; financial position; or that they felt their drug use led to legal problems; housing problems; or difficult learning things."}
[4] Brands B, Paglia-Boak, Sproule B, Leslie K, Adlaf E. Nonmedical use of opioid analgesics among Ontario students. Can Fam Physician 2010;56:256-62.
[5] Chen CY, Lin KM. Health consequences of illegal drug use. Curr Opin Psychiatry. 2009 May;22(3):287-92.
[6] Council of Ministers of Education. Sexuality and sexual health. In: Canadian Youth, Sexual Health and HIV/AIDS Study: factors influencing knowledge, attitudes and behaviours. Toronto: The Council; 2003. p55-130.
[7] Wells K. Substance abuse and child maltreatment. Pediatr Clin North Am. 2009 Apr;56(2):345-62.
[8] Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry. 2003 Jun;160(6):1041-52.
[9] The Sassi Institute. Substance Abuse Subtle Screening Inventory(s). Accessed online 25Mar, 2010 at http://sassi.com/ .
[10] AUDIT Links: http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf ; https://provider.ghc.org/open/caringForOurMembers/patientHealthEducation/alchoaudit.pdf
[11] Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med. 2005;6(2):107-12.
[12] Gourlay DL, Heit HA. Universal precautions revisited: managing the inherited pain patient. Pain Med. 2009 Jul;10 Suppl 2:S115-23.
[13] Kahan M, Srivastava A, Wilson L, Gourlay D, Midmer D. Misuse of and dependence on opioids: study of chronic pain patients. Can Fam Physician. 2006;52(9):1081-7. Accessed online Jan 04, 2009 at: http://www.cfp.ca/cgi/reprint/52/9/1081
[14] RxFiles Sample Opioid Treatment Agreement. Accessed Dec 30, 2009 at http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.doc
[15] Sample Exit Strategy: http://www.painknowledge.org/physiciantools/opioid_toolkit/components/Exit_Strategy.pdf ; Other: When: Clinical goals not met, Abuse/addiction identified; How: Taper, Adjuvant medications, Refer to addiction services prn.
[16] Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med. 2003 Nov 13;349(20):1943-53.
[17] Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues.J Pain Symptom Manage. 1996 Apr;11(4):203-17.
[18] National Institute on Drug Abuse (NIDA). Principles of Drug Addiction Treatment: A Research Based Guide. Accessed Dec 29, 2009 at http://www.drugabuse.gov/PDF/PODAT/PODAT.pdf
[19] Standrige J, Adams S, Zotos A. Urine Drug Screening: A valuable office procedure. AFP 2010:81:635-40. [See also Jin M, Regier L. Urine Drug Screening – RxFiles Q&A. March 2011. Accessed online at http://www.rxfiles.ca/rxfiles/uploads/documents/members/Urine-Drug-Screening-UDS-QandA.pdf]
[20] Prescription Opioid Analgesics and Stimulants Marketed in Canada. Accessed March 09, 2010 at: http://www.purdue.ca/pdf/Pill_Brochure_English.pdf
[21] Saskatchewan Link: http://www.health.gov.sk.ca/alcohol-and-drug-services?Anc=bbe26497-3aae-49ff-afdc-fc3f7c2ef48f&Pa=35f808e1-f386-4fec-ba90-b5ce33ffd1f0
[22] Cohen L, Collins F, Young A, McChargue D, Leffingwell T, Cook K. Pharmacology and Treatment of Substance Abuse. Evidence- and Outcome-Based Perspectives. Published 2009 by Routledge, New York.
[23] National Institute on Drug Abuse (NIDA). Commonly Abused Drugs. Accessed online Dec 30, 2009 at: http://www.drugabuse.gov/DrugPages/DrugsofAbuse.html
[24] National Institute on Drug Abuse (NIDA): Drugs of abuse information. Accessed Dec 30, 2009 at: http://www.drugabuse.gov/drugpages/
[25] Leslie K. Youth substance use and abuse: challenges and strategies for identification and intervention. CMAJ. 2008 Jan 15;178(2):145-8.
[26] Medical Letter. Acute Reactions to Drugs of Abuse. 2002;44(1125):21-24.
[27] UpToDate 2009. Accessed Dec 30, 2009 @ www.uptodate.com
[28] Teitelbaum S, DuPont R, Bailey J. Cannabis (marijuana) use disorders in adults: Treatment, prognosis, and long-term medical effects. UpToDate 2009.Accessed Dec 30, 2009 @ www.uptodate.com

TOP

[29] RxFiles Cannabinoids – An Overview in RxFiles Drug Comparison Charts book. Accessed online Dec 30, 2009 at http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-QandA-cannabinoids.pdf
[30] Christie B. Heroin contaminated with anthrax has killed 11 people. BMJ. 2010 Feb 15;340:c937. doi: 10.1136/bmj.c937. Accessed online Feb 22, 2010 at: http://www.bmj.com/cgi/content/extract/340/feb15_1/c937
[31] Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. CMAJ. 2009 Dec 8;181:891-6.
[32] Butt P, McLeaod M, Becker-Irvine C. Opioid Withdrawal Protocol accessed online 17 Mar, 2010 at: http://www.quadrant.net/cpss/pdf/Opioid_Withdrawal_Protocol.pdf
Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010 Dec 9;363(24):2320-31.
[33] Centre for Addiction and Mental Health (CAMH): Alcohol; accessed Dec 30, 2009 at: http://www.camh.net/About_Addiction_Mental_Health/Drug_and_Addiction_Information/alcohol_dyk.html
[34] CDC: Alcohol FAQ accessed Dec 30, 2009 at: http://www.cdc.gov/alcohol/faqs.htm
[35] Wilson J. In the clinic: Alcohol use. Ann Intern Med. 2009;150:ITC3-1-15; quiz ITC3-16. Access online 03Mar, 2009 at http://www.annals.org/content/150/5/ITC3-1.full.pdf+html?itcabout
Ruidavets Jean-Bernard, Ducimetière Pierre, Evans Alun, et al. Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). BMJ 341:doi:10.1136/bmj.c6077 (Published 23 Nov 2010)
Rösner S, Hackl-Herrwerth A, Leucht S, et al. Opioid antagonists (naltrexone) for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD001867. DOI: 10.1002/14651858.CD001867.pub3. Naltrexone appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.
McCambridge J, McAlaney J, Rowe R (2011) Adult Consequences of Late Adolescent Alcohol Consumption: A Systematic Review of Cohort Studies. PLoS Med 8(2): e1000413. doi:10.1371/journal.pmed.1000413
Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 2011; DOI:10.1136/bmj.d671.
Brien SE, Ronksley PE, Turner BJ, et al. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ 2011; DOI: 10.1136/bmj.d636.
Sheron N, Hawkey C, Gilmore I. Projections of alcohol deaths-a wake-up call. Lancet. 2011 Feb 18.
[36] Myrick H, Malcolm R, Randall PK, Boyle E, Anton RF, Becker HC, Randall CL. A double-blind trial of gabapentin versus lorazepam in the treatment of alcohol withdrawal. Alcohol Clin Exp Res. 2009 Sep;33(9):1582-8.
[37] Martinotti G, di Nicola M, Frustaci A, Romanelli R, Tedeschi D, Guglielmo R,et al. Pregabalin, tiapride and lorazepam in alcohol withdrawal syndrome: a multi-centre, randomized, single-blind comparison trial. Addiction. 2010 Feb;105(2):288-99.
[38] Shinn A, Greenfield S. Topiramate in the treatment of substance-related disorders: a critical review of the literature. J Clin Psych 2010; doi:104088/jcp.08r04062gry.
[39] Urbina A, Jones K. Crystal methamphetamine, its analogues, and HIV-infection: medical and psychiatric aspects of a new epidemic. Clin Infect Dis. 2004;38:890-894.
[40] Schifano F, Corkery J, Naidoo V, Oyefeso A, Ghodse H. Overview of Amphetamine-Type Stimulant Mortality Data - UK, 1997-2007. Neuropsychobiology. 2010 Jan 29;61(3):122-130.
[41] Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. Lancet. 1999;352:1751-1752.
[42] Kish SJ. Pharmacologic mechanisms of crystal meth. CMAJ. 2008;178(13):1679-82.
[43] Winslow BT, Voorhees KI, Pehl KA. Methamphetamine abuse. Am Fam Physician. 2007 Oct 15;76(8):1169-74.
[44] Centers for Disease Control and Prevention (CDC). Agranulocytosis associated with cocaine use - four States, March 2008-November 2009. MMWR Morb Mortal Wkly Rep. 2009 Dec 18;58(49):1381-5.
Buchanan Jennie A., Heard Kennon, Burbach Cynthia, et al. Prevalence of Levamisole in Urine Toxicology Screens Positive for Cocaine in an Inner-City Hospital. JAMA. 2011;305(16):1657-1658.doi:10.1001/jama.2011.531
Muirhead Trevor T., Eide Melody J.. Toxic Effects of Levamisole in a Cocaine User-Images. N Engl J Med 2011; 364:e52.
[45] Goldstein RA, DesLauriers C, Burda AM. Cocaine: history, social implications, and toxicity--a review. Dis Mon. 2009 Jan;55(1):6-38.
Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. Circulation. 2010 Dec 14;122(24):2558-69.
Gardy JL, Johnston JC, Sui SJ, et al. Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. N Engl J Med. 2011 Feb 24;364(8):730-9.
[46] Health Canada: Safe Use of Energy Drinks. Accessed online at http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/food-aliment/boissons-energ-drinks-eng.php. {Excessive drinking of energy drinks or mixing them with alcohol can have serious health effects. Energy drinks are meant to supply mental and physical stimulation for a short period of time. They usually contain caffeine, taurine (an amino acid, one of the building blocks of protein), vitamins and glucuronolactone, a carbohydrate. Energy drinks should not be confused with sports drinks such as Gatorade® or Powerade®. Sports drinks re-hydrate the body and provide sugars, which the body burns to create energy and replenish electrolytes.}
[47] RxFiles: Weight Loss – Herbal Products Chart from RxFiles Drug Comparison Charts book. Accessed Dec 30, 2009 at: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-WeightLoss-HerbalProducts.pdf
[48] Reccoppa L, Malcolm R, Ware M. Gabapentin abuse in inmates with prior history of cocaine dependence. Am J Addict. 2004 May-Jun;13(3):321-3.
[49] Pharmacist's Letter/Prescriber's Letter. Quetiapine (Seroquel) Abuse. Oct 2007;23(23):Number 231008.
[50] RxFiles: Smoking Cessation Chart from RxFiles Drug Comparison Charts book. Accessed Dec 30, 2009 at: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Smoking-Cessation.pdf
[51] DeBeck K, Kerr T, Li K, Fischer B, Buxton J, Montaner J, Wood E. Smoking of crack cocaine as a risk factor for HIV infection among people who use injection drugs. CMAJ. 2009 Oct 27;181(9):585-9.
[52] Centre for Addiction and Mental Health (CAMH): Exposure to Psychotropic Medications and Other Substances during Pregnancy and Lactation: A Handbook for Health Care Providers; accessed Dec 30, 2009 at: http://www.camh.net/Publications/Resources_for_Professionals/Pregnancy_Lactation/index.html
[53] Jones, K. Kaltenbach, M.G. Coyle, S.H. Heil, K.E. O'Grady, A.M. Arria. Re-building Lives: Helping Women Recover from Opiod Addiction During Pregnancy. Counselor magazine, Monday, 28 September 2009 16:11. Accessed online Jan 04, 2010 at http://www.counselormagazine.com/feature-articles-mainmenu-63/32-women-specific/970-he-jones-k-kaltenbach-mg-coyle-sh-heil-ke-ogrady-am-arria
Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010 Oct 26;341:c5475. doi: 10.1136/bmj.c5475.
Cleary BJ, Donnelly JM, Strawbridge JD, et al. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol. 2010 Dec 7.
[54] Tenenbein M. Do you really need that emergency drug screen? Clin Toxicol Phila). 2009 Apr;47(4):286-91.
[55] Cork A, Ferns T. Managing alcohol related aggression in the emergency department (Part II). Int Emerg Nurs. 2008 Apr;16(2):88-93.
[56] Wolf L. Considerations in triage for the intoxicated patient. J Emerg Nurs. 2008 Jun;34(3):272-3.
[57] Frithsen IL, Simpson WM Jr. Recognition and management of acute medication poisoning. Am Fam Physician. 2010 Feb 1;81(3):316-23.
[58] Haber PS, Demirkol A, Lange K, Murnion B. Management of injecting drug users admitted to hospital. Lancet. 2009 Oct 10;374(9697):1284-93.
[59] Jena AB, Goldman DP, Foster SE, Califano JA Jr. Prescription medication abuse and illegitimate internet-based pharmacies. Ann Intern Med. 2011 Dec 20;155(12):848-50.
[60] Vonghia L, Leggio L, Ferrulli A, Bertini M, Gasbarrini G, Addolorato G; Alcoholism Treatment Study Group. Acute alcohol intoxication. Eur J Intern Med. 2008 Dec;19(8):561-7.
[61] Malone D, Friedman T. Drunken patients in the general hospital: their care and management. Postgrad Med J. 2005 Mar;81(953):161-6.
[62] Beckley I, Ansari NA, Khwaja HA, Mohsen Y. Clinical management of cocaine body packers: the Hillingdon experience. Can J Surg. 2009 Oct;52(5):417-21.
[63] Chen CY, Lin KM. Health consequences of illegal drug use. Curr Opin Psychiatry. 2009 May;22(3):287-92.
[64] Flood M, Buckwalter KC. Recommendations for mental health care of older adults: Part 2--an overview of dementia, delirium, and substance abuse. J Gerontol Nurs. 2009 Feb;35(2):35-47

TOP

Additional articles: (For transplant general area of **interest only** –not utilized as a reference for this chart)

Ahmad S, Shlobin OA, Nathan SD. Pulmonary complications of lung transplantation. Chest. 2011 Feb;139(2):402-11.

Asberg A, Humar A, Jardine AG, et al. VICTOR Study Group. Long-term outcomes of CMV disease treatment with valganciclovir versus IV ganciclovir in solid organ transplant recipients. Am J Transplant. 2009 May;9(5):1205-13.

Asberg A, Jardine AG, Bignamini AA, et al. on behalf of the VICTOR Study Group. Effects of the Intensity of Immunosuppressive Therapy on Outcome of Treatment for CMV Disease in Organ Transplant Recipients. Am J Transplant. 2010 May 10.

Benck U, Hoeger S, Brinkkoetter PT, et al. Effects of donor pretreatment with dopamine on survival after heart transplantation: a cohort study of heart transplant recipients nested in a randomized controlled multicenter trial. J Am Coll Cardiol 2011;58:1768 –77.

Bloom, RD & Reese, PP. Chronic Kidney Disease after Nonrenal Solid-Organ Transplantation. J Am Soc Nephrol 2007:18:3031-3041.

Bonser RS, Taylor R, Collett D, Thomas HL, Dark JH, Neuberger J, on behalf of members of the Cardiothoracic Advisory Group to NHS Blood and Transplant and the Association of Lung Transplant Physicians (UK). Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. Lancet 2012.

Bostom AG, Carpenter MA, Kusek JW, et al. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the folic Acid for vascular outcome reduction in transplantation trial. Circulation. 2011 Apr 26;123(16):1763-70. (no reduction in CV disease)

Braun M, Young J, Reiner CS, et al. Ovarian toxicity from sirolimus. N Engl J Med. 2012 Mar 15;366(11):1062-4.

Bravo, C. Prevalence and management of gastrointestinal complications in lung transplant patients: MIOS study group. Trans Proceed 2007;39:2409-2412.

Brewer J, Colegio OR, Phillips PK, et al. Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol* 2009; 145:1391-1396.

British Transplantation Society. United Kingdom guidelines for living donor kidney transplantation. 2011. www.bts.org.uk/transplantation/standards-and-guidelines/.

Budde K, Becker T, Arns W, et al. on behalf of the ZEUS Study Investigators. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. Lancet. 2011 Feb 18.

Burt RK, Shah SJ, Dill K, Grant T, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet. 2011 Aug 6;378(9790):498-506.

Burton JR, Burton I, Pearson GJ. Clopidogrel-precipitated rhabdomyolysis in a stable heart transplant patient. Ann Pharmacother. 2007 Jan;41(1):133-7. Epub 2007 Jan 2.

Chamberlain K, Baker MR, Kandaswamy P, et al. On behalf of the Guideline Development Group. Donor identification and consent for deceased organ donation: summary of NICE guidance. BMJ. 2011 Sep 1;343:d5249.

Chow EJ, Mueller BA, Baker KS, et al. Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. Ann Intern Med. 2011 Jul 5;155(1):21-32.

Christie JD, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Lung and Heart-Lung Transplantation Report-2009. J Heart Lung Transplant. 2009 Oct;28(10):1031-49.

Ciancio G, Gaynor JJ, Zarak A, et al. Randomized Trial of Mycophenolate Mofetil Versus Enteric-Coated Mycophenolate Sodium in Primary Renal Transplantation With Tacrolimus and Steroid Avoidance: Four-Year Analysis. Transplantation. 2010 Nov 23.

Ciavarella, D et al. Update on gingival overgrowth by cyclosporine A in renal transplants. Med Oral Patol Oral Cir Bucal 2007;12E19-25.

Costanzo Maria Rosa, Costanzo Maria Rosa, Dipchand Anne. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. The Journal of Heart and Lung Transplantation - August 2010 (Vol. 29, Issue 8, Pages 914-956, DOI: 10.1016/j.healun.2010.05.034). http://www.jhltonline.org/article/S1053-2498(10)00358-X/fulltext

Cypel Marcelo, Yeung Jonathan C., Liu Mingyao, et al. Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation. N Engl J Med 2011; 364:1431-1440.

Dardas T, Mokadam N, Pagani F, et al. Transplant registrants with implanted left-ventricular assist devices have insufficient risk to justify elective organ procurement and transplantation network status 1A time. J Am Coll Cardiol 2012 ;60:36-43.

Das S, Cherian SV, Das N, et al. Persistent dyspnea in a 59-year-old woman receiving immunosuppressants (sirolimus induced diffuse alveolar hemorrhage). Chest. 2011 Sep;140(3):818-22.

Delmonico FL, Domínguez-Gil B, Matesanz R, Noel L. A call for government accountability to achieve national self-sufficiency in organ donation and transplantation. Lancet 2011; 378: 1414–18.

Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy. 2010 Aug;30(8):842-54.

Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010 Mar;10(3):547-57.

Eapen M, Klein JP, Sanz GF, et al. Effect of donor–recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis. Lancet Oncol 2011; published online Oct 7. DOI:10.1016/S1470-2045(11)70260-1.

Ebeling PR. Approach to the patient with transplantation-related bone loss. J Clin Endocrinol Metab. 2009 May;94(5):1483-90.

Eid AJ, Arthurs SK, Deziel PJ, et al. Clinical predictors of relapse after treatment of primary gastrointestinal cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2010 Jan;10(1):157-61.

Eid AJ, Razonable RR. New developments in the management of cytomegalovirus infection after solid organ transplantation. Drugs. 2010 May 28;70(8):965-81. doi: 10.2165/10898540-000000000-00000.

Ekberg H, Tedesco-Silva H, Demirbas A, et al. ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007 Dec 20;357(25):2562-75.

Ekberg H, Bernasconi C, Nöldeke J, et al. Cyclosporine, tacrolimus and sirolimus retain their distinct toxicity profiles despite low doses in the Symphony study. Nephrol Dial Transplant. 2010 Jan 26.

Elbarbry FA, Marfleet T, Shoker AS. Drug-drug interactions with immunosuppressive agents: Review of the in vitro functional assays and role of cytochrome P450 enzymes. *Transplantation* 2008;85(9):1222-1229.

Ekser Burcin, Ezzelarab Mohamed, Hara Hidetaka, et al, Clinical xenotransplantation: the next medical revolution?, The Lancet, Available online 20 October 2011.

Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011 Nov 2;306(17):1891-901.

Farge D, Gluckman E. Autologous HSCT in systemic sclerosis: a step forward. Lancet. 2011 Aug 6;378(9790):460-2.

FDA July/11 Bristol-Myers Squibb informed healthcare professionals about the REMS that is required for Nulojix (belatacept) to ensure that the benefits of Nulojix outweigh the risks of PTLD and PML, both of which can be fatal. Patients treated with Nulojix are at an increased risk for developing PTLD, predominantly involving the CNS. PML reported in patients receiving Nulojix at higher than recommended doses.

Feng S, Ekong UD, Lobritto SJ et al. Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of **parental living donor liver transplants**. JAMA. 2012 Jan 18;307(3):283-93.

Ferguson R, Grinyó J, Vincenti F, et al. Immunosuppression with Belatacept-Based, Corticosteroid-Avoiding Regimens in De Novo Kidney Transplant Recipients. Am J Transplant. 2010 Nov 29. doi: 10.1111/j.1600-6143.2010.03338.x.

Fishbein, Thomas M. Intestinal Transplantation. N Engl J Med 2009 361: 998-1008

Fleischhlauer K, Shaw BE, Gooley T, for the International Histocompatibility Working Group in Hematopoietic Cell Transplantation. Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic cell transplantation: a retrospective study. Lancet Oncol 2012

Francis GS, Greenberg BH, Hsu DT, et al. ACCF/AHA/ACP/HFSA/ISHLT 2010 clinical competence statement on management of patients with advanced heart failure and cardiac transplant: a report of the ACCF/AHA/ACP Task Force on Clinical Competence and Training. Circulation. 2010 Aug 10;122(6):644-72.

Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012;185:763–768.

TOP

Gabardi S, Catella J, Martin ST, et al. Maintenance Immunosuppression with Intermittent Intravenous IL-2 Receptor Antibody (basiliximab) Therapy in Renal Transplant Recipients. Ann Pharmacother. 2011 Sep;45(9):e48.
Gallagher MP, Kelly PJ, Jardine M, Perkovic V, Cass A, Craig JC, Eris J, Webster AC. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. J Am Soc Nephrol. 2010 May;21(5):852-8.
Gallegos-Orozco JF, Vargas, HE. Liver Transplantation: From Child to MELD. Med Clin N Am 93 (2009)931-950.
Garcia GG, Harden P, Chapman J; The global role of kidney transplantation. Lancet. 2012 Mar 7.
Garg A, Meirambayeva A, Huang A, Kim S, Prasad GVR, Knoll G, et al. Cardiovascular disease in kidney donors: matched cohort study. BMJ 2012;344:e1113.
George Timothy J., Arnaoutakis George J., Merlo Christian A., et al. Association of Operative Time of Day With Outcomes After Thoracic Organ Transplant. JAMA. 2011;305(21):2193-2199.doi:10.1001/jama.2011.726
Gill John S., Tonelli Marcello. Penny Wise, Pound Foolish? Coverage Limits on Immunosuppression after Kidney Transplantation. N Engl J Med 2012 February 1, 2012 (10.1056/NEJMp1114394)
Golshayan D, Pascual M, Vogt B. Mycophenolic acid formulations in adult renal transplantation - update on efficacy and tolerability. Ther Clin Risk Manag. 2009 Aug;5(4):341-51. Epub 2009 May 4.
Grgic Tatjana, Mis Lydia, Hammond Julia M. Everolimus: A New Mammalian Target of Rapamycin Inhibitor for the Treatment of Advanced Renal Cell Carcinoma. Articles Ahead of Print published on 1 January 2011, DOI 10.1345/aph.1M288. Ann Pharmacother ;45:78-83.
Guerra G, Ciancio G, Gaynor JJ, et al. Randomized trial of immunosuppressive regimens in renal transplantation. J Am Soc Nephrol. 2011 Sep;22(9):1758-68. (Tacrolimus/mycophenolate more favourable).
Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005161.
Haddad H, Isaac D, Legare JF, et al. Canadian Cardiovascular Society Consensus Conference update on cardiac transplantation 2008: Executive Summary. Can J Cardiol. 2009 Apr;25(4):197-205.
Halpern SD, Barnes B, Hasz RD, Abt PL. Estimated supply of organ donors after circulatory determination of death: a population-based cohort study. JAMA. 2010;304(23):2592-2594.
Hanaway Michael J., Woodle E. Steve, Mulgaonkar Shamkant, et al. and John Holman, M.D. for the INTAC Study Group. Alemtuzumab Induction in Renal Transplantation. N Engl J Med 2011; 364:1909-1919.
Heilman RL, Mazur MJ, Reddy KS. Immunosuppression in simultaneous pancreas-kidney transplantation: progress to date. Drugs. 2010 May 7;70(7):793-804.
Heinze G, Kainz A, Hörl WH, Oberbauer R. Mortality in renal transplant recipients given erythropoietins to increase haemoglobin concentration: cohort study. BMJ. 2009 Oct 23;339:b4018. doi: 10.1136/bmj.b4018.
Heisel, O et al. New Onset Diabetes Mellitus in Patients Receiving Calcinuerin Inhibitors: A Systematic Review and Meta-Analysis. Am J Transplant 2004:4:583-595.
Hirschfield G M, Gibbs P, Griffiths W J H. Adult liver transplantation: what non-specialists need to know BMJ 2009;338:b1670, doi: 10.1136/bmj.b1670 (Published 22 May 2009)
Hodson EM, Craig JC, Strippoli GF, Webster AC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD003774.
Holdaas H, Fellström B, Jardine AG, et al. Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet. 2003 Jun 14;361(9374):2024-31.
Horvat Lucy D., Cuerden Meaghan S., Kim S. Joseph, et al. Informing the Debate: Rates of Kidney Transplantation in Nations With Presumed Consent. Ann Intern Med Nov 16, 2010 153:641-649.
Hunt SA, Haddad F. The changing face of heart transplantation. J Am Coll Cardiol. 2008 Aug 19;52(8):587-98.
Ibrahim HN, Foley R, Tan L-P, Rogers T, Bailey R, Guo H, et al. Long-term consequences of kidney donation. N Engl J Med 2009;360:459-69.
Jacquet, A et al. Prevention of calcineurin inhibitor nephrotoxicity in renal transplantation. Transplant Immunology 2008; 20:29-31.
Jansman FG, Reyners AK, van Roon EN, et al; Scientific Institute for Dutch Pharmacists (WINAp), the Dutch Society for Medical Oncology (NVMO); Dutch Society of Clinical Pharmacology and Biopharmacy (NVKF&B). Consensus-Based Evaluation of Clinical Significance and Management of Anticancer Drug Interactions. Clin Ther. 2011 Apr 1.
Jardine AG, Gaton RS, Fellstrom B, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet 2011; 378: 1419–27.
Kainz Alexander, Wilflingseder J, Mitterbauer C, Et al. Steroid Pretreatment of Organ Donors to Prevent Postischemic Renal Allograft Failure: A Randomized, Controlled Trial. *Ann Intern Med* August 17, 2010 153:222-230.
Kajstura J, Rota M, Hall SR, et al. Evidence for human lung stem cells. N Engl J Med 2011;364:1795-806.
Kapoor A. Malignancy in kidney transplant recipients. Drugs. 2008;68 Suppl 1:11-9.
Karabsheh S et al. Clinical and hemodynamic effects of Renin-Angiotensin system blockade in cardiac transplant recipients. Am J Cardiol. 2011 Dec 15;108(12):1836-9.
Kasiske BL, Israni AK, Snyder JJ, Skeans MA, Peng Y, Weinhandl ED. A simple tool to predict outcomes after kidney transplant. Am J Kidney Dis. 2010 Nov;56(5):947-60.
Keough-Ryan TM, Prasad GV, Hewlett T, Shapiro RJ; Canadian Community Nephrology Study Group. Similar outcomes for Canadian renal transplant recipients followed up in transplant centers and satellite clinics. Transplantation. 2010 Sep 27;90(6):591-6.
Kittleson Michelle M., Kobashigawa Jon A.. Management of Advanced Heart Failure: The Role of Heart Transplantation. Circulation 123: 1569-1574, doi:10.1161/CIRCULATIONAHA.110.972810
Kopolovic I, Turner R. Donation and transplantation of allogeneic hematopoietic stem cells. CMAJ. 2011 Jul 4.
Krämer BK, Charpentier B, Bäckman L, et al. for the Tacrolimus Prolonged Release Renal Study Group. Tacrolimus Once Daily (ADVAGRAF) Versus Twice Daily (PROGRAF) in De Novo Renal Transplantation: A Randomized Phase III Study. Am J Transplant. 2010 Sep 14.
Kumar D, Michaels MG, Morris MI, et al. American Society of Transplantation H1N1 Collaborative Study Group. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Lancet Infect Dis. 2010 Aug;10(8):521-6.
Langer D, Burtin C, Schepers L, et al. Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. Am J Transplant. 2012 Jun;12(6):1584-92.
Larsen CP, Grinyó J, Medina-Pestana J, et al. Belatacept-Based Regimens Versus a Cyclosporine A-Based Regimen in Kidney Transplant Recipients: 2-Year Results From the BENEFIT and BENEFIT-EXT Studies. Transplantation. 2010 Nov 11.
LaRosa, Christopher, Glah, Caryle, Baluarte, H. Jorge, et al. Solid-Organ Transplantation in Childhood: Transitioning to Adult Health Care. Pediatrics 2011 127: 742-753
Lebranchu Y, Thierry A, Toupance O, et al. Effi cacy on renal function of early conversion from cyclosporin to sirolimus 3 months after renal transplantation: Concept Study. Am J Transplant 2009; 9: 1115–23.
Leichtman Alan B., McCullough Keith P., Wolfe Robert A., Improving the Allocation System for Deceased-Donor Kidneys. NEJM March 16, 2011.
Lim AK, Manley KJ, Roberts MA, Fraenkel MB. Fish oil for kidney transplant recipients. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005282.
Maalouf NM, Shane E. Osteoporosis after solid organ transplantation. J Clin Endocrinol Metab. 2005 Apr;90(4):2456-65. Epub 2004 Dec 28. Review. Erratum in: J Clin Endocrinol Metab. 2005 Jul;90(7):4118.
Manitpisitkul W, Drachenberg C, Ramos E, et al. Maintenance immunosuppressive agents as risk factors for BK virus nephropathy: a case-control study. Transplantation. 2009 Jul 15;88(1):83-8.
Mañalich R, Paez G, Valero R, Manyalich M. IRODaT: the International Online Registry for Organ Donation and Transplantation 2007. Transplant Proc 2009; 41: 2030–34.
Martin ST, Torabi MJ, Gabardi S. Influenza in Solid Organ Transplant Recipients (February). Ann Pharmacother. 2012 Jan 10.
Mateen FJ, Muralidharan R, Carone M, et al. Progressive Multifocal Leukoencephalopathy (PML) in Transplant Recipients. Ann Neurol. 2011 March 7; Accepted manuscript online: 1-87.
Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790-800.
Moore Jason; McKnight Amy Jayne; Simmonds Matthew J.; et al. Association of Caveolin-1 Gene Polymorphism With Kidney Transplant Fibrosis and Allograft Failure. JAMA. 2010;303(13):1282-1287.
Momper JD, Ridenour TA, Schonder KS, et al. The Impact of Conversion From Prograf to Generic Tacrolimus in Liver and Kidney Transplant Recipients With Stable Graft Function. Am J Transplant. 2011 Jun 30.
Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. 2011 Jul 28;365(4):318-26.
Moulik M, Breinholt JP, Dreyer WJ, et al. Viral Endomyocardial Infection Is an Independent Predictor and Potentially Treatable Risk Factor for Graft Loss and Coronary Vasculopathy in Pediatric Cardiac Transplant Recipients. J Am Coll Cardiol. 2010 Aug 10;56(7):582-592.
Muzaale AD, Dagher NN, Montgomery RA, et al. Estimates of early death, acute liver failure, and long-term mortality among live liver donors. Gastroenterology 2012;142:273–280
Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med 2003; 349: 2326–33.
Nankivell Brian J., Alexander Stephen I., Rejection of the Kidney Allograft. N Engl J Med 2010; 363:1451-1462.
Nankivell BJ, Kuypers DRJ. Diagnosis and prevention of chronic kidney allograft loss. Lancet 2011; 378: 1228–37.
National Institute for Health and Clinical Excellence. Organ donation: improving donor identification and consent rates for cadaveric organ donation. (Clinical guideline 135.) 2011. http://guidance.nice.org.uk/CG135
Nelson JS, Jackson AL, Darling JM, Gerber DA. Chest pain and progressive shortness of breath in a 60-year-old woman following liver transplantation. Chest. 2011 Feb;139(2):464-8.

TOP

Ng VL, Alonso EM, Bucuvalas JC, et al; Studies of Pediatric Liver Transplantation (SPLIT) Research Group. Health Status of Children Alive 10 Years after Pediatric Liver Transplantation Performed in the US and Canada: Report of the Studies of Pediatric Liver Transplantation Experience. J Pediatr. 2012 May;160(5):820-826.e3.
Other herpesviruses: HHV-6,HHV-7,HHV-8,HSV-1and -2, VZVAm J Transplant 2004; 4 (Suppl. 10): 66–71 Blackwell MunksgaardBlackwell Munksgaard 2004
Ohler, L & Cupples, S. Core Curriculum for Transplant Nurses. Mosby, Inc. 2008
Palmer SC, McGregor DO, Strippoli GF. Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005015.
Palmer Scott M., Limaye AP., Banks M, et al; Extended Valganciclovir Prophylaxis to Prevent Cytomegalovirus After Lung Transplantation: A Randomized, Controlled Trial. Ann Intern Med June 15, 2010 152:761-769.
Patel Jignesh K, Kobashigawa Jon A. Cardiology Patient Page: Heart Transplantation. Circulation. 2011;124:e132-e134, doi:10.1161/CIRCULATIONAHA.110.017319
Patlolla, V. et al. Efficacy of Anti-IL-2 Receptor Antibodies Compared to no Induction and to Antilymphocycte Antibodies in Renal Transplantation. Am J Transplant. 2007;7:1832-1841.
Paya, C et al. Efficacy and Safety of Valganciclovir vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in Solid Organ Transplant Recipients. Am J Transplant. 2004 Apr;4(4):611-20.
Penninga L, Møller CH, Gustafsson F, et al. Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials. Eur J Clin Pharmacol. 2010 Sep 30.
Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med 2010.
Pharm PT et al. Cardiovascular disease posttransplant. Seminars in Nephrology 2007;27(4):430-440.
Phipps S, Peasant C, Barrera M, et al. Resilience in Children Undergoing Stem Cell Transplantation: Results of a Complementary Intervention Trial. Pediatrics. 2012 Feb 6.
Pierce Dwayne A, Reeves-Daniel Amber M. Ranolazine-Tacrolimus Interaction. Articles Ahead of Print published on 1 November 2010, DOI 10.1345/aph.1P297. Ann Pharmacother ;44:1844-1849.
Prasad GV, Ruzicka M, Burns KD, Tobe SW, Lebel M. Hypertension in dialysis and kidney transplant patients. Can J Cardiol. 2009 May;25(5):309-14.
Rabinstein AA, Yee AH, Mandrekar J, et al. Prediction of potential for organ donation after cardiac death in patients in neurocritical state: a prospective observational study. Lancet Neurol 2012
Ramalho, V & Ramalho, H. Comparison of azithromycin and oral hygiene program in the treatment of cyclosporine-induced gingival hyperplasia. Renal Failure 2007;29:265-270.
Ravanan R, Udayaraj U, Ansell D, et al. Variation between centres in access to renal transplantation in UK: longitudinal cohort study. BMJ 2010;341:c3451
Robert N, Wong GW, Wright JM. Effect of cyclosporine on blood pressure. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007893. There appears to be a dose-related effect with lower doses (1-4 mg/kg/d) increasing mean BP by an average of 5 mmHg and higher doses (>10 mg/kg/d) increasing mean BP by 11 mmHg on average.
Samuel SM, Foster BJ, Tonelli MA, et al; the Pediatric Renal Outcomes Canada Group. Dialysis and transplantation among Aboriginal children with kidney failure. CMAJ. 2011 Jul 12;183(10):E665-E672.
Scandling John D., Busque Stephan, Shizuru Judith A. Induced Immune Tolerance for Kidney Transplantation. N Engl J Med 365;14 nejm.org october 6, 2011.
Scandling JD, Busque S, Shizuru JA, et al. Induced immune tolerance for kidney transplantation. N Engl J Med. 2011 Oct 6;365(14):1359-60.
Schena FP, Pascoe MD, Alberu J, et al. Sirolimus CONVERT Trial Study Group. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation. 2009 Jan 27;87(2):233-42.
Segev Dorry L.; Muzaale Abimereki D.; Caffo Brian S.; et al. Perioperative Mortality and Long-term Survival Following Live Kidney Donation. JAMA. 2010;303(10):959-966.
Sharif A. Should Metformin be Our Antiglycemic Agent of Choice Post-transplantation? American Journal of Transplantation 2011;11(7):1376-1381. Accessed online 03 Aug 2011 at: http://www.medscape.com/viewarticle/745820
Sheil AG. Cancer in renal allograft recipients in Australia and New Zealand. *Transplant Proc* 1977; 9: 1133–36.
Shilliday IR, Sherif M. Calcium channel blockers for preventing acute tubular necrosis in kidney transplant recipients. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003421.
Shore PM, Huang R, Roy L, Darnell C, Grein H, Robertson T, Thompson L. Potential for Liver and Kidney Donation After Circulatory Death in Infants and Children. Pediatrics. 2011 Aug 22.
Shullo MA, Schonder K, Teuteberg JJ. Elevated tacrolimus levels associated with intravenous azithromycin and ceftriaxone: a case report. Transplant Proc. 2010 Jun;42(5):1870-2.
Silva HT Jr, Yang HC, Abouljoud M, et al. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF & cyclosporine/MMF in de novo kidney transplant recipients. Am J Transplant. 2007 Mar;7(3):595-608.
Singh TP, Almond CS, Taylor DO, et al. Racial and Ethnic Differences in Wait-List Outcomes in Patients Listed for Heart Transplantation in the United States. Circulation. 2012 May 15.
Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306 (17):1874-1883.
Stamp L, Searle M, O'Donnell J, Chapman P. Gout in solid organ transplantation: a challenging clinical problem. Drugs. 2005;65(18):2593-611.
Stock Peter G., Barin Burc, Murphy Barbara, et al. Outcomes of Kidney Transplantation in HIV-Infected Recipients. N Engl J Med 2010; 363:2004-2014
Strachnan et al. Is oral azithromycin effective for the treatment of cyclosporine-induced gingival hyperplasia in cardiac transplant recipients? J Clin PharmTher 2003;28:329-338.
Strippoli GF, Hodson EM, Jones CJ, et al. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005133.
Summers DM, Johnson RJ, Allen J, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. Lancet. 2010 Aug 18.
Tan J, Wu W, Xu X,et al. Induction therapy with autologous mesenchymal stem cells in living-related kidney transplants: a randomized controlled trial. JAMA. 2012 Mar 21;307(11):1169-77.
Tedla, F et al. Hypertension after Renal Transplant. The Journal of Clinical Hypertension 2007; 9(7):538-545.
Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. N Engl J Med 1995;333:333-6.
Teschner S, Gerke P, Geyer M, et al. Leflunomide therapy for polyomavirus-induced allograft nephropathy: efficient BK virus elimination without increased risk of rejection. Transplant Proc. 2009 Jul-Aug;41(6):2533-8.
Thabut Gabriel; Christie Jason D.; Kremers Walter K.; et al. Survival Differences Following Lung Transplantation Among US Transplant Centers. JAMA. 2010;304(1):53-60.
Thiruchelvam Paul T R, Willicombe Michelle, Taube David et al.. Renal transplantation. BMJ 2011; 343 doi: 10.1136/bmj.d7300 (Published 14 Nov 2011)
Thornton JD, Alejandro-Rodriguez M, León JB, et al. Effect of an iPod Video Intervention on Consent to Donate Organs: A Randomized Trial. Ann Intern Med. 2012 Apr 3;156(7):483-90.
Todd JL, Palmer SM. Bronchiolitis obliterans syndrome: the final frontier for lung transplantation. Chest. 2011 Aug;140(2):502-8.
Tong A, Tjaden L, Howard K, Wong G, Morton R, Craig JC. Quality of life of adolescent kidney transplant recipients. J Pediatr. 2011 Oct;159(4):670-675.e2.
Topilsky Y, et al. Sirolimus as primary immunosuppression attenuates allograft vasculopathy with improved late survival and decreased cardiac events after cardiac transplantation. Circulation. 2012 Feb 7;125(5):708-20.
Torpy JM, Lynm C, Golub RM. JAMA patient page. Liver transplantation. JAMA. 2012 Jan 18;307(3):320.
Vaidya OU, House JA, Coggins TR, et al. Effect of Renal Transplantation for Chronic Renal Disease on Left Ventricular Mass. Am J Cardiol. 2012 Apr 5.
Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. JAMA 2006; 296: 2823–31.
van der Beek MT, Berger SP, Vossen AC, et al. Preemptive versus sequential prophylactic-preemptive treatment regimens for cytomegalovirus in renal transplantation: comparison of treatment failure and antiviral resistance. Transplantation. 2010 Feb 15;89(3):320-6.
van Gelder T. Mycophenolate Blood Level Monitoring: Recent Progress. Am J Transplant. 2009 Jun 10.
Van Laecke S, Van Biesen W, Verbeke F, et al. Posttransplantation Hypomagnesemia and Its Relation with Immunosuppression as Predictors of New-Onset Diabetes after Transplantation. Am J Transplant. 2009 Jul 16.
van Leeuwen MT, Webster AC, McCredie MR, et al. Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. BMJ. 2010 Feb 11.
van Walraven, Carl, Austin, Peter C, Knoll, Greg. Predicting potential survival benefit of renal transplantation in patients with chronic kidney disease. CMAJ 2010 0: cmaj.091661.
Vanlemmens C, Di Martino V, Milan C, et al. TRANSCIAL Study Group. Immediate listing for liver transplantation versus standard care for Child-Pugh stage B alcoholic cirrhosis: a randomized trial. Ann Intern Med. 2009 Feb 3;150(3):153-61.
Vanrenterghem Y, Bresnahan B, Campistol J, et al. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). Transplantation. 2011 May 15;91(9):976-83.
Ven Gelder, T & Shaw, L. The Rationale foe and limitations of Therapeutic drug monitoring for MMF in transplantation 2005;80(2S)oct 14

TOP

Volk ML, Biggins SW, Huang MA, et al. Decision making in liver transplant selection committees: a multicenter study. Ann Intern Med. 2011 Oct 18;155(8):503-8.
Vos R, Vanaudenaerde BM, Verleden SE, et al. A randomized placebo-controlled trial of azithromycin to prevent bronchiolitis obliterans syndrome after lung transplantation. Eur Respir J. 2010 Jun 18.
Vos R, Vanaudenaerde BM, Ottevaere A, et al. Long-term **azithromycin** therapy for **bronchiolitis obliterans** syndrome: Divide and conquer? J Heart Lung Transplant. 2010 Jul 7.
Weber M, Dindo D, Demartines N, Ambühl PM, Clavien PA. Kidney transplantation from donors without a heartbeat. N Engl J Med. 2002;347(4):248-255.
Webster A, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003961.
Weir MR, Mulgaonkar S, Chan L, et al. Mycophenolate mofetil-based immunosuppression with sirolimus in renal transplantation: a randomized, controlled Spare-the-Nephron trial. Kidney Int 2010; online Dec 29.
Wilkinson et al. Guidelines for the treatment & management of new-onset diabetes after transplant. Clin Transplant 2005:19:291-298.
Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 341: 1725–30.
Yamashita T, Ando Y, Okamoto S, et al. Long-term survival after liver transplantation in patients with familial amyloid polyneuropathy. Neurology. 2012 Feb 28;78(9):637-43.

Organ Transplant Facts:

Canada: There were 2,083 solid organ transplants in Canada, as compared with 2,188 in 2007, according to Canadian Organ Replacement Register statistics (http://cihi.ca /cihiweb/dispPage.jsp?cw_page=AR3230_E&cw_topic=3230). The total number of organ donors also decreased, to 1038 from 1046 in 2007.
Roughly 4380 Canadians were on waiting lists for transplants as of Dec. 31, 2008. — Sabrina Doyle, Ottawa, Ont. http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=media_20091222_e

Organ Donor Activity in Canada, 1999 to 2008 http://secure.cihi.ca/cihiweb/products/CORR_AiB_EN_20091222_rev20100106.pdf

During the past decade, the number of organ donors in Canada increased from 812 to 1,038 per year; living donors accounted for 69% of this increase. While there were increases in organ donation during the past decade, the demand for organs also grew. For example, in the case of kidneys, the incidence rate of end-stage renal disease increased from 149 to 168 per million population. The availability of donated organs in Canada rose by more than one-quarter (28%) over the past decade, but this increase is not keeping pace with demand. More than 1,000 Canadians donated organs in 2008, up from 812 in 1999, according to a new study released today by the Canadian Institute for Health Information (CIHI). With an increase in the number of Canadians with organ failure, combined with medical advancements that are keeping these patients alive longer, the results show an increase in the demand for organs. Last year, about 215 Canadians died while waiting for an organ transplant. A national paired exchange program has been launched for donor and recipient pairs who do not match as an initiatives to maximize the number of live-donor organs available at http://www.ccdt.ca/english/ldpe/index.htm called the Living Donor Paired Exchange Registry (LDPE).

According to the Canadian Organ Replacement Registry's 2008 annual report, there were an estimated 33,832 people with end-stage renal disease in Canada at the end of 2006, an increase of 69.7% since 1997. Of these, 20,465 were on dialysis and 13,367 were living with a functioning kidney transplant.

US Dept of Health and Human Services: Organ Procurement and Transplantation Network (OPTN) Data reports: http://optn.transplant.hrsa.gov/latestData/viewDataReports.asp

References – Transplantation Drug Treatment – www.RxFiles.ca

[1] Micromedex. 2010
2 Briggs G, Freeman, Roger, Yaffe, Sumner, ed. Drugs in Pregnancy and Lactation. 9th ed: TechBooks
3 e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2007 [cited 2007 Jul 30]. Available from: http://www.e-cps.ca. Also available in paper copy from the publisher.
4 Schonder Kristine S, Johnson Heather J, "Chapter 92. Solid-Organ Transplantation" (Chapter). Joseph T. DiPiro, Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, L. Michael Posey: Pharmacotherapy: A Pathophysiologic Approach, 7e: http://www.accesspharmacy.com/content.aspx?aID=3210287.
5 Ross, H & Hendry, P et al. 2001 Canadian Cardiovascular society consensus conference on cardiac transplantation. Can J Cardiol 2003:19(6)
6 Kasiske B et al. (2004) National Kidney Foundation: clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 4 (Suppl 7): S13–S53
7 Rigatto, C& Parfrey, P. Therapy Insight: management of cardiovascular disease in the renal transplant recipient. Nature Clinical Practice Nephrology 2006;2:514-526.
8 De Vitto, D & Song, M. Risk profile for cardiovascular morbidity and mortality after lung transplantation. Nurs Clin N Am 2008;43:37-53.
9 Estes CM, Westhoff C. Contraception for the transplant patient. Semin Perinatol. 2007 Dec;31(6):372-7. Review.
10 Helderman, JH & Goral, S. Gastrointestinal complications of transplant immunosuppresion. Review. Am J Nephrol 2002;13:277.
11 Clive, DM. Renal transplant-associated hyperuricemia and gout. J Am Soc Nephrol 2000; 11:974.
12Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant. 2004; 4 (Suppl. 10): 160–163
13 Avery RK, Michaels M. Update on immunizations in solid organ transplant recipients: what clinicians need to know. Am J Transplant. 2008 Jan;8(1):9-14. Epub 2007 Dec 18.
14 Stein, E. et al. Post-transplant osteoporosis. Endocrinol Metab Clin N Am 36 (2007) 937-963
15 Epstein–Barr virus and lymphoproliferative disorders after transplantation. Am J Transplant 2004; 4 (Suppl. 10): 59–65
16 Preiksaitis JK. New developments in the diagnosis and management of posttransplant lymphoproliferative disorders in solid organ transplant recipients. CID 2004;34:1016-23
Trappe R, Oertel S, Leblond V, et al, for the German PTLD Study Group and the European PTLD Network. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2011; online Dec 13.
17 Cytomegalovirus. American Journal of Transplantation 2004; 4 (Suppl. 10): 51–58
18 Preiksaitis, J et al. Canadian society of transplant consensus workshop on cytomegalovirus management in solid organ transplantation final report. American Journal of Tranplantation 2005;5:218-227.
Kalil Andre C., Mindru Cezarina, Florescu Diana F. Effectiveness of Valganciclovir 900 mg versus 450 mg for Cytomegalovirus Prophylaxis in Transplantation: Direct and Indirect Treatment Comparison Meta-analysis Clin Infect Dis. ciq143 first published online Dec 28, 2010 doi:10.1093/cid/ciq143
19 Davidson et al. New onset diabetes after transplantation: 2003 International Consensus Guidelines. Transplantation 2003:75;10
20 Marchetti, P. New-Onset Diabetes after transplantation. J Heart Lung Transplantation 2004;23:S104-201
21 Ponticelli, C & Passerini, P. Gastrointestinal complications in renal transplant recipients. Transplant International 2005;18:643-650.
22 Ojo, A.O. Renal disease in recipients of nonrenal solid organ transplantation. Semin Nephrol. 2007; 27(4): 498-507
23 Park, JM & Luan FL. Management of hypertension in solid-organ transplantation. Progress in Transplantation 2005;15(1):17-23.
Dunn BL, Teusink AC, Taber DJ, et al; Management of hypertension in renal transplant patients: a comprehensive review of nonpharmacologic and pharmacologic treatment strategies. Ann Pharmacother. 2010 Jul-Aug;44(7-8):1259-70.
24 Orens, JB & Garrity, ER. Lung Transplantation and Organ Allocation. Proc Am Thorac Soc. 2009;6:13-19
Thabut Gabriel; Christie Jason D.; Kremers Walter K.; et al. Survival Differences Following Lung Transplantation Among US Transplant Centers. JAMA. 2010;304(1):53-60.
Mascia Luciana, Pasero Daniela, Slutsky Arthur S., et al. Preliminary Communication Effect of a Lung Protective Strategy for Organ Donors on Eligibility and Availability of Lungs for Transplantation: A Randomized Controlled Trial. *JAMA*. 2010;304(23):2620-2627.doi:10.1001/jama.2010.1796.
25 Simonson SG et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. Clin Pharmacol Ther. 2004 Aug;76(2):167-77.
26. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2006 Mar;130(3):940-87.
27. Stamp L, Searle M, O'Donnell J, Chapman P. Gout in solid organ transplantation: a challenging clinical problem. Drugs. 2005;65(18):2593-611.
28. Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD005019.
Riella LV, Gabardi S, Chandraker A. Dyslipidemia and Its Therapeutic Challenges in Renal Transplantation. Am J Transplant. 2012 May 11.
29. Burton JR, Burton I, Pearson GJ. Clopidogrel-precipitated rhabdomyolysis in a stable heart transplant patient. Ann Pharmacother. 2007 Jan;41(1):133-7. Epub 2007 Jan 2.

TOP

30. Mascia Luciana, Pasero Daniela, Slutsky Arthur S., et al. Preliminary Communication Effect of a Lung Protective Strategy for Organ Donors on Eligibility and Availability of Lungs for Transplantation: A Randomized Controlled Trial. *JAMA*. 2010;304(23):2620-2627.doi:10.1001/jama.2010.1796.
31. Torpy Janet M., Lynm Cassio, Golub Robert M.. JAMA Patient Page : Kidney Transplantation. *JAMA*. 2011;305(6):634.doi:10.1001/jama.305.6.634.
32. Pavlakis Martha. Live Kidney Donation: A 36-Year-Old Woman Hoping to Donate a Kidney to Her Mother. *JAMA*. 2011;305(6):592-599.Published online January 18, 2011. doi:10.1001/jama.2011.56.
33. Vitale A, Ramirez MR, Zanus G, et al, on behalf of the Italian Liver Cancer group. Barcelona Clinic Liver Cancer staging and transplant survival benefi t for patients with hepatocellular carcinoma: a multicentre, cohort study. Lancet Oncol 2011.
34. Trappe R, Oertel S, Leblond V, et al, for the German PTLD Study Group and the European PTLD Network. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2011; online Dec 13.
35. Kharfan-Dabaja MA, et al. A novel therapeutic cytomegalovirus DNA vaccine (TransVax) in allogeneic haemopoietic stem-cell transplantation: randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis 2012; online Jan 10.
36. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in liver transplant recipients: a systematic review and meta-analysis. Liver Transpl 2012;18:621–629.
37. Vos R, Vanaudenaerde BM, Verleden SE, Ruttens D, Vaneylen A, Van Raemdonck DE, Dupont LJ, Verleden GM.Antiinflammatory and Immunomodulatory Properties of Azithromycin Involved in Treatment and Prevention of Chronic Lung Allograft Rejection.Transplantation. 2012 Mar 28. [Epub ahead of print]
38. Vos R, Vanaudenaerde BM, Ottevaere A, Verleden SE, De Vleeschauwer SI, Willems-Widyastuti A, Wauters S, Van Raemdonck DE, Nawrot TS, Dupont LJ, Verleden GM.Long-term azithromycin therapy for bronchiolitis obliterans syndrome: divide and conquer?J Heart Lung Transplant. 2010 Dec;29(12):1358-68. Epub 2010 Jul 8.

TOP