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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/>

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>

SchHARR 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

Clinical significance **CALCULATORS**: UBC: <http://spph.ubc.ca/sites/healthcare/files/calc/clinsig.html>; Wisconsin: <http://intsmain.is.mcw.edu/clincalc/bayes.html>

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

Diabetes: Landmark Trials Summary Table: <http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf>
ACCORD-ADVANCE Comparison: <http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-A1C-ACCORD-vs-ADVANCE-COMPARISON.pdf>
ACCORD: <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/HTN-LandmarkHypertensionTrials.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>

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>
& Update 2004: <http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Update-Oct04.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>

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>

MISC.:

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>

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- Jadad A, Enkin M. Randomized Controlled Trials: Questions, Answers and Musings 2nd edition. Blackwell Publishing 2007; BMJ Books
- Edited by: Geyman J, Deyo R, Ramsey S. Evidence-Based Clinical Practice: Concepts and Approaches. Butterworth Heinemann 2000.
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- 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).)
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2009 Canadian -10yr risk of Cardiovascular (CVD) disease (based on Framingham Heart Study).

RISK*	MEN										WOMEN															
AGE	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	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	0	2	4	5	7	8	9	10	11	12						
TOTAL CHOL <4.1 mmol/l																										
4.1-5.2																										
5.2-6.2																										
6.2-7.2																										
≥7.2																										
HDL mmol/l	<0.9	0.9-1.2	1.2-1.3	1.3-1.6						≥1.6	<0.9	0.9-1.2	1.2-1.3	1.3-1.6						≥1.6						
	+2	+1	0	-1						-2	+2	+1	0	-1						-2						
SYSTOLIC BP	Not Treated										Not Treated					Treated										
<120	-2										-3					0										
120-129	0										0					2										
130-139	1										1					3										
140-159	2										2					4										
≥160	3										4					5										
SMOKER																										
No																										
Yes	0										3															
Diabetic																										
No																										
Yes	0										4															
TOTAL POINTS																										
POINTS	MEN: actual 10yr CVD risk %													WOMEN actual 10yr CVD risk %												
<3	-2-1	2-3	4-5	6	7	8	9	10	11	12	13-14	15-16	>17	<-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	9	11	13	15-18	21-25	>29	<1% (10yr % Risk→)	1	2	3	4-5	6	7	8	10	11-13	15-18	21-27	≥30

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

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

Risk assessment tool: Cardiovascular 5yr CVD table

¹ New Zealand Guideline Group. http://www.nzgg.org.nz/library/gl_complete/bloodpressure/table1.cfm (access verified Jan 30/03).

² Jackson R. Updated New Zealand cardiovascular disease risk-benefit prediction guide. BMJ 2000;320:709-10.

³ 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.

⁴ Canadian Hypertension Society -2010 Canadian Hypertension Recommendations Working Group-downloadable Summary & Slides; www.hypertension.ca

⁵ 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.

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⁶ Canadian 2008 Guidelines (Sept 2008): <http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf>

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⁷ 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.

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- Bulughapitiya U, Siyambalapatiya 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))
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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-)

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Additional Links:

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

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

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BETA-BLOCKER (BB): Comparison Chart

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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.

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.

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.

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.

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.

Sipahi I, Tuzcu EM, Wolski KE, Nicholls SJ, Schoenhagen P, Hu B, Balog C, Shishebor 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.

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The Cardiac Insufficiency Bisoprolol Study II (**CIBIS-II**): a randomised trial. Lancet. 1999 Jan 2;353(9146):9-13.

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

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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.

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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 (**AFIRM**) 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.

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.
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- ⁵ **1999 World Health Organization**—International Society of Hypertension Guidelines:Management of Hypertension. J Hypertens 1999;17:151-183.
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- ⁷ Drugs for hypertension. Med Lett Drugs Ther 2001;43:17-22.
- ⁸ [Drugs in Pregnancy & Lactation](#), 8th Ed. Briggs GE, et al. Wilkins; Baltimore, MD. 2008.
- 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**.
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- 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 Rugenenti P, Fassi A, Ilieva AP, ET AL. Preventing Microalbuminuria in Type 2 Diabetes (**BENEDICT**). N Engl J Med. 2004 Oct 31
- 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.
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- ¹⁹ Rugenenti 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:

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

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Thiazide Like Diuretics and Miscellaneous Antihypertensives

- 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.
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- 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.
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 - 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.
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 - 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.
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 - 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 α -1-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.
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ORAL ANTIPLATELET & ANTITHROMBOTIC AGENTS

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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.
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- 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.)
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Brain Natriuretic Peptide (BNP) has diagnostic value for both types of HF and is recommended where available, when diagnosis is 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 HF³

	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

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

RISK*	MEN										WOMEN																			
AGE	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	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	0	2	4	5	7	8	9	10	11	12										
TOTAL CHOL <4.1 mmol/l	<div style="border: 1px solid black; padding: 5px; display: inline-block;"> Guidelines use "13" but this appears to be an error; should be "12" .based on reference. </div>																													
4.1-5.2																					0									
5.2-6.2																					1									
6.2-7.2																					2									
≥ 7.2																					3									
HDL mmol/l	<0.9	0.9-1.2	1.2-1.3	1.3-1.6						≥1.6	<0.9	0.9-1.2	1.2-1.3	1.3-1.6						≥1.6										
	+2	+1	0	-1						-2	+2	+1	0	-1						-2										
SYSTOLIC BP mmHg	Not Treated										Not Treated					Treated														
	<120	120-129	130-139	140-159	≥160	<120	120-129	130-139	140-159	≥160	<120	120-129	130-139	140-149	150-159	>160	<120	120-129	130-139	140-149	150-159	>160								
		-2	0	1	2	3	4	5				-3	0	1	2	4	5				-1	2	3	5	6	7				
SMOKER	No										No																			
	Yes										Yes																			
Diabetic	No										No																			
	Yes										Yes																			
TOTAL POINTS																														

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

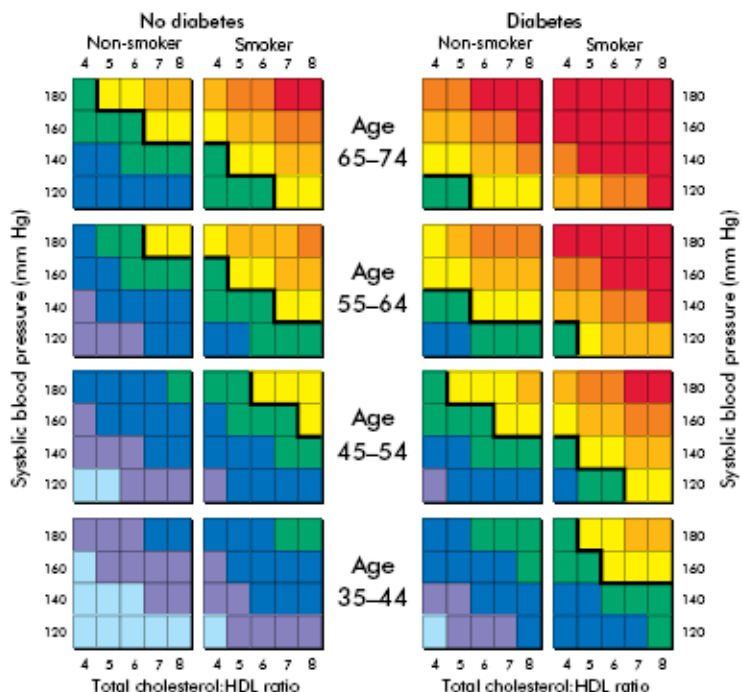
Patients with **High risk**→ ALL pts with **CAD,CVD,PAD; most with DIABETES** ≥45yr, ≥50yr, younger with risk factors & **chronic renal dx** GFR <30ml/min regardless of risk score.

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

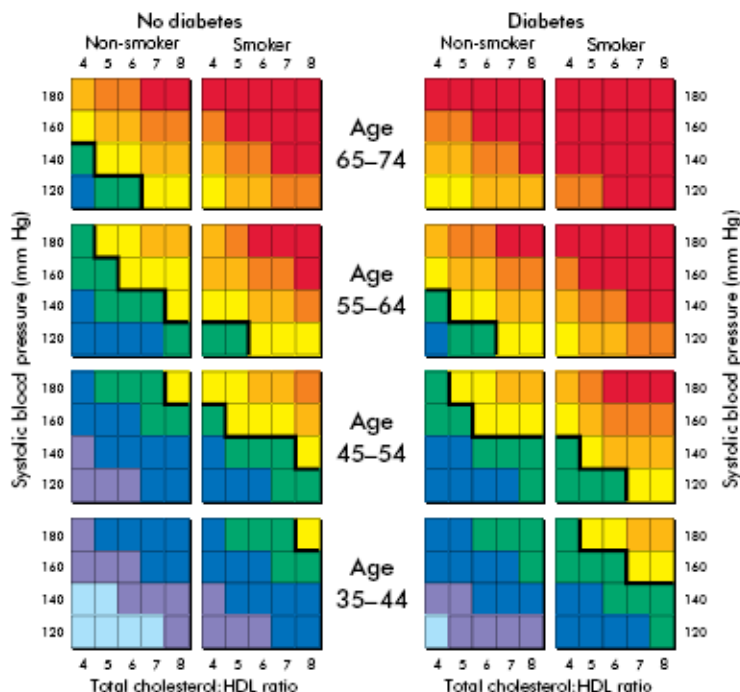
For suggested **lipid targets**, see bottom of page 15.

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

Risk level women



Risk level men



Also assess family history (↑2x the 10yr CVD risk) physical inactivity, obesity & LVH.

- Risk Factors**
INTERHEART, CDN, JNC7:
- ♦ ↑ApoB/ApoA1 ratio
 - ♦ Smoking, Diabetes
 - ♦ ↑BP
 - ♦ Obesity: waist/hip ratio (♂ ≥0.95; ♀ ≥0.85)
 - ♦ BMI >25
 - ♦ Waist (♂ >102cm/40inch, ♀ >88cm/35inch)
 - ♦ stress & depression;
 - ♦ lack of: vegetables, fruits, exercise & alcohol;
 - ♦ Low HDL ≤1
 - ♦ Family hx of premature heart dx (Age: ♂ <55, ♀ <65)
 - ♦ Age (♂ >55, ♀ >65)
 - ♦ Microalbuminuria

Key

5-year cardiovascular disease (CVD) risk (fatal and non-fatal)

- >30% (Red)
- 25-30% (Orange)
- 20-25% (Yellow)
- 15-20% (Light Yellow)
- 10-15% (Green)
- 5-10% (Blue)
- 2.5-5% (Purple)
- <2.5% (Light Blue)

Using the Charts

- Identify the chart relating to the person's sex, diabetic status, smoking history and age.
- Within the chart choose the cell nearest to the person's age, systolic blood pressure (SBP) and total cholesterol (TC):HDL ratio. People who fall exactly on a threshold between cells are placed in the cell indicating higher risk.

Note: The risk charts now include values for SBP alone, as this is the most informative of conventionally measured blood pressure parameters for cardiovascular risk. Diastolic pressures may add some predictive power, especially at younger ages (eg, a diastolic pressure consistently >100 mm Hg in a patient with SBP values between 140 and 170 mm Hg).

Certain groups may have CVD risk underestimated using these charts. See Cardiovascular Guidelines Handbook (2009 Edition) for details.

Risk level: 5-year CVD risk (fatal and non-fatal)	Benefits: NNT for 5 years to prevent one event (CVD events prevented per 100 people treated for 5 years)		
	1 Intervention (25% risk reduction)	2 Interventions (45% risk reduction)	3 Interventions (59% risk reduction)
30%	13 (7.5 per 100)	7 (14 per 100)	6 (16 per 100)
20%	20 (5 per 100)	11 (9 per 100)	9 (11 per 100)
15%	27 (4 per 100)	15 (7 per 100)	12 (8 per 100)
10%	40 (2.5 per 100)	22 (4.5 per 100)	18 (5.5 per 100)
5%	80 (1.25 per 100)	44 (2.25 per 100)	36 (3 per 100)

NNT = Number needed to treat
Based on the conservative estimate that each intervention:
aspirin, BP treatment (lowering SBP by 10 mm Hg) or **lipid modification** (↓ LDL-C by 20%) reduces cardiovascular risk by about 25% over 5 years.
Note: Cardiovascular events are defined as MI, new angina, ischemic stroke, TIA, PVD, HF & CV death.

NZ-CVD-5yr Risk Tool: quick/easy way to estimate risk of CHD and stroke; the Framingham 10yr risk assessment may also be used to estimate CHD risk. Antihypertensive benefit greater in those at highest risk!

Table: TARGETS Canadian

	(Normal BP 120/80)	Consider Treatment	Target
BLOOD PRESSURE ^{2010, 28}	NO RISK FACTORS or target organ damage	≥160/100	<140/90
Importance of accurate measurement e.g. 5 min resting	ISOLATED SYSTOLIC HTN (ISH)	SBP >160	SBP <140
	MODERATE-HIGH RISK Patient	≥140/90	<140/90
	♦ If HOME BP Measurement	≥135/85	<135/85
	DIABETES or RENAL Disease	≥130/80	<130/80
	♦ If PROTEINURIA >1g/d	≥125/75	<125/75
LIPID ^{2009, 23}	Risk (CDN based on Framingham 10yr CVD risk)	LDL	Apo B
Target <2 or ↓LDL ≥50%	HIGH * (10yr CVD ≥20%)	Target → <2 or ↓LDL ≥50%	<0.8
If LDL is <3.5, then for ♂>50yr or ♀>60yr check hsCRP check twice 2 weeks apart, not during acute illness, if hsCRP>2 mg/l → then consider treatment. ^{Jupiter trial}	MODERATE (10yr CVD 10-19%)	Treat if → >3.5	>0.8
Caution: High statin dose in low risk pts.	LOW (10yr CVD <10%)	Treat if → ≥5	>6
		Primary target → alternate to LDL	-alternate to LDL
		*High Risk: ALL with CAD, CVD & PAD. Most DIABETES older with risk factors & chronic renal dx. Cr<30ml/min	
		HIGH Risk: Treat with medication & lifestyle changes concomitantly.	
		LOWER Risk: May try lifestyle changes for 3-6 months before drug therapy if targets not met.	
		If Low/Mod risk: guidelines suggest ↓LDL by ≥50% but remember simvastatin 40mg, atorvastatin 10mg & pravastatin 40mg, has strong outcome evidence eg. *MI, stroke & death from landmark trials but only ↓LDL by 18-35%.	
BLOOD GLUCOSE ^{2008, 29}	Target for most	Normal range	→consider achieving
	A1C q3-6 mon (calibrate meter qyr)	≤7	≤6 if can be done
	FPG (mmol/L)	4-7	4-6 safely without
	PPBG (mmol/L) 2hr post	5-10	5-8 hypoglycemia etc..
	Individualized Target Treatment Goals: consider age ³⁰ , life expectancy, co-morbidity and risk of hypoglycemic side effects. Monitor: A _{1c} q3-6 months; calibrate meter yearly.		

A_{1c}=glycosolated hemoglobin A_{1c} BP=blood pressure CAD=coronary artery disease CVD= cardiovascular disease Dx=disease FPG=fasting plasma glucose HDL=high density lipoprotein Hx=history LDL=low density lipoprotein PAD=peripheral arterial disease PPBG=postprandial (2hr) blood glucose TG=triglycerides ♂=male ♀=female © www.RxFiles.ca May 2010

LIPID LOWERING THERAPY: DYSLIPIDEMIA Comparison Chart

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- 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)
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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.

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NOTE: Additional RxFiles Related Materials & Drug Comparison Charts: see www.RxFiles.ca (eg. Lipid Landmark Trials; Comparison Charts: ACEI, Beta-Blocker, Antithrombotic, Lipid Lowering)

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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% C	Common: less irritating than BP, burning, stinging, pruritus & 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 2 nd line monotherapy agent ³ (also for seborrhea & psoriasis) ⊗Not commonly recommended (less potent than equal strength BP) D: ↑ 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
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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/>

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November 8, 2006 – Medics 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) dapson 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 08 /CNW/ - QLT Inc. (NASDAQ: QLT; 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.

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DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of Saskatoon Health Region (SHR). Neither the authors nor Saskatoon Health Region nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of SHR, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources. Additional information and references online at www.RxFiles.ca

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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

EXTRAS:

Eczeema in Children – NICE guideline approach <http://www.nice.org.uk/guidance/ta669/pdf/2016-11-18>

Tx Escalator			Systemic treatment
		Bandages	Phototherapy
		Topical calcineurin inhibitors	Bandages
		Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Mild potency corticosteroids	Mild potency corticosteroids	Mild potency corticosteroids
	emollients	emollients	emollients
	Mild	Moderate	Severe
	Atopic eczema severity		

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Topical Corticosteroids: Comparison Chart

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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.

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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

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Other drugs for Glaucoma:

- Osmotic Agents (used for acute rises in IOP)
 - Glycerol – onset 10 min; max effect in 1-2 hours
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- 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.
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- 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**.
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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 a woman 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.
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Antihyperglycemic agents- Oral Anti-Hyperglycemic Agents -OAHA {(HYPOGLYCEMIC AGENTS (OHA))} - Comparison Chart

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(InfoPOEMs: On the basis of firm 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)) & (Jain A. Treating obesity in individuals and populations. BMJ. 2005 Dec 10;331(7529):1387-1390.) (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.) (Maggard MA, Shugarman LR, Suttrop M, 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):l55.)
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- ACCORD** Study Group. Effects of Combination **Lipid** Therapy (simvastatin with fenofibrate) in Type 2 Diabetes Mellitus. N Engl J Med 2010 0: NEJMoa1001282.
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- 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.
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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 glucose 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).

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.

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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.

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-bcci_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. **Junyuo 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.

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

Nov/08 Health Canada 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.

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.

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.

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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.

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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.

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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

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Howard BV, et al. Coronary heart disease risk equivalence in diabetes depends on **concomitant risk factors**. *Diabetes Care*. 2006 Feb;29(2):391-7.

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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.

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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.

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.

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-))

International Expert Committee. 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]

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Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for **obesity**. *Drugs*. 2005;65(10):1391-418.

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.

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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

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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.

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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.

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Clinical Knowledge Summary - Diabetes – NHS – UK: Link http://www.cks.library.nhs.uk/diabetes_type_2

Health Canada – Advisory on rosiglitazone (Avandia) (June 01, 2007) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/profi/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>

Background considerations:

- **Weighing the benefits & risks of intensive therapy:** [See also Diabetes - Landmark Outcome Trials Chart²³]
 - 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.²⁴ (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.²⁵)
 - Individualization of antihyperglycemic therapy has become a common theme^{26,27} 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%)²⁸.
 - 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 Society²⁹ 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.³⁰

- **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 disease¹⁵

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%.³¹
- 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%20Dec2009.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-mpps/medeff/advisories-avis/prof/2008/gluc_met_nth-aah-eng.php

Reagents: **NOTE:** (Adapted from Hamilton Family Health Team – Table)

Why consideration of reagents 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.
- Strips with glucose dehydrogenase (GDH) pyrroloquinolinequinone (PQQ) will have cross-reactivity with maltose, galactose or xylose but are unaffected by pO2.
- Strips with glucose oxidase are affected by pO2 in the blood but not by maltose, galactose and xylose
- 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.

Total Spending in Canadian Publicly and Privately Funded Drug Plans on Blood Glucose Test Strips Exceeded \$330 Million (2006)

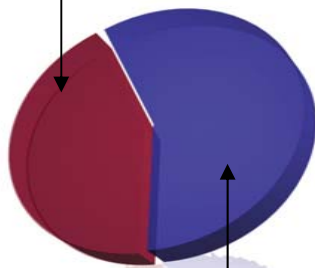
Some estimate that if spending were changed to reflect the evidence, more than \$150 million would be freed up to be spent elsewhere without adversely affecting health outcomes.

[Data from eight publicly funded drug plans in Canada (British Columbia, Manitoba, Newfoundland and Labrador, Non-Insured Health Benefits, Nova Scotia, Ontario, Quebec and Saskatchewan) plus data from 67% of privately funded drug plans that submitted data to Brogen Inc.]



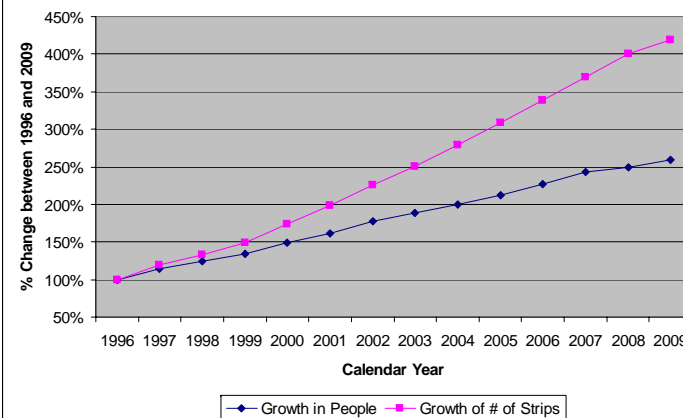
Thanks to CADTH-COMPU for assistance the development of this document. See online for Copyright and Disclaimer information. Copyright 2010 Saskatoon Health Region www.RxFiles.ca

Patients with diabetes who are using insulin
\$144,000,000

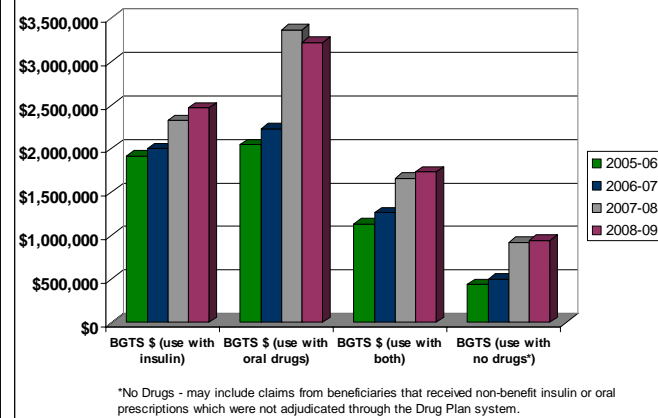


Patients with diabetes who are **not** using insulin
\$188,000,000

Growth of Blood Glucose Test Strip Users and Strips Saskatchewan Drug Plan



Cost of Blood Glucose Test Strips (Saskatchewan Drug Plan Paid)



Data provided from Saskatchewan Health; used by permission.

Additional articles:

Hovorka R, Allen JM, Eleri 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.

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Extras

Recently Discontinued Insulin Devices (within last 3 years): **HumaPen Ergo** (discontinued 2007) & **Novolin-Pen 3**

<p>AutoPen 24 (3ml penfill)</p> <p>A) green – up to 21 units 1-21 units in 1 unit increments</p> <p>B) blue – up to 42 units 2-42 units in 2 unit increments</p>	 A blue and purple insulin pen with "Autopen 24" printed on the blue body. The purple cap is on the right side.	<p>LANTUS (glargine)</p> <ul style="list-style-type: none">♦ free with Lantus insulin	<ul style="list-style-type: none">♦ 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 overdialled♦ if insufficient insulin in cartridge, number remaining on dial will show remaining dose to be given
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Jet injectors (eg. AdvantaJet, Medi-Jector) avoid the use of needles, are expensive, & require frequent cleaning.

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Temporary Extras:

- Pen devices: ↑ portability, convenience & ease of use; but ↑ potential for contamination, needle sticks, malfunction & cost
- CSII: greater ↓ A1c than basal-bolus with IAs

• 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

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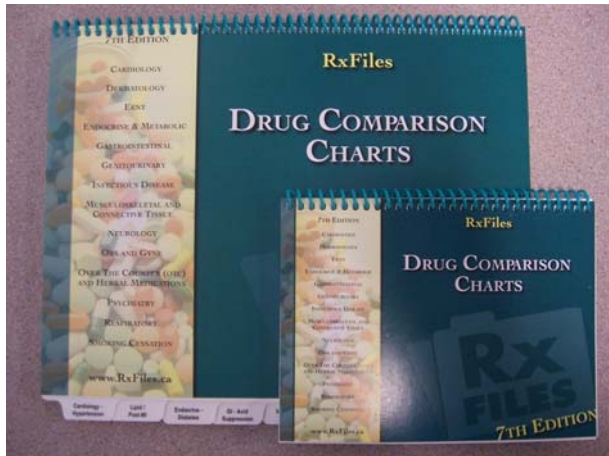
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www.RxFiles.ca

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 observation that "with every one percent 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). Current evidence call this assumption into question.

- 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 that 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... (See also; <http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf>).
- 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,^{b860} 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 than 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).

There is some discordance 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, may also be 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.*}

Multifactorial intervention - blood pressure, lipids, possibly ASA, lifestyle – in addition to glucose control, is essential in reducing macrovascular endpoints!

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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.

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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 **Lexsel 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 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 II 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 **Natural 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, Brazilian 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 BURNING (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.

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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.changeforlifeline.com

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

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

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Extras (RxFiles Herbal Weight Loss)

Glucosamin (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

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- 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 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.
- 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.

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- 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 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 II 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 **Natural 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 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.

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Cochrane reviews CD:

- TNF- α 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 \uparrow 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 than 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)

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- 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 than 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)

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Acid Suppression - Comparison Chart Supplement

RxFiles

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- ²² Armstrong D, Marshall JK, Chiba N, et al.; Canadian Association of Gastroenterology GER Consensus Group. Canadian Consensus Conference on the management of **gastroesophageal reflux disease in adults** - update 2004. *Can J Gastroenterol*. 2005 Jan;19(1):15-35.
- ²³ 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.

Albeldawi M, Qadeer MA, Vargo JJ. Managing **acute upper GI bleeding**, preventing recurrences. *Cleve Clin J Med*. 2010 Feb;77(2):131-42.

Andriulli A, Annesse V, Caruso N, et al. Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: a series of meta-analyses. *Am J Gastroenterol* 2005; 100:207-19. (InfoPOEMs: In all groups, proton pump inhibitors reduce rebleeding and the need for surgery, particularly when used in combination with endotherapy, but do not affect mortality. (LOE = 1a.)

Andriulli A, Loperfido S, Focareta R, et al. High- versus low-dose proton pump inhibitors after **endoscopic hemostasis** in patients with peptic ulcer bleeding: a multicentre, randomized study. *Am J Gastroenterol*. 2008 Dec;103(12):3011-8. Intensive regimen (pant or omeprazole 80 mg bolus followed by 8 mg/h as continuous infusion for 72 h) or a standard regimen (40 mg bolus daily followed by saline infusion for 72 h). After the infusion, all pts were given 20 mg PPI bid po. N=238. Following **endoscopic hemostasis of bleeding ulcers, standard-dose PPIs infusion was as effective as a high-dose regimen** in reducing risk of recurrent bleeding.

Bajaj JS, Zadornova Y, et al. Association of proton pump inhibitor therapy with **spontaneous bacterial peritonitis** in cirrhotic patients with ascites. *Am J Gastroenterol*. 2009 May;104(5):1130-4. Epub 2009 Mar 31.

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.

Beaumont H, Boeckstaens GE. Does the Presence of a Hiatal Hernia Affect the Efficacy of the Reflux Inhibitor Baclofen During Add-On Therapy? *Am J Gastroenterol*. 2009 Jul;104(7):1764-1771. Epub 2009 Jun 2. This study shows that **baclofen** is also effective in patients with GERD with +HH, further underscoring the potential of reflux inhibitors as treatment of GERD.

Bhatt DL, 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: 10.1161/CIRCULATIONAHA.108.191087. Available at: <http://circ.ahajournals.org> <http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.191087>

Blume H, Donath F, Warnke A, Schug BS. Pharmacokinetic **drug interaction** profiles of proton pump inhibitors. *Drug Saf*. 2006;29(9):769-84.

Bour B, et al. Long-term treatment of gastro-oesophageal reflux disease patients with frequent symptomatic relapses using rabeprazole: **on-demand** treatment compared with continuous treatment. *Aliment Pharmacol Ther*. 2005 Apr 1;21(7):805-12.

Calvet X, Gomollon F. What is potent acid inhibition, and how can it be achieved? *Drugs*. 2005;65 Suppl 1:13-23.

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))

Caos A, Breiter J, Perdomo C, Barth J. Long-term prevention of erosive or ulcerative gastro-oesophageal reflux disease relapse with **rabeprazole** 10 or 20 mg vs. placebo: results of a 5-year study in the United States. *Aliment Pharmacol Ther*. 2005 Aug 1;22(3):193-202.

Centanni M, Gargano L, Canettieri G, Viceconti N, Franchi A, Delle Fave G, Annibale B. **Thyroxine** in goiter, Helicobacter pylori infection, and chronic gastritis. *N Engl J Med*. 2006 Apr 27;354(17):1787-95.

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.**

Chang AB, et al. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for **chronic cough** associated with gastro-oesophageal reflux. *BMJ*. 2005 Dec 5; [Epub] **CONCLUSION:** Use of a proton pump inhibitor to treat cough associated with GORD has some effect in some adults. The effect, however, is less universal than suggested in consensus guidelines on chronic cough and its magnitude of effect is uncertain. (InfoPOEMs: Treatment for gastroesophageal reflux disease (GERD) in patients with chronic cough may be effective in some patients, but the effect is not universal or consistent. It might be worth a try, but don't expect many patients to improve. (LOE = 1a))

Chiba N. Proton pump inhibitors in acute healing and maintenance of erosive or worse esophagitis: a systematic overview. *Can J Gastroenterol*. 1997 Sep;11 Suppl B:66B-73B.

Cremonini F, Wise J, Moayyedi P, Talley N. Diagnostic and therapeutic use of proton pump inhibitors in non-cardiac chest pain. *Am J Gastroenterol* 2005; 100:1226-32. (InfoPOEMs: The use of a proton pump inhibitor (PPI) is useful in the diagnosis of gastroesophageal reflux disease (GERD) and an effective treatment for patients with noncardiac chest pain. Because some smaller studies with negative results may not have been published, the estimate of the degree of benefit of PPIs in this study may be on the high side. (LOE = 1a.)

Davila RE, Rajan E, Adler DG, Egan J, et al. Standards of Practice Committee. ASGE Guideline: the role of **endoscopy** in the patient with lower-GI bleeding. *Gastrointest Endosc*. 2005 Nov;62(5):656-60.

Delaney B, Ford A, Forman D, Moayyedi P, Qume M, Delaney B. Initial management strategies for **dyspepsia**. *Cochrane Database Syst Rev*. 2005 Oct 19;(4):CD001961 & ACP Journal Club. **AUTHORS' CONCLUSIONS:** Proton pump inhibitor drugs (PPIs) are effective in the treatment of dyspepsia in these trials which may not adequately exclude patients with gastro-oesophageal reflux disease (GORD). The relative efficacy of histamine H2-receptor antagonists (H2RAs) and PPIs is uncertain early investigation by endoscopy or H. pylori testing may benefit some patients with dyspepsia but is not cost effective as part of an overall management strategy.

DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease (**GERD**). *Am J Gastroenterol* 2005; 100:190-200. (InfoPOEMs: This guideline provides recommendations for management of gastroesophageal reflux disease. Endoscopy is recommended only for patients with alarm symptoms, poor response to therapy, or severe or long-term symptoms. H2 blockers or PPIs are effective in most patient, and many can be **labeled to low doses** or off treatment all together. (LOE = 1))

Dickman R, Schiff E, Holland A, et al. Clinical trial: **acupuncture** vs. doubling the proton pump inhibitor dose in refractory heartburn. *Aliment Pharmacol Ther*. 2007 Oct 30;26(10):1333-1344. Epub 2007 Sep 17. Adding acupuncture is more effective than doubling the proton pump inhibitor dose in controlling gastro-oesophageal reflux disease-related symptoms in patients who failed standard-dose proton pump inhibitors. (InfoPOEMs: In this small, short-term study, adding twice weekly acupuncture to standard-dose proton pump inhibitor (PPI) treatment was more effective in controlling symptoms than doubling the PPI dose. Acupuncture may be useful for some patients, but the long-term benefits, if any, have not been established. (LOE = 1b))

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Dial S, Delaney JA, Schneider V, Suissa S. Proton pump inhibitor use and risk of community-acquired **Clostridium difficile**-associated disease defined by prescription for oral vancomycin therapy. *CMAJ*. 2006 Sep 26;175(7):745-8.

Dodd JM, Crowther CA, Robinson JS. Oral **misoprostol** for induction of labour at term: randomised controlled trial. *BMJ*. 2006 Mar 4;332(7540):509-13. Epub 2006 Feb 2.

Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *N Engl J Med*. 2006 Oct 26;355(17):1834-6.

Epstein David, et al. **REFLUX** trial group. **Laparoscopic fundoplication** compared with medical management for gastro-oesophageal reflux disease: cost effectiveness study. *BMJ* 2009;339:b2576, doi:10.1136/bmj.b2576

- Fiocca R, Mastracci L, Engström C, et al. Long-Term Outcome of Microscopic Esophagitis in Chronic GERD Patients Treated With Esomeprazole or Laparoscopic Antireflux Surgery in the **LOTUS** Trial. *Am J Gastroenterol.* 2009 Nov 10.
- Fock KM, Teo EK, Ang TL, et al. **Rabeprazole** vs esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. *World J Gastroenterol.* 2005 May 28;11(20):3091-8.
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- Garbis H, et al. Pregnancy outcome after exposure to ranitidine and other H2-blockers A collaborative study of the European Network of Teratology Information Services. *Reprod Toxicol.* 2005 Mar-Apr;19(4):453-8.
- Garcia Rodriguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of **oesophageal and gastric adenocarcinoma**: a nested case control study in the UK. *Gut.* 2006 Nov;55(11):1538-44. Epub 2006 Jun 19.
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- Gee DW, Andreoli MT, Rattner DW. Measuring the effectiveness of **laparoscopic antireflux surgery**: long-term results. *Arch Surg.* 2008 May;143(5):482-7. Contrary to the medical literature, our results demonstrate that patients undergoing primary LF by an experienced surgical team have near-normal GERD-HRQL scores at long-term follow-up and low reoperation rates and are satisfied with their decision to undergo surgery. Results following redo LF are not as good, highlighting the importance of proper patient selection and surgical technique when performing primary LF.
- 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)
- Gill SK, O'Brien L, Einarson TR, et al. The safety of proton pump inhibitors (**PPIs in pregnancy**): a meta-analysis. *Am J Gastroenterol.* 2009 Jun;104(6):1541-5; quiz 1540, 1546. Epub 2009 Apr 28. On the basis of these results, PPIs are not associated with an increased risk for major congenital birth defects, spontaneous abortions, or preterm delivery. The narrow range of 95% CIs is further reassuring, suggesting that PPIs can be safely used in pregnancy.
- Gillessen A, Beil W, Modlin IM, Gatz G, Hole U. **40 mg pantoprazole and 40 mg esomeprazole** are equivalent in the healing of esophageal lesions & relief from gastroesophageal reflux disease-related symptoms. *J Clin Gastroenterol.* 2004 Apr;38(4):332-40. (n=227) In patients with gastroesophageal reflux disease, 40 mg pantoprazole daily and 40 mg esomeprazole daily are equally effective for healing of esophageal lesions and relieving gastroesophageal reflux disease-related symptoms.
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- 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.
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- Grant AM, Wileman SM, Ramsay CR, Mowat NA, Krukowski ZH, Heading RC, Thursz MR, Campbell MK; REFLUX Trial Group. Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial. *BMJ.* 2008 Dec 15;337:a2664. doi: 10.1136/bmj.a2664. At least up to 12 months after surgery, **laparoscopic fundoplication** significantly increased measures of health status in patients with GORD.
- Guillet R, et al.; National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing **enterocolitis** in very low birth weight infants. *Pediatrics.* 2006 Feb;117(2):e137-42. Epub 2006 Jan 3.
- Health Canada **Aug/07** is advising consumers that it is currently reviewing new preliminary safety information regarding **serious cardiac events** in patients using Losec (omeprazole) and Nexium (esomeprazole), two prescription drugs used to treat acid-related stomach disorders. (**Feb 27, 2008** Health Canada Completes Safety Review of Losec (omeprazole) and Nexium (esomeprazole) OTTAWA - Further to its Information Update dated August 9, 2007, Health Canada is informing Canadians of the results of its review of safety information for Losec (omeprazole) and Nexium (esomeprazole), two prescription drugs used to treat conditions where a reduction of gastric acid secretion is required, such as ulcers and reflux. In Canada, omeprazole is also sold in generic form as Apo-omeprazole, Ratio-omeprazole and Sandoz-omeprazole. Esomeprazole is only sold under the trade name Nexium. Nexium (esomeprazole) Based on its review of the data available at this time, Health Canada has concluded that there is no evidence supporting an increased cardiovascular risk associated with the long-term use of esomeprazole. The Department will continue to monitor safety issues related to esomeprazole by conducting further analysis of ongoing long-term studies as this data becomes available. Losec (omeprazole) After a thorough analysis, based on the data available to us at this time, we are unable to definitively conclude if there is a potential for increased cardiovascular risk associated with the long-term use of omeprazole. We will continue to evaluate should more conclusive data become available, and will advise Canadians if any further regulatory actions are required.)
- Health Canada Aug/09 **Plavix & PPI Interaction** http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2009/plavix_hpc-cps-eng.pdf
- Heidelbaugh JJ, Inadomi JM. Magnitude and Economic Impact of **Inappropriate Use of Stress Ulcer Prophylaxis** in Non-ICU Hospitalized Patients. *Am J Gastroenterol.* 2006 Oct;101(10):2200-5. Epub 2006 Sep 4.
- Heidelbaugh JJ, Goldberg KL, Inadomi JM. **Overutilization of proton pump inhibitors**: a review of cost-effectiveness and risk in PPI. *Am J Gastroenterol* 2009;104:S27-S32.
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- Ho PM et al. Risk of adverse outcomes associated with concomitant use of **clopidogrel** and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009 Mar 4; 301:937.
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- 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 specific 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.
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- Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. **Body-mass index** and symptoms of gastroesophageal reflux in women. *N Engl J Med.* 2006 Jun 1;354(22):2340-8.
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- Jones R, Charlton J, Latinovic R, Gulliford MC. **Alarm symptoms** and identification of non-cancer diagnoses in primary care: cohort study. *BMJ.* 2009 Aug 13;339:b3094. doi: 10.1136/bmj.b3094. Clinically relevant diagnoses are made in a high proportion of patients presenting with alarm symptoms. For every four to seven patients evaluated for haematuria, haemoptysis, dysphagia, or rectal bleeding, relevant diagnoses will be identified in one patient within 90 days.
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- Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of **reflux oesophagitis**. *Cochrane Database Syst Rev.* 2007 Apr 18;(2):CD003244. PPI therapy is the most effective

therapy in oesophagitis but H2RA therapy is also superior to placebo. There is a paucity of evidence on prokinetic therapy but no evidence that it is superior to placebo.

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- 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. (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 patients with reflux, either. (LOE = 2b-))
- 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. Esomeprazole improved PEF in subjects with asthma who presented with both GERD and nocturnal respiratory symptoms (NOC). In subjects without both GERD and NOC, no improvement could be detected. N=770 16weeks
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- Laine L, Shah A, Bermanian S. Intra-gastric pH With **Oral vs Intravenous** Bolus Plus Infusion Proton Pump Inhibitor Therapy in Patients With Bleeding Ulcers. *Gastroenterology.* 2008 Mar 10. [Epub ahead of print] Frequent oral PPI may be able to replace the currently recommended intravenous bolus plus infusion PPI (intravenous lansoprazole (90-mg bolus followed by 9-mg/h infusion) or oral lansoprazole (120-mg bolus followed by 30 mg every 3 hours) therapy in patients with bleeding ulcers, although the possibility that intravenous PPIs are superior cannot be definitively excluded given our relatively wide confidence intervals. Intravenous PPI provides more rapid increase in pH, reaching mean pH of 6 approximately 1 hour sooner than oral PPI.
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- 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.
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- Lau JY, Leung WK, Wu JC, et al. **Omeprazole before endoscopy** in patients with gastrointestinal bleeding. *N Engl J Med.* 2007 Apr 19;356(16):1631-40. Infusion of high-dose omeprazole before endoscopy accelerated the resolution of signs of bleeding in ulcers and reduced the need for endoscopic therapy. (InfoPOEMs: An overnight infusion of omeprazole prior to endoscopy in patients with acute upper GI hemorrhage reduces the need for intervention and speeds discharge from the hospital. (LOE = 1b))
- Law R, Maltepe C, Bozzo P, Einarson A. Treatment of **heartburn and acid reflux** associated with nausea and vomiting during **pregnancy**. *Can Fam Physician.* 2010 Feb;56(2):143-4.
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- 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.
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Web Sites:

American College of Physicians: ACP Special Report: Understanding and Treating Heartburn http://www.acponline.org/patients_families/pdfs/health/heartburn_report.pdf
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The Rx Files - H. pylori Eradication

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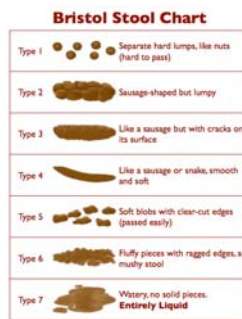
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Notes:

- **VSL#3** is a probiotic mixture that contains *Bifidobacterium* (*B. longum*, *B. infantis* and *B. breve*); *Lactobacillus* (*L. acidophilus*, *L. casei*, *L. delbrueckii* ssp. *Bulgaricus*, and *L. plantarum*); and *Streptococcus salivarius* ssp. *thermophilus*.
- **Probiotic Mixture: Lactobacillus rhamnosus GG, L. rhamnosus LC705, Bifidobacterium breve Bd99 and Propionibacterium freudoenreichii ssp. shermanii JS.** A total of 8-9x10⁹ CFU/day; equal amount of each strain.

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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/>
BIV-Over-treatment of PONV: 1) low doses of ondansetron, 1mg iv q6h, adequate; 2) allow for onset, 30 minutes <http://www.brighamandwomens.org/pharmacoevid/Research/EduMaterials/antiemetics3.05.04-web.pdf>
Other: Fosopreitant: Injectable form of **EMEND**. Not in Canada.

References: RxFiles Nausea & Vomiting – Management / Treatment Chart www.rxfiles.ca

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Adapted from Timmins Palliative Care (P. Critchley MD, T. Dolanjski Pharmacist) Prepared by: L. Regier BSc, B. Jensen BSc

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Erectile Dysfunction Comparison Chart (ED) Treatment Chart

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Apomorphine (CR sublingual tabs) ApoKyn (USA)	Centrally acting agent stimulates dopamine sites in the hypothalamus 	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	
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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 Tadalafil.

FDA July/09 found **Steam** (Nutracoastal Trading LLC's dietary supplement) product contains sulfoildenafil, an analog of sildenafil.

FDA Nov/09 notified consumers that **Stiff Nights**, a product sold as a dietary supplement, contains sulfoildenafil, a chemical similar to sildenafil (Viagra).

FDA Nov/09 & RockHard Laboratories notified consumers that **RockHard Weekend**, a product sold as a dietary supplement, contains sulfoildenafil, 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 Sulfoildenafil.

FDA Mar/10 & Natural Wellness notified consumers that **MaxXtreme**, a product sold as a dietary supplement contains sildenafil close in structure to sildenafil and is expected to possess a similar pharmacological and adverse event profile as well as the drug phenolamine 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.

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.

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.

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.

Health Canada Jan/06 Natural health product **Libidifit** 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/2006/006_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; Deguozechengtianxia** 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 **varденаfil**.

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, Enhenix 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 **varденаfil**, 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 varденаfil. **True Man and Energy Max** are used as sexual enhancement/ erectile dysfunction products and were found to contain an analogue of sildenafil or varденаfil.

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. **Dequozhanjiang** 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.

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 phenolamine.

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, Ereextra, Yilishen, Blue Steel, Hero, & Natural 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-Itly-Power (VIP)** Tabs. The U.S. Food and Drug Administration has warned consumers not to use Viril-Itly-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, Enhenix 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 varденаfil.

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 varденаfil. 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 xanthoantrafil (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 sulfoildenafilafil (lot# 80214) & undeclared tadalafil (lot# 90260).

Syntrex 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 acetic acid. U.S. FDA: **RockHard Weekend** contains sulfoildenafilafil.

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 Feb/10: **2H & 2D-** Hong Kong Department of Health (HKDH) warned consumers not to buy or use 2H & 2D after 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 sulfoildenafilafil, 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.

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 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).

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Web Links:

American Academy of Family Physicians Web site: <http://familydoctor.org>
 American Urological Association Foundation Web site: <http://www.urologyhealth.org/adult/index.cfm?cat=11&topic=174>
 National Institutes of Health Web site: <http://www.nlm.nih.gov/medlineplus/erctiledysfunction.html>

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Extras:

in Europe dapoxetine *Priligy* has official indication for Premature Ejaculation

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- ¹² RxFiles Androgen Chart: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Androgens.pdf>
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Extras:

- 1) ACs, Other: **propranolol** -less effective & ↑ SE than flavoxate & oxybutynin. ¹¹ NICE states not to use!; 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-op³². Some report use in nocturnal diuresis¹¹
dicyclomine -insufficient data to recommend over other agents, dose 20-40mg qid.¹¹
- 4) **Flavoxate**: Not used for OAB currently¹ but may be used in discomfort associated with BPH. Efficacy might be comparable to propantheline according to older, short-term studies¹¹.
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 improvement¹¹.
- 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: discolored 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%; NNT=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

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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

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.

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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}

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References

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¹ Therapeutic Choices 5th Edition
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Saskatchewan Ministry of Health Funded Vaccines Other Than Routine Childhood Immunizations (Table 9-2)
Eligibility Criteria for Those at Increased Risk [Excerpted from Saskatchewan Immunization Manual (Section: 9-20; Revised June 2008)]

Criteria	H. influenzae b (Hib)	Hepatitis A (HA)	Hepatitis B (HB)	Influenza (Inf)	Meningococcal Conjugate (Men-C) &/or Polysaccharide (Men-P)	MMR	Pneumococcal conjugate (Pneu-C-7) &/or polysaccharide (Pneu-P-23)	Tetanus Diphtheria (Td)	Rabies (Rab)	Vari-cella (Var)
Age ≥65 years				X			X ¹			
All adults – every 10 years								X		
Alcoholism				X			X ¹			
Anemia				X						
Animal bites								X ¹⁰	X ¹⁰	
Children 6-23 months of age				X						
Children 12 months to 18 years on chronic ASA therapy										X ⁴
Children 6 months to 18 years on chronic ASA therapy				X						
Children under 7 years of age whose families have immigrated to Canada from regions of high Hepatitis B prevalence			X							
Children aged 1-15 years living in Northern Health Regions or on reserve in Saskatchewan		X ²								
Chronic Cerebrospinal fluid leak							X			
Chronic cardiorespiratory disease (including bronchopulmonary dysplasia, and asthma) requiring regular medical follow-up or hospital care				X						
Chronic cardiorespiratory disease, especially cyanotic congenital HD, cardiac failure, bronchopulmonary dysplasia, excluding asthma unless on oral corticosteroid therapy							X			
Chronic liver disease, regardless of cause, including cirrhosis		X	X	X			X ¹			
Chronic metabolic disease				X						
Chronic renal failure from nephrotic syndrome			X	X			X			X ⁴
Cochlear implant recipients	X				X		X			
Complement, properidin and factor D deficiency					X					
Cystic Fibrosis				X			X			X ⁴
Diabetes				X			X			
Predialysis, peritoneal, and hemodialysis			X	X			X			X ⁴
Hemoglobinopathy				X			X			
Hemophilia		X	X							
Hepatitis A household and intimate social contacts <small>as recommended by MHO</small>		X								
Hepatitis B household contacts, who are non immune, including child care settings			X							
Hepatitis C, if hepatitis A and/or B non-immune		X	X							
HIV infection	X	X ⁷	X ⁷	X		X ⁴	X			X ⁴
Humoral Immune System Deficiencies: - disorders of antibody production or function - lymphoreticular malignancies - hematopoetic malignancies - antibody dyscrasias - protein wasting syndromes	X			X			X			

Criteria	H. influenzae b (Hib)	Hepatitis A (HA)	Hepatitis B (HB)	Influenza (Inf)	Meningococcal Conjugate (Men-C) &/or Polysaccharide (Men-P)	MMR	Pneumococcal conjugate (Pneu-C-7) &/or polysaccharide (Pneu-P-23)	Tetanus Diphtheria (Td)	Rabies (Rab)	Vari-cella (Var)
Immunosuppression for therapy or underlying disease (e.g. cancer, Hodgkin's disease, leukaemia, lymphoma, myelodysplasias, congenital immune deficiency)	X			X			X			
Infants of HBsAg+ mothers			X ¹¹							
Infants born to women at increased risk for hepatitis B infection (i.e. injection drug users) whose infectious status is unknown or negative at time of delivery			X ¹²							
Injection drug users (street drugs) and their sexual partners/household contacts			X					X		
Meningococcal disease - household and intimate social contacts to a case, as recommended by MHO					X					
Percutaneous (needle stick) or high risk mucosal exposure			X					X		
Pregnancy				X						
Rubella non-immune women, unless previously received at least 2 doses (see Section 3-75)						X				
Residents of institutions for the developmentally challenged			X ¹³							
Residents of special care homes and other chronic care facilities				X			X ¹			
Sexual assault victims			X							
Sexual partners of HBsAg positive persons			X							
Sexual partners-multiple			X							
Spleen: - Asplenia, functional or anatomic, or - Hyposplenia due to (sickle cell anemia, thalassemia major, essential thrombocytopenia, celiac disease and inflammatory bowel disease)	X ⁵			X	X ⁶		X			
Transplant recipients – bone marrow, solid organs, stem cell transplants ³ (see section 3-85 & 3-90)	X ⁴	X ⁸	X ⁸	X	X ⁸	X ⁴	X	X ⁸		X ⁴
Wound management								X ⁹		

Footnotes

- ¹ Applies only to pneumococcal polysaccharide vaccine (23 valent).
- ² Recommended for children living in the northern health regions or on reserve in Saskatchewan (Creighton, Air Ronge, La Ronge excluded from the program). The first dose is given at 1 year of age with a second dose at 18 months. It is also acceptable to provide the first dose at 18 months with the second dose at 2 years of age. Children who received an initial dose as part of this program should receive their 2nd dose regardless of their place of residence. Children who were eligible for immunization when this program started in 1997 are eligible until they turn 15 years of age.
- ³ Transplant recipients also may receive a repeat series of routine childhood vaccines, as recommended by the medical centre where they received the transplant and following consultation with an MHO.
- ⁴ Only given following consultation with MHO. (Medical Health Officer)
- ⁵ Vaccination with the age-appropriate primary series should be completed (if not already completed) for all children < 5 years with asplenia. One dose of Hib vaccine is recommended for all asplenic individuals ≥ 5 years of age regardless of previous Hib immunization
- ⁶ Eligible for both conjugate vaccine products: Men – C and Men – P.
- ⁷ Only men who have sex with men and IDU (Intravenous drug user)
- ⁸ Use if indicated based on recommendation from Transplant Physician/Team and MHO (Medical Health Officer)
- ⁹ Refer to Section 8-30
- ¹⁰ Refer to Section 8-35
- ¹¹ Initiate at birth with HBIG
- ¹² Initiate at 2 months of age
- ¹³ Routine blood work prior to immunization of residents is not indicated

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Extras:

- ♦ **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.
- ♦ Impetigo: [Retapamulin Allergo topical USA; for impetigo if resistance]

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.

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.

AOM: Prophylactic tx no longer recommended

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 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))
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CDC Guidelines. MMWR Recomm Rep. 2005 Dec 9;54(RR-14):1-16.

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Health Canada February, 2006 advises diabetic patients not to use the antibiotic Tequin http://www.hc-sc.gc.ca/ahe-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)
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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)
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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.
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124. Camilleri M. Clinical practice. **Diabetic gastroparesis**. *N Engl J Med*. 2007 Feb 22;356(8):820-9.
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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.
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Extras

Combos to Avoid: Early virologic failure: abacavir + lamivudine (or emtricitabine) + tenofovir ; didanosine + lamivudine (or emtricitabine) + tenofovir; didanosine + tenofovir + NNRTI; emtricitabine(or lamivudine) + tenofovir + nevirapine⁶⁸; didanosine + emtricitabine(lamivudine) + atazanavir

↑SE: Didanosine + stavudine (peripheral neuropathy, 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)⁶⁹ or indinavir (will maintain hormone levels)

{Refractory large volume diarrhea, HIV related: octreotide (50-500mcg sc tid)^{\$\$\$}}^{70,71}

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Rx Files – Drugs for Influenza

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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.
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- 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.
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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 (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/>

Primaquine 26.3mg tab (= 15mg base) **X** **C/D**
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 July 06².
 • **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

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 hypozoitotes 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**

Primaquine eradicates latent parasites in the liver.

Drug Treatment of Malaria: Tx will vary depending on species of malaria. For severe: (IV quinine or artesunate) + (Atovaquone/proguanil or doxycycline or clindamycin)

Other Investigational Drugs: **IV artesunate:** investigational in the USA for treatment of severe malaria. (May be accessed in Canada through the Canadian Malaria Network. It is an alternative to quinine with less side effects, although limited long term experience with potential side effects from recurrent use.)

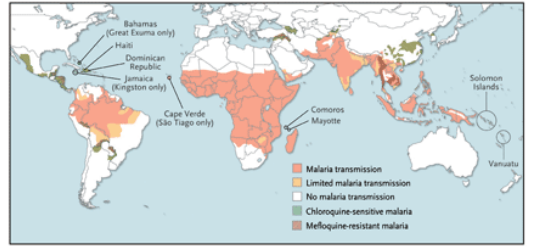
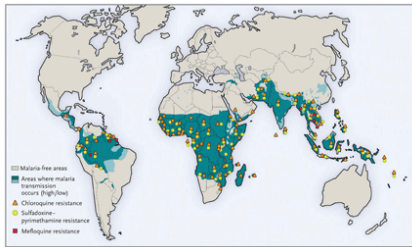
[Recent historical resistance trends: (chloroquine sensitive areas: travel to Caribbean including Haiti and rural areas of Dominican Republic; travelers visiting resort areas not generally at risk; travel to Central America except Panama, Mexico, Argentina; parts of China / Middle east; geographic risk and resistance trends change over time.)
Appropriate malaria risk (1 month stay without chemoprophylaxis): (source: CCDR 2000 Malaria Recommendations, p.3)

Oceania (Papua New Guinea, Iran, Java, 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.

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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. **CCD Map:** <http://cdc.malaria.nscs.uic.edu/>

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<p>Hydroxychloroquine PLAQUENIL 200mg tab (Not used very often! Licensed for malaria in USA)</p> <p>Second-line: chloroquine sensitive malaria - Only in chloroquine-sensitive <i>P. falciparum</i> malaria prevention (Ophthalmological exam periodically if used weekly long term; risk very low in first 5yrs.)</p>	<p>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</p>	<p>19</p> <ul style="list-style-type: none"> • Caution: pts with hepatic failure, G6PD deficiency, pre-existing auditory damage; psoriasis, prophyria (Pregnancy: considered safe) • 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 Interaction¹⁷: Assume same as chloroquine
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American Lung Association

www.lungusa.org/site/apps/nlnet/content3.aspx?c=dvLUK9O0E&b=2060321&content_id={71CC3CFD-4B3E-49C8-AA88-D76EAE1FB9F5}¬oc=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

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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. 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	◆ <i>E. coli, P. mirabilis, K. pneumonia, S. aureus</i>
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} , sulfonyleureas ^{↑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	◆ <i>E. coli, K. pneumonia, S. aureus, Enterococcus faecalis</i> ; (not <i>proteus, pseudomonas</i>)
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 <i>E. coli, Enterococci, & Staph</i> ◆ avoid in renal dysfunction (CrCl <50ml/min); limited tissue penetration; <u>not</u> useful in complicated UTI

Ciprofloxacin {Alternately, norfloxacin & levofloxacin; not moxifloxacin as lower concentration in urine}

Coverage	◆ <i>E. coli, P. mirabilis, K. pneumonia, P. aeruginosa, +/- S. aureus</i> (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; <u>pseudomonal</u> coverage with ciprofloxacin & norfloxacin. ◆ lower doses suitable for uncomplicated UTI; higher doses for complicated UTI & pyelonephritis

Amoxicillin/Clavulanic Acid (Amox/Clav)

Coverage	◆ <i>E. coli, P. mirabilis, K. pneumonia, S. aureus, Enterococcus faecalis</i>
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	◆ usually less effective than SMX/TMP, esp for <i>S. saprophyticus</i> ; however <i>E. Coli</i> resistance uncommon Note: other beta-lactams (amoxicillin, 1 st gen cephalosporins) are alternatives although generally less effective clinically than SMX/TMP.
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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 mirabilis*; 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

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URINARY TRACT INFECTIONS (UTI), ADULT – TREATMENT OPTIONS

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1. Where is your pain the worst? (*this is to differentiate back-dominant vs. leg-dominant pain*) *Leg pain below the knee is most helpful
2. Is the pain intermittent (*even for a few seconds*) or constant?
3. How do the symptoms limit you? Personal care, house, yard, recreation, work.

Intermittent back-dominant pain is mechanical and benign and patient can be reassured

About 90% of patients with acute low back problems spontaneously recover activity tolerance within 1 month. Reassure patient regarding excellent prognosis in most cases of LBP.

Red Flags for potentially serious conditions

Possible fracture	Possible tumor or infection	Possible cauda equina syndrome
Major trauma, such as MVA or fall from height Minor trauma or even strenuous lifting in potentially osteoporotic patient** **Major risks for osteoporosis: - elderly > 65 - post menopausal - steroid use - alcohol - past OP #	Age over 50 or under 20 History of cancer. Constitutional symptoms such as recent fever or chills or unexplained weight loss. Recent factors for spinal infection; recent bacterial infection (e.g. urinary tract infection, TB); IV drug abuse; or immune suppression (steroids, transplant, or HIV). Pain at rest; pain that is worse when supine; severe nighttime pain.	Saddle anesthesia/numbness Recent onset of bladder dysfunction, such as urinary retention, increased frequency or overflow incontinence Severe or progressive neurological deficit in the lower extremity. (sudden bilateral leg weakness)
Examination		
Investigations (if no red flags – not needed in first 4-6 weeks as almost never result in meaningful change in clinical management)		
Lumbar-sacral x-ray	CBC, ESR, CRP, U/A	Immediate consultation
Further imaging? (CT, MRI)	Further imaging? (CT, Bone scan)	Imaging

Natural History of acute low back pain:

- Most people will have improvement in 4-6 weeks and recurrence in 12 months. {30-60% recover ≤1wk; 60-90% within 6wks; 95% within 12wks; however ≤30% will go on to have recurrent or persistent symptoms.}

Prevention is Important!

- Encourage: home exercise program for back health, cardiovascular fitness (walking, etc.), optimize healthy weight, back care principles in lifting, ergonomic interventions for healthy posture.

Advanced imaging studies - limit to:

- Progressive neurological deficits
- Minimal improvement despite 6wks of conservative tx
- Uncontrolled pain
- Cauda Equina Syndrome

Associations with chronic pain syndrome (CPS):

- ♦ Defined by the coexistence of multiple factors of psychosocial dysfunction e.g.:
 - ↓ activity; kinesiophobia
 - depression
 - somatic focus
 - relationship problems
 - pain behaviors
 - medication abuse
 - low self esteem
 - may be issues of secondary gain in some cases; however, in most cases, pain is real*List not exhaustive; consider psychosocial indicators*

♦ Consider CPS when pain history of > 6 months.

♦ Evaluation by multidisciplinary team is useful (chronic pain specialist, physical therapist, psychologist, etc.)

♦ Treatment:

- Education on benign nature of non-specific LBP & helpful role of physical activity as tolerated
- Physical therapy combined with psychological tx
- Home or other exercise program
- ⇒ {consider option of a structured 12 wk program, such as a group program}
- Suitable medication

♦ Progress should be evaluated based function as well as overall pain reduction. This often requires a paradigm shift where function is emphasized more than pain. Acceptance that pain elimination may not be an achievable goal.

♦ Assist client to focus on positive incremental gains that can be seen with a long-term plan!

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.

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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.

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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



CHRONIC NON-MALIGNANT PAIN (CNMP) General Pharmacological Considerations – Supplement Tables

The attached tables supplement the RxFiles newsletter – Opioids in Chronic Non-Malignant Pain Original-Oct-2005

Table 1: Pain Conditions – Specific Drug Therapy Options

- This table lists specific pain related conditions and therapy options that are often included in CNMP. Where possible it notes evidence from randomized controlled trials (RCTs) including numbers needed to treat (NNT) for one patient to benefit, and numbers needed to harm (NNH) for one person to withdraw from therapy due to an adverse event. Cochrane/systematic reviews or meta-analysis have been included. In some cases, evidence is very limited.
- Dosages noted are those that were commonly studied or required to see a benefit. This often varies for the conditions listed. For example, the usual effective doses of amitriptyline in fibromyalgia are in the 10-50mg/day range; in post-herpetic neuralgia, the average effective amitriptyline dose was 75mg/day.
- Therapies that have conflicting evidence or have been ineffective are also noted as such.
- Non-drug therapies are essential for the effective long-term management of CNMP.

Table 2: Overview of Drugs Used in Treatment of Chronic Non-Malignant Pain (CNMP)

- This chart notes some of the CNMP drug options, initial and usual doses, comparative cost, and comments related to various drugs used in pain management. For more detail see also RxFiles Drug Comparison Chart book.

Pearls that might change your Practice

- Amitriptyline is one of the best studied TCAs used in various pain conditions, but **nortriptyline** in a dose of 25-≥50mg HS may often be effective and better tolerated (less sedation, less dry mouth, less weight gain, etc.).
- **Gabapentin doses** with evidence for effectiveness in neuropathic pain are often in the 900-1800mg/day range (~1800mg commonly required in trials); some patients lack benefit due to subtherapeutic dose.
- If you want a patient to have an adequate trial on a drug that often has side effects, start at a low dose, **titrate up gradually**, and **counsel** that side effects often diminish with 1-2 weeks. Initial and usual target doses are noted where applicable in Table 2. A gradual tapering can also reduce withdrawal syndromes.
- Choose a drug that may cover multiple complaints. (e.g. a person with frequent headache/migraine and weight gain concerns may benefit from topiramate; however remember tolerability, cost and evidence lacking in CNMP)
- Topical agents (capsaicin, NSAIDs, lidocaine 5%, morphine if painful open ulcer) may have a role in **select** conditions.
- **Sleep** is a frequent concern. If pain is a cause of poor sleep, consider a longer-acting analgesic to cover the nighttime period and/or agents that are helpful in sleep/pain disorders (amitriptyline 10-50mg HS, methotrimemprazine 5-25mg HS).
- **Other anecdotal pearls:** 1) corticosteroid spray topically to decrease fentanyl patch irritation. 2) Haldol 0.5mg HS-BID PRN to reduce severe nausea but avoid sedation. 3) Favor gabapentin dosing towards bedtime (e.g. 300mg BID, 600mg HS) to reduce daytime side effects. 4) If fentanyl patch required but too potent, uncover only half of patch (or tape half) to decrease dose. 5) In some locales, generic hydromorphone has lower street value than Dilaudid. 6) 10% of Caucasians can not metabolize ^{CYP2D6} codeine or tramadol to active metabolites; thus considered opioid naïve.

New Drugs Included in the Tables

1. **Pregabalin LYRICA**
 - An anticonvulsant indicated for post-herpetic neuralgia and diabetic neuropathy (NNT: >3; NNH: 3.7-16 depending on dose).
 - It is similar to, but has not been directly compared to the alternative – **gabapentin**. It is new – thus lacking long-term safety data, and costs more than generic gabapentin or TCAs (see chart). Side effects such as dizziness, somnolence, weight gain, edema and abnormal thinking are likely to be a concern at higher dosages.
 - The risk of peripheral edema increases with glitazones (e.g. **ACTOS, AVANDIA**)
 - {Systematic Review Oct 2007: drugs for neuropathic pain: http://www.ohsu.edu/drugeffectiveness/reports/documents/NP_Final%20Report_Original.pdf}
2. **Tramadol**
 - Tramadol is a weak mu opioid agonist with actions on serotonin and noradrenaline. A Cochrane review found it to be effective in neuropathic pain (n=338; doses of 100-400mg/day; NNT=3.8^{CI=2.8-6.3}; NNH=8.3^{CI=6-17}). It has been previously available in other countries but is relatively new to North America. It carries an increased seizure risk and potential for a Addiction although risk is thought to be lower than comparative opioids.
 - **Tramadol/Acetaminophen TRAMACET:** is a short acting combo product for treatment of acute pain with a maximum of 5 days or for mod-severe pain in adults. Its use in CNMP will be limited by the need for frequent dosing, the acetaminophen component, and the relatively high cost compared to Tylenol #3 and other opioids.
 - **Tramadol long-acting ZYTRAM, TRIDURAL, RALIVIA:** is available in Canada as of 2007. These formulations are more suitable for the treatment of chronic pain / neuropathic pain.
3. **SATIVEX** –information included in RxFiles Q&A - Cannabinoids an Overview at www.rxfiles.ca

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- ³ Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. *Neurology.* 1986 Jul;36(7):995-7.
- ⁴ Dodick D, Freitag F. Evidence-based understanding of medication-overuse headache: clinical implications. *Headache.* 2006 Nov;46 Suppl 4:S202-11.
- ⁵ 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.
- ⁶ Wiffen P, McQuay H, Moore R. Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev.* 2005 Jul 20;(3):CD005451.
- ⁷ Grosseth G, Cuccia G, Alkense 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-)
- ⁸ Turk U, Ilhan S, Alp R, Sur H. Botulinum Toxin and Intractable Trigeminal Neuralgia. *Clin Neuropharmacol.* 2005 July/August;28(4):161-162.
- ⁹ 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.
- ¹⁰ Baout J, Vinik AJ, 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 Diabetics peripheral neuropathic pain treatment. Pharmacist's Letter Aug 2006.)
- ¹¹ 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 WJ, 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))
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- ¹³ Seward B, Rutkove. A 52-Year-Old Woman With Disabling Peripheral Neuropathy: Review of Diabetic Polyneuropathy. *JAMA.* 2009;302(13):1451-1458.
- ¹⁴ 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.
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- ²² Watson CP, Moubin 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.
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Additional articles:

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Pain Links:

Geriatrics: <http://www.geriatricsandaging.ca>

RxFiles Drug Comparison Charts – See order form at www.RxFiles.ca

Also – Binder Index of RxFiles Newsletters, Q&A’s and Comparison Charts – are updated and posted on website!

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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/

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NSAIDS, COXIBs & OTHER ANALGESICS: Comparison Chart

¹ Micromedex 2010

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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.

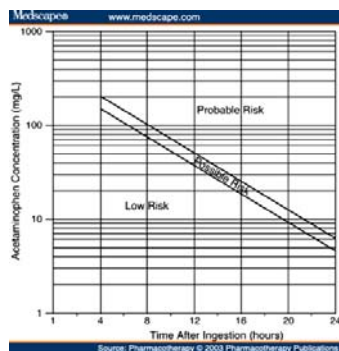
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Long-term use of NSAIDs is associated with a reduced incidence of oral cancer (including in active smokers), but also with an increased risk of death due to cardiovascular disease. These findings highlight the need for a careful risk-benefit analysis 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 $\geq 150\text{mg/kg}$ and 8hr post, may start n-acetylcysteine while awaiting levels; TOXIC levels: 4hr level $>993\text{umol/L}$; 6hr $>728\text{umol/L}$; 8hr $>496.5\text{umol/L}$; 24hr $>29.8\text{umol/L}$ } (LFTs: AST usually \uparrow first) Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med*. 2008 Jul 17;359(3):285-92.



(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.

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-Sukhni 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.

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-))

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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))

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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>

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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.

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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, Paradis 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.

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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.

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.

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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>

Dart 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.

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. Cephalgia. 2006 May;26(5):537-47.

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.

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 Med. 2009 Jan 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. Epub 2008 Mar 28.

Etiman 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.

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.

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.

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 tendonitis 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.

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-)

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.

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 Prohibits sale of Bextra http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/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 undecleared 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 Homeopathy 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 chlorpheniramine.

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, Castellsgue 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.

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.

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.

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

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.

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.

Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to **acetaminophen and asthma** in children. *Obstet Gynecol*. 2009 Dec;114(6):1295-306.

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.**

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.

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.

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.

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Mamdami 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 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))

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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-))

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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 prioritize risks (consider alternatives); prescribe lowest dose for shortest time possible.}

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Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with **acute renal failure**: A population-based, nested case-control analysis. *Am J Epidemiol.* 2006 Nov 1;164(9):881-9. Epub 2006 Sep 27. There was a significant association for both selective and nonselective NSAIDs with acute renal failure, but confirmatory studies are required.

Scott PA, Kingsley GH, Smith CM, et al. Non-steroidal anti-inflammatory drugs and **myocardial infarctions**: comparative **systematic review** of evidence from observational studies and randomized controlled trials. *Ann Rheum Dis.* 2007 Oct;66(10):1296-304. Epub 2007 Mar 7. (The comparative risk of myocardial infarction (MI) with cyclo-oxygenase-2-specific drugs and traditional non-steroidal anti-inflammatory drugs (NSAIDs) was determined. METHODS: The results of studies of a suitable size in colonic adenoma and arthritis that had been published in English and from which crude data about MIs could be extracted-were evaluated. Medline, Embase and Cinahl (2000-2006) databases, as well as published bibliographies, were used as data sources. Systematic reviews examined MI risks in case-control and cohort studies, as well as in randomised controlled trials (RCTs). RESULTS: 14 case-control studies (74 673 MI patients, 368 968 controls) showed no significant association of NSAIDs with MI in a random-effects model (OR 1.17; 95% CI 0.99 to 1.37) and a small risk of MI in a fixed-effects model (OR 1.32; 95% CI 1.29 to 1.35). Sensitivity analyses showed higher risks of MI in large European studies involving matched controls. Six cohort studies (387 983 patient years, 1 120 812 control years) showed no significant risk of MI with NSAIDs (RR 1.03; 95% CI 1.00 to 1.07); the risk was higher with rofecoxib (RR 1.25; 95% CI 1.17 to 1.34) but not with any other NSAIDs. Four RCTs of NSAIDs in colonic adenoma (6000 patients) showed an increased risk of MI (RR 2.68; 95% CI 1.43 to 5.01). Sixteen RCTs in arthritis (45 425 patients) showed more MIs with cyclo-oxygenase-2-specific drugs (Peto OR 1.6; 95% CI 1.1 to 2.4), but fewer serious upper gastrointestinal events (Peto OR 0.40; 95% CI 0.31 to 0.53). CONCLUSION: The overall risk of MI with NSAIDs and cyclo-oxygenase-2-specific drugs was small; rofecoxib showed the highest risk. There was an increased MI risk with cyclo-oxygenase-2-specific drugs compared with NSAIDs, but less serious upper gastrointestinal toxicity.)

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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.

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New coxib - Etoricoxib (**ARCOXIA**) - NOT approved by FDA (April, 2007)

Lumiracoxib – hepatic toxicity – deregulation in Australia. <http://www.medadnews.com/News/index.cfm?articleid=467159>

OPIOID ANALGESIC: COMPARISON CHART

Extras:

- 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; may have ↓ GI effects but similar CNS effects to other opioids. (50-75,100mg tabs e.g. 50mg q4-6h prn.)
- Morphine + naltrexone (EMBEDA): available in USA; naltrexone added to ↓ abuse risk.
- hydrocodone + ibuprofen (REPREXAIN, VICOPROFEN, others): available in USA. (5/200, 7.5/200, 10/200 mg)
- Oxycodone + ibuprofen (COMBUNOX): available in USA. (5 / 400 mg)
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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 8th edition, 2008.

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. Pharmacist's Letter. Dec 2005).

⁸ Other Opioid Conversion (e.g. tramadol): <http://databaseinnovationsdraft.com/OpioidConversionChart2007.pdf>

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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.

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Analgesic options for patients with **allergic-type opioid** reactions. Pharmacist's Letter/Prescriber's Letter 2006;22(2):220201.

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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.)

Babb, Malaika, Koren, Gideon, Einarson, Adrienne. Treating **pain during pregnancy**. Can Fam Physician 2010 56: 25-27.

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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.

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.

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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.

Opioid Intolerance:

- **Pseudoallergy (COMMON!** – may use non-opioid, lower opioid dose, alternate opioid even from same class, addition of H1 diphenhydramine +/- H2 ranitidine 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 Feb 07}

- **Oral Oxymorphone (Opana, Opana ER)**
 - i. **Potency** is about 10x more potent than morphine! Caution!
 - ii. Immediate release: 5, 10mg tabs
 - iii. Extended release; 5, 10, 20, 40 mg tabs

Additional References & Links:

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

Treatment Agreements:

Medscape discussion on use in primary care. <http://www.medscape.com/viewarticle/711659?src=mp&spon=30&uac=93517FV>
RxFiles sample: <http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.doc>

Extras, Links & References:

♦ **AMETOP: tetracaine** (amethocaine) **4% Gel** : Adults (including geriatrics) & children over 1 month of age: Apply contents of the tube to the skin starting from the centre of the area to be anesthetized & cover with an occlusive dressing. The contents expellable from 1 tube (approximately 1g) will cover & anesthetize an area of up to 30cm² (6x5 cm (- 3/4 area of a credit card)). Smaller areas of anesthetized skin may be adequate in infants & small children. Adequate anesthesia can usually be achieved for venepuncture following a 30-minute application time, & for venous cannulation following a 45-minute application time; after which the gel should be removed with a gauze swab & the site prepared with an antiseptic wipe in the normal manner. It is not necessary to apply tetracaine gel for longer than the above times & anesthesia is maintained for 4 to 6 hrs in most patients after a single application. [Clinical Trial in progress: Ametop vs Maxilene: <http://www.druglib.com/trial/02/NCT00353002.html>]

♦ **EMLA (lidocaine and prilocaine)** – for intact skin, requires occlusion, needs to be applied for at least one hour **Dose** — To attain adequate anesthesia, 1 to 2 g of EMLA cream should be applied per 10 sq cm (approximate size of a Canadian “toonie”) of skin and covered with an occlusive dressing for 45 to 60 minutes. The maximum application areas recommended for children are Less than 10 sq cm — 100 sq cm (~ 2.5x area of a credit card); 10 to 20 sq cm — 600 sq cm; Greater than 20 sq cm — 2000 sq cm ; causes vasoconstriction.

See www.usask.ca/pediatrics/services/pain for information for parents on children's pain

- ♦ **acetaminophen use with vaccination:** may ↓ immunogenicity ∴ avoid if possible.
- ♦ **Benzocaine** –in NG tube placement controversial¹⁰ Causes methemoglobinemia!!! **AVOID!**
- ♦ **Lidocaine iontophoresis (Numbly Stuff):** mild electric current penetrates skin more quickly; effective in 10-20min. ⁹⁹ EMLA similar or slightly better.^{60,61} (Tingle may be bothersome.)
- ♦ **TAC** tetracaine 0.5% / epinephrine 0.05% / cocaine ≤11.8%. ♦**AE:** seizures, arrhythmias, fatal: requires narcotic storage (LET preferred)
- ♦ **Cancer Pain:** Reference ⁶²
- ♦ **Urethral Catheterization:** lidocaine gel 2 min prior to insertion while setting up then use as the lubricant as well (video: <http://www.ahshealthcare.com/topics/meds/addpartments/urology/catheterization/index.htm>)
- ♦ **Acetaminophen vs ibuprofen:** <http://www.cps.ca/english/statements/DT/dt98-01.htm> For fever.⁶³
- ♦ **SHR Peds Pain Links:** <http://www.usask.ca/pediatrics/services/pain/>
- ♦ **CADTH.** Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency: A Review of Clinical Outcomes and Economic Evaluation http://cadth.ca/media/pdf/00428_Short-Acting-Procedural-Sedation_to_e.pdf

Health Canada Advisory, March 2009: Caution regarding serious adverse events, including fatalities, with excessive application of topical anesthetics in adults & peds!

References {RxFiles Pediatric Pain Chart: Treatment Considerations, Q&As}

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Pain Intensity Scoring:

- ♦ Choose a scale that is age appropriate to patient & become familiar with using!
- ♦ Interpret in light of any other pain related physical factors (e.g. heart rate)
- ♦ Also interpret according to trends for improvement or worsening of pain control
- ♦ Sherbrooke algorithm for acute pain in children (post-op): gave regular analgesic according to pain scale: {0-3: acetaminophen; 3-6: naproxen + acetaminophen; 6-9: morphine + naproxen + acetaminophen; 9-10: notify MD. Overall ↓ in pain scores & a ↓ in opioid requirement.}
- ♦ Other links: **Visual Analogue Scale:** suitable for age 7+ ([McGrath PA, Seifert CE, Speechley KN, et al.](http://www.mcgill.ca/ce) A new analogue scale for assessing children's pain: an initial validation study. *Pain.* 1996 Mar;64(3):435-43.) **Oucher Scale:** age 3-12. <http://www.oucher.org/history.html> BMJ Clinical Review: Pain Management and Sedation for Children in the Emergency Setting: http://www.bmj.com/cgi/content/full/339/oct30_1/b4234

FLACC SCALE – for assessing pain in very young children non-verbal; suitable for cognitively impaired			
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

♦ Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.

♦ From *The FLACC: A behavioral scale for scoring postoperative pain in young children*, by S Merkel and others, 1997, *Pediatr Nurse* 23(3), p. 293-297. Copyright 1997 by Jannetti Co. University of Michigan Medical Center.

Faces Pain Scale – Revised (FPS-R) – age 4+

This is a thumbnail image. The full-size FPS-R with instructions is available on page 3 at <http://painsourcebook.ca/pdfs/pps92.pdf> Numbers are not shown to children.

0 2 4 6 8 10

From: Hicks CL, von Baeyer CL, Spafford PA, Van Korlaar I, Goodenough B. The *Faces Pain Scale – Revised*. Toward a common metric in pediatric pain measurement. *Pain* 2001;93:173-183. ©2001 International Association for the Study of Pain. Reprinted with permission.

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Extras

Table: Ten-year absolute fracture risk for women⁹

Age (years)	Low Risk < 10%	Moderate Risk 10% - 20%	High Risk > 20%
	LOWEST T-SCORE Lumbar spine, total hip, femoral neck, trochanter		
50	> - 2.3	- 2.3 to - 3.9	< - 3.9
55	> - 1.9	- 1.9 to - 3.4	< - 3.4
60	> - 1.4	- 1.4 to - 3.0	< - 3.0
65	> - 1.0	- 1.0 to - 2.6	< - 2.6
70	> - 0.8	- 0.8 to - 2.2	< - 2.2
75	> - 0.7	- 0.7 to - 2.1	< - 2.1
80	> - 0.6	- 0.6 to - 2.0	< - 2.0
85	> - 0.7	- 0.7 to - 2.2	< - 2.2

Table 3: Ten-year absolute fracture risk for men⁹

Age (years)	Low Risk < 10%	Moderate Risk 10% - 20%	High Risk ^a > 20%
	LOWEST T-SCORE Lumbar spine, total hip, femoral neck, trochanter		
50	>-3.4	<=-3.4	---
55	>-3.1	<=-3.1	---
60	>-3.0	<=-3.0	---
65	>-2.7	<=-2.7	---
70	>-2.1	-2.1 to -3.9	<-3.9
75	>-1.5	-1.5 to -3.2	<-3.2
80	>-1.2	-1.2 to -3.0	<-3.0
85	>-1.3	-1.3 to -3.3	<-3.3

These tables were published in Can Assoc Radiol J 56, Siminoski K et al, Recommendations for Bone Mineral Density Testing in Canada, page 178-188, Copyright Canadian Association of Radiologists 2005

^a Blank spaces appear because men are not considered to be at high risk until age 70.

- Using the 10-year fracture risk estimate to determine treatment decisions has some **limitations**:
 - It is based on epidemiological data²⁵ from a cohort of Swedish men & women that
 - Counted **all** fractures (not just osteoporotic fractures) of hip, forearm, proximal humerus, and vertebra, and
 - Correlated them to the **femoral neck** bone mineral density.
 - Osteoporosis Canada recommends using the **lowest** T-score at lumbar spine, total hip or trochanter as well as the femoral neck to predict combined fracture risk despite the fact the data²⁵ is derived from the femoral neck BMD only.
 - There is currently no data to link the BMD from the other sites to long-term fracture risk.
- However there is evidence that the approach is valid.
 - A recent retrospective cohort study of Manitoba women compared the 10-year risk estimates with development of hip, clinical vertebral, forearm, and humerus fractures. It also looked at the effect of previous fractures and systemic corticosteroid use on development of fractures. See **Table 4** for results.²⁶

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QFractureScore <http://www.qfracture.org/>

Simple Calculated Osteoporosis Risk Estimation (SCORE) tool <http://osteod.org/tools.php> (sensitivity 91%, specificity 40%)^{BMD}

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-very common (up to 90% during course of dementia), a major cause of distress to patients, families & caregivers; risk to self plus others, & huge cost in terms of institutionalization.

-not just agitation but non-agitated Sx (apathy, withdrawal, daytime somnolence {circadian rhythm disturbances}, depression, disinhibition etc.)

Diagnosis: (Evaluate behavior → **ABC's Antecedents** (causes: **Physical Intellectual Emotional Cultural Environmental Social**), **Behaviors & Consequences**)

◆ History ^{Down's Sx}, physical exam, cognitive tests ^{Feldman CMAJ'08} & nurse observations; collateral family info essential! ◆ **Lab Tests-Recommended:** CBC, electrolytes, calcium, B12, serum glucose & TSH; **Optional:** BUN & SCr, magnesium, LFTs, arterial blood gases, ECG, CT/MRI if suggestion of structural lesion eg. renal failure, brain tumor, normal pressure hydrocephalus, subdural hemorrhage ◆ **Eliminate delirium source** ^{Young BMJ'07} - eg. **meds** eg. opiates, benzos, anticholinergics /**withdrawal reactions** /**DI's**, dehydration & infections (if indicated: urinalysis/C&S, chest x-ray, lumbar puncture ^{if suspicion of meningitis})

Tx: (attempt **taper/withdraw** of meds after a **3 month behavioral stability period**) {Tx comorbidity ^{eg. infection, pain, constipation, depression, psychosis}}

- ◆ Appropriate **environmental, exercise & behavioral** measures should be explored! Reserve **drug therapy for situations** where non-pharmacological interventions have been fully explored & implemented or in cases of **significant dangerous risk**. Specify problem behavior (eg. "agitation" is less useful than "screaming", "hitting when bathed"). Identify what brings it on & what makes it go away. Identify whom the behavior is bothering (pt, caregiver/staff or other pts). **Human interactions** ^{eg. activity}, adequate staff ^{eg. nursing home} & proper environment most critical.
- ◆ If drug treatment (ie. Sx have no physical cause, are unrelated to other medications or unresponsive to non-pharmacological interventions), generally start with **1/3 to 1/2 of usual adult** dose & titrate up slowly individualizing dosages for each pt
- ◆ If receiving treatment, **reevaluate** drug regimen & non-pharmacologic strategies at regular intervals (ie. 3-6 months)

Start Low, Go Slow!

DEPRESSION:
(anxiety often coexists thus use antidepressants with anxiolytic properties)

- ↓ mood, apathy ^{may worsen} & amotivation

Mild → non pharmacologic

Moderate to severe →
ANTIDEPRESSANT Tx

SSRI/venlafaxine → **1st line**

In general → may be good for depression, depression assoc. agitation, emotionality & irritability
Allow >6 week for adequate trial at an adequate dose

↓

SSRIs: **SE:** nausea, vomiting, restlessness, falls, insomnia, ↓weight, agitation ^{initially} & hyponatremia
Citalopram 10-30mg/d, **sertraline** 25-100mg/d, **fluvoxamine** 25-150mg/d, **paroxetine** 10-30mg/d etc.
Venlafaxine: 37.5-225mg XR od {Similar SE as SSRI, but has high GI SE & may ↑ blood pressure}
Bupropion ⚡ 100-150mg bid or 150-300mg XL ⚡ ⚡ to activate pt with withdrawal or psychomotor retardation
TCA's: Avoid anticholinergics → less with **nortriptyline** 10-75mg hs & desipramine 25-150mg/d;
SE: hypotension, blurred vision, urinary hesitancy, cardiac conduction changes
Mirtazapine: consider if anorexia/anxiety/sleep problem; **RD** ^{form} if difficulty swallowing; ≤7.5-45mg/d
Moclobemide: role in anxiety & mood dx but may ↑ stimulation; 100mg od-300mg bid
Trazodone: low doses used for sedation & some anxiolytic effect;
monitor for hypotension, serotonin syndrome & rare priapism in ♂
Consider **ECT** in management of treatment resistant or severe depression

PSYCHOSIS/AGITATION:
Psychosis:
1) Positive Sx -delusions & hallucinations or paranoia
2) Negative Sx -poverty of thought, apathy & social withdrawal

BPSD:
Agitation -pacing, chanting, psychomotor, agitation etc.
Aggression
ANTIPSYCHOTIC Tx
-first designate target Sx (**not wandering or mild Sx**)
-try to minimize **sedation**, ↑confusion, hypotension & **EPS**
-**target Sx** (hallucinations, delusions, hostility, **aggression**, agitation, & violent/high risk behavior)

haloperidol 0.25-2mg/day
risperidone 0.25-2mg/day
quetiapine 12.5-150mg/day
olanzapine ⚡ ▼ 1.25-10mg/day } monitor for SE & may attempt med tapering q6month

◆ Newer agents as effective but generally better tolerated.
Monitor for **SE:** sedation, hypotension, falls¹²⁵, EPS (drooling, rigidity & akinesia), anticholinergic SE ^{dry mouth, delirium, constipation},
↑weight/lipids/diabetes, ? ↑stroke/death & tardive dyskinesia.
◆ Pts with **Lewy bodies** (15% of dementias) have
↑sensitivity to neuroleptic meds (quetiapine an option)

Start Low, Go Slow!

Start Low, Go Slow, But go!

ANXIETY:

-use non-pharmacological intervention
-minimize provocation

-consider **antidepressant** therapy if anxiety is secondary to depression or very chronic in nature

-consider
ANTI-ANXIETY Medication

lorazepam 0.5-2mg/day
oxazepam 5-30mg/day
bupirone 10-30mg/day
trazodone 25-100mg/day
alprazolam 0.125-2mg/day
clonazepam 0.125-3mg/day (caution long-acting)

Benzodiazepines-caution!
SE: sedation, ataxia, altered sleep architecture, motor & **cognitive** impairment & propensity to cause withdrawal Sx when D/C. Paradoxical excitation, **disinhibition** & **falls** may occur. An intermediate acting such as temazepam/oxazepam/lorazepam can be best used for **short term**, if possible sleep/anxiety states or before planned anxiety provoking situations

Bupirone: ⚡
low sedation, ↓DI's, ↓ withdrawal & ↓ impairment of motor fx; option → chronic anxiety but **onset ~3wk** delay

APATHY
Tx with external activity & environmental measures. Possible options with concerns: methylphenidate & dopamine agonists.

MOOD STABILIZERS: some use in agitation, aggression, hostility, sleep-wake disturbance cycle & mania
◆ **divalproex** 125-750mg/day -fewer **SE:** sedation, diarrhea, tremor, nausea, weight gain, hair loss & ↑ liver tests & fewer DI's, but less evidence for use.
◆ **carbamazepine** 100-600mg/day -more **SE:** sedation, ataxia, falls, skin rash, headache, leukopenia & ↑ liver tests & multiple DI's
BETA BLOCKER-propranolol 10-80mg/d; possible ↓ aggression; SE: ↓ heart rate & hypotension CI: asthma, PVD & possibly depression Hx
CHOLINESTERASE INHIBITORS -modest cognitive, functional & **behavioral** benefits; may help **apathy**, hallucinations & delusions (not better than placebo for agitation ^{Howard NEJM'07}), may help **Lewy Body dementia** to ↓ visual sx's.
Consider **cholinesterase inhibitors** in Alzheimer's (**donepezil, galantamine, rivastigmine**) ⚡ ⚡; SE: n/v, fatigue, anorexia, ↓ heart rate
Memantine ⚡ ⊗ is a recently approved NMDA receptor antagonist which may have a role similar to cholinesterase inhibitors.

CI contraindication DI drug interaction Dx disorder fx function HR heart rate Hx history n/v nausea/vomiting Pt patient PVD peripheral vascular disease SE side effect Sx symptom Tx treatment ⚡ Exception Drug Status Sask. ⚡ non-formulary in Sask. ⊗ not covered by NIHB ▼ covered by NIHB ⚡ prior approval NIHB

Behavioral & Psychological Symptoms of DEMENTIA (BPSD) Treatment 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 2010

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Useful Web sites:

Alzheimer Society Canada www.alzheimer.ca

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- (Yousry TA, Major EO, Ryschewitsch 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 Program 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 Elan 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
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- FDA Sep/09 documents 13 PML cases <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107198.htm>
- October 27, 2009 — The European Medicines Agency (EMA) 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 EMA 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 EMA notes. The release was a round-up of EMA 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, the US Food and 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.
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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.
- ♦ PROPHYLAXIS: 1st line: beta-blockers (propranolol, metoprolol), TCAs, valproic acid, topiramate.

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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.

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Canonica 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.

Canonica 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 & wild Mexican yam) in a susceptible patient. *Postgrad Med J.* 2005 Apr;81(954):266-7.

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 flashes. *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.

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.

FDA Concern over Bio-Identicals Jan/08: **Bio-Identicals: Sorting Myths from Facts** <http://www.fda.gov/consumer/updates/bioidenticals010908.html>.

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.

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.

Genistein: Alteritano 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, Alteritano M, et al. Effects of the phytoestrogen genistein on hot flashes, 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):134. Twenty-four months of tx with genistein has positive effects on BMD in osteopenic postmenopausal women.

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.

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 flashes: 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 flashes. (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. **Progesterin** 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-Celinkier 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.

Huang AJ, Grady D, Jacoby VL, Blackwell TL, Bauer DC, Sawaya GF. **Persistent hot flashes** in older postmenopausal women. Arch Intern Med. 2008 Apr 28;168(8):840-6. For a **substantial minority of women, hot flashes are a persistent source of discomfort** into the late postmenopausal years. Identification of risk factors for hot flashes may help guide evaluation and treatment in this population.

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):11.

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.

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.

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.

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.

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.

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, Andreassen AH, Jacobsen RK, Nielsen LH, Agger C, Lidgaard 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 estradiol, or vaginal estrogens were not associated with a risk of breast cancer.

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.

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.

Morch Lina Steinrud; Lokkegaard Ellen; Andreassen Anne Helms; et al. Hormone Therapy and **Ovarian Cancer**. JAMA. 2009;302(3):298-305.

Motivata 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 Flashes: 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 flashes. (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.

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) }

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.

Osmer 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]

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;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-))

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 this result.

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)

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.

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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-)

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Suckling J, Lethaby A, Kennedy R. **Local oestrogen for vaginal atrophy** in postmenopausal women. *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD001500.

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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.

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))

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Osteoporosis:

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- Alonso-Coello P, Garcia-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.
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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.
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- 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.
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- 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.
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- 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))
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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.

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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.

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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.

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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 [Forsteo]) 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. **Lasofloxifene** in postmenopausal women with osteoporosis. *N Engl J Med* 2010 Feb 25; 362:686.

de Groen PC, Lubbe DF, Hirsch LJ, Dafiotis 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.

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.

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.

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.

Gnant M, Mlineritsch B, Schippering 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):131.

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.

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.hs-sc.ca/dhp/mps/medeff/advisories-avis/prof/2006/evista_hpc-ops_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 women who take raloxifene 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))

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)

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.

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))

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.

Kakkaria 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.

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 (**SEFP**) 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.

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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.

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.

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):135. 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.

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Mackey DC, Liu 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 evidence suggests that many agents are effective in preventing osteoporotic fractures, data are insufficient to determine the relative efficacy or safety of these agents.

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.

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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))

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.

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.

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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.

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.

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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.

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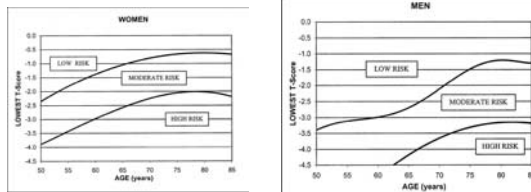
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HERBAL DRUG INTERACTION CHART

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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).

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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 piperidino vardenafil, an analog of vardenafil, the active ingredient in Levitra, another FDA-approved prescription drug for ED. Neither the thione analog of sildenafil nor piperidino 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 hazard 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 **Virility 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/universallab04_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 sulfoildenafil, 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 of sibutramine & phenolphthalein.

FDA Nov/09 & RockHard Laboratories notified consumers that **RockHard Weekend**, a product sold as a dietary supplement, contains sulfoildenafil, 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 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 Sulfoildenafil.

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 **MaxXtreme**, 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.

Fish Oil Testing: Independent test for contaminants Nutrasource Diagnostics at the University of Guelph 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.
- 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-))
- 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.
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- Health Canada is warning Aril/06 consumers not to use advises consumers not to use unapproved 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 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; **Saifi**, 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 Herbs 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 Herbs 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

Health 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; Deguozechengtianxia** 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 **Vigoret 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 **Lexsel 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/07 is advising consumers not to use a product called **Eden Herbal Formulations Serenity Pills II** because it contains the undeclared drug **estazolam**.

Health Canada April/07 is 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, Enhenix 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 SleepPlus TCM or BYL SleepPlus**, 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 methylidienolone 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 **Kui 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. **Deguozechengtianxia** 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 mehydrolin. **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 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 phenolamine.
- Health Canada June/08 is advising that **Desire** contains Phenolamine, 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 Shanghai, Strong Testis, Shanghai Ultra, Shanghai Ultra X, Lady Shanghai, Shanghai Regular (also known as Shanghai Chaojimengnan), Actra-Sx, An unknown product containing the plant Lycium barbarum L., Adam Free, NaturalUp, Erexta, Yilishen, Blue Steel, Hero, & Natural 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-Itly-Power (VIP) Tabs**. The U.S. Food and Drug Administration has warned consumers not to use Viril-Itly-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, Enhnix 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 II 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.
- 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, Menery 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 **Natural 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 sulfoildenafil (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, Brazilian Pure, Anti-aging Vital Rez V, Weight Loss Vital Acai, 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 acetic acid. U.S. FDA: **RockHard Weekend** contains sulfoildenafil; & **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.

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 & 2D after 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 sulfoildenafil, 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 Capsule after 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.

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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.

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))

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.

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Perri D, Dugoua JJ, Mills E, Koren G. Safety & efficacy of echinacea (*E. angustifolia*, *purpurea* & *pallida*) during pregnancy & lactation. *Can J Clin Pharmacol*. 2006 Fall;13(3):e262-7. Epub 2006 Nov 3.

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)

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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.

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.

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

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- 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>
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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
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.

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BENZODIAZEPINE (BZ) COMPARISON CHART

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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

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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):322-9. 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.) (Juurink 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.) (Olsson 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 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.

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ANTIPSYCHOTIC COMPARISON CHART

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SEDATIVE COMPARISON CHART

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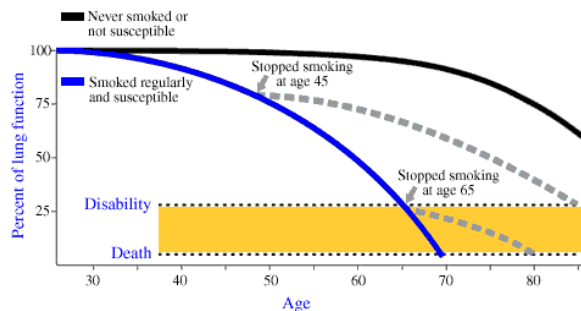
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Web sites:

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>

Global Initiative for Asthma (GINA) <http://www.ginasthma.com>

INHALATIONAL DEVICES and MONITORING TOOLS

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www.inspiratory.com "In-check DIAL" bibliography

Cochrane Reviews – Other Therapies Summary (<http://www.update-software.com/publications/cochrane>)

1. **Acupuncture:** lack evidence for acupuncture, acupressure or electrostimulation.
2. **Exercise:** Most trials too small to reliably associate any effect of intervention.
One trial offered evidence for exercise aiding smoking cessation.
3. **Anxiolytics:** Lack evidence but possible effect.
4. **Mecamylamine** (nicotine antagonist): Limited data (2 small studies); not effective alone, may enhance effectiveness of NRT
5. **Opioid antagonist (naltrexone):** -limited data (2 studies), not possible to confirm or refute whether it helps smokers quit; need larger trials
6. **Silver acetate:** little evidence to support, may be reflective of poor compliance

7. **Lobeline:** no evidence from long-term trials that it can aid smoking cessation
8. **Other Antidepressants:** moclobemide trial showed significant effect at 6 months, none @12 months; SSRI's no evidence of clinically important benefits; venlafaxine trial failed to show significant increase in cessation compared to nicotine patch & counseling alone, but confidence intervals do not exclude effect
9. **Nicotine:** the different forms of NRT were all significantly more effective than control
10. **Clonidine:** some evidence for being efficacious, but appropriateness not well defined & needs more trials.³
11. **Topiramate:** potential to be useful in smoking cessation, especially in those with alcohol dependence, but more data is required before conclusions should be drawn.³⁵
12. Other references of interest: ^{36,37,38,39,40,41,42,43,44,45,46}, Tools to assess dependence. E.g. Fagerstrom Tolerance Scale ⁴⁷

CHAMPIX / Varenicline – for Smoking Cessation

■ **Perspective – at 52wks**

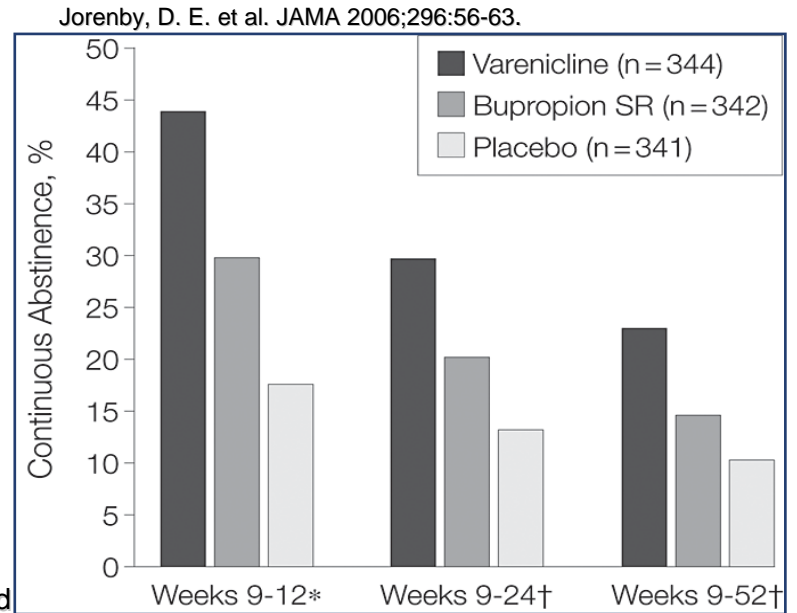
⇒ note: most of the industry ad claims look a bit more impressive due to analysis of the 52 week trials at their 12 week mark {e.g. at 12 weeks, company states 4x better than placebo and 2x better than Zyban}. Cessation success rates decline steadily throughout the 1 year period. An analysis at 52 weeks is more realistic and helpful in predicting long-term success:

- 2.8x better than Placebo
- NNT= 8 (95% CI: 6, 11)
- 1.6x better than Bupropion (Zyban)
- NNT= 14 (95% CI: 9, 34)

■ **Additional 12 wks: NNT=15**
(1 extra success for every 15 people who take an extra 12 weeks.)

■ **Considerations:**

- Funding by maker of Champix
- Relatively new drug – limited safety data
- Cost: \$390/12 weeks
 - \$200 more per 12wk course than Zyban
- SE:
 - nausea 30%;
 - wt gain (12 wk) 2.6kg vs 2kg for Zyban
 - behavior & mood changes?
 - FDA MedWatch ^{Feb/08}: 491 suicidal reports; 39 completed



Summary: Compared to ZYBAN, 12 weeks of varenicline (Champix) offers:

- Advantages: - one extra person successfully quitting at 1 year for every 14 patients treated. ^{based on 2 RCTs}
- Disadvantages: - more nausea, weight gain, and potentially mood/behavior changes
- relatively new drug with some potential unknowns (in terms of adverse reactions, drug interactions, etc)
- \$200 more per person (not bad for 1/14 who might get extra benefit, but not good for the other 13 people.)
- Qualifier: - above based on studies, all funded by the manufacturer with the potential for associated bias

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. ^{xviii,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.}

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Modified Fagerström Test for Nicotine Dependence

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.

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- 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>
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Health Canada July/07 Unauthorised 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>)

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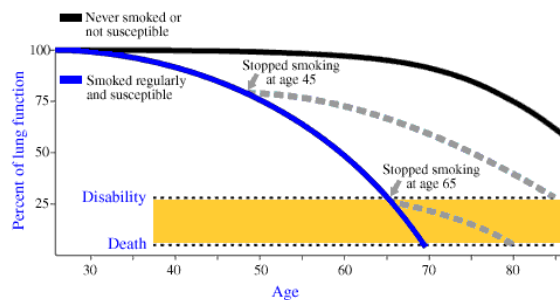
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May/09 **CNN**: The average potency of marijuana, which has risen steadily for three decades, has **exceeded 10 percent** for the first time, the U.S. government will report on Thursday. Scientists working for the government predict that potency, as 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>
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- 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>
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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.
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Additional information about Mircera (Web-only)

<p>Methoxy polyethylene glycol-epoetin beta MIRCERA ¹¹</p> <p>Single-dose vials (solution): 50, 100, 200, 300, 400, 600, 1000 µg/mL</p> <p>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</p>	<p>✓ Tx of anemia with CKD</p> <p>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.</p>	<p>SubQ in ND-CKD & PD-CKD; IV or SubQ in HD-CKD</p> <p>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.</p> <p>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)</p> <p>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.</p>	<p>✗ ⊗</p> <p>Not on formulary. Not yet avail. in Canada, but NOC received Mar 2008</p>
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Erythropoiesis Stimulating Agents (ESA) in Anemia of Chronic Kidney Disease (CKD): Therapeutic Alternatives

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Management Of Substance Abuse In Emergency

Aim: ↓ morbidity & mortality; ↓ risk of relapse; consider plan short & long term

Management issues:

- **Infections:** soft tissue; other (endocarditis, HIV, hepatitis, etc.)
- **Overdose vs Intoxication vs Withdrawal**
- **Consider detailed assessment if:**
 - o Acknowledgment of drug use
 - o Physical signs such as track marks, nasal septum atrophy
 - o Urine drug screen +ve {Note: emergency drug screen is unlikely to significantly affect impact upon management in the ER.}⁵⁰

- **Approach for engagement**
 - o Accept patient autonomy
 - o Non-judgemental approach
 - o Collaborative approach with patient
 - o Confidentiality
 - o Proactive discussion on medications and behaviours
- **Managing Potentially Violent Patient⁵¹:**
 - o Maintain autonomy & dignity of users, intervene early, approach patients with caution, don't startle, avoid provocation, be aware of your own

demeanour, use calm language, don't make promises, provide options and choice, remove dangerous objects from your person, know exits, don't turn back on patient, role for distraction, be firm & compassionate, depersonalize issue; avoid confronting, but if necessary maintain distance, avoid corners, explain intension, ask for facts & encourage reasoning, ask for weapons to be put down not handed over, know how to call for help.

Antipsychotics are not 1st line for substance abuse withdrawal. If in a controlled setting, temporary use of a long acting benzodiazepine may be preferred.

Intoxication: Common Presentations – Possible Causes^{52,53}

- **Unresponsive:** hypoglycemics, narcotics, alcohol, cyanide, carbon monoxide, tranquilizers, hydrocarbons, barbiturates
- **Seizures:** hypoglycemics, amphetamines, cocaine, hallucinogens, anticonvulsants, TCAs, PCP, mescaline
- **Hyperthermia:** salicylates, Ecstasy, atropine, amphotericin B, phenytoin
- **Hypothermia:** ethanol, narcotics, sedatives/hypnotics, TCAs, barbiturates, carbon monoxide.

	Intoxication Management [Primary assessment ABCs: airway, breathing, circulation]
Opioids	Intoxication {coma, lethargy, stupor; constipation, N&V; flushing, pruritis; hypotension; miosis; resp depression} <ul style="list-style-type: none"> ♦ supportive tx: regular assessment of cardio/respiratory safety ♦ airway protection; ♦ correction of hypoxia ⇒ naloxone option: short term duration; balance reversal of resp depression with opioid withdrawal (naloxone can be considered if opioid toxicity suspected). ♦ consider type of opioid for duration of risk & naloxone effect ♦ consider N-acetyl-para-aminophenol level if overdose cause is unknown (r/o acetaminophen as possible agent)
Stimulant	Supportive tx {agitation, diaphoresis, hypertension, hyperthermia, mydriasis, psychosis, seizures, ↑HR} <ul style="list-style-type: none"> - oral diazepam for agitation & hypertension e.g cocaine induced - IV diazepam or midazolam short acting if severe agitation/anxiety - Optional: sedating antipsychotic - Monitor: hyperthermia, hypothermia, cardiac, electrolytes - HTN: benzodiazepines; alternatively nitroprusside, NTG - α-blockers. {avoid β-blockers as will result in unopposed α constriction}
Alcohol	Supportive tx {most immediate life-threatening complications in kids are hypoglycaemia & respiratory depression} <ul style="list-style-type: none"> ♦ airway; ♦ IV access (fluid management); correct hypoglycaemia with dextrose soln & electrolytes; ♦ thiamine

* Hemodialysis may be an option in life threatening intoxication. Hemodialysis may be useful to remove barbiturates, sedatives, hypnotics, anticonvulsants, alcohols, analgesics, solvents, etc.

Extras (RxFiles - Substance Abuse)

- o if using cocaine/other stimulants then detox is the only option. Rapid detox is not recommended during pregnancy.
- o Patients should only be "nodding" (falling asleep on methadone) if the dose is too high, they are a new start, or if they are using BZD's at the same time – may consider a tox screen to assess if patient is also using any other drugs
- o In Saskatoon methadone doses goes up by 10mg increments and down by 5mg increments for dose adjustments with some physicians.
- o Using both oral LA morphine (Kadian) in addition to methadone when starting patients is sometime done to prevent acute withdrawal & allow for methadone titration (e.g. a few weeks of dual treatment); controversial.
- o IV drug abusers: considerations see reference⁵⁴
- o Other substances of abuse: volatile inhalants, Listerine mouthwash

Acute Alcohol Intoxication^{55,56}

- **Blood Alcohol Levels (BAL):** <50mg/dl (< 10.9mmol/l): impairment in skills, ↑ talkativeness, relax; >100 mg/dl = impaired judgement, ↓ coordination & reactions, mood/personality change; >200 mg/dl: amnesia, diplopia, N&V; >300-500 mg/dl = ↑ risk of respiratory depression, coma & death
- **DSM-IV: A)** recent EtOH, **B)** clinically significant behavioural/psychological change e.g. aggression, mood, impairment **C)** one or more of [1. slurred speech, 2. ↓ coordination, 3. unsteady gait, 4. nystagmus, 5. ↓ attention/memory, 6. stupor/coma, other.]
- **Other effects & associations:** Respiratory, GI, alcoholic hepatitis. ↑ risk of injury, ↑ risk of life years lost, ↑ violent crimes.
- **Tx:** 1) Stabilize patient: [airway, resp fx, prevent aspiration, mechanical ventilation prn, IV access & correction of hypoglycaemia, electrolytes (dextrose, Mg, folate, thiamine, multivitamins); 2) Sedate patient (droperidol, haloperidol); 3) evaluate for chronic EtOH abuse; Ref: Ostacher MJ et al. Impact of substance use disorders on recovery from episodes of depression in bipolar disorder patients: Prospective data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2009 Dec 15; [e-pub ahead of print].

Management of Cocaine Body Packers⁵⁷:

Hx: # & type of packets; other agents; GI symptoms; **Investigations:** ECG, CBC/SCr, etc., chest & abdom x-rays;
Management if asymptomatic: admit, 4 hr observations of vitals, oral gastric lavage till all packets passed, light/normal diet, IV access, daily evaluation for intox/bowel obstruction.

Lifespan Spectrum of Complications: *Pregnancy* - obstetrical complications, fetal distress, stillbirth, low birth weight; *adolescent & young adult* – self inflicted injuries, homicides, premature morbidity; *Later life* - ↑ decline. {Associate health problems: non-fatal overdose, ↑ infections IV and NIDU (HCV; Hepatitis A, B); liver fibrosis cannabis, periodontitis cannabis; psychiatric (psychosis, anxiety, depression) various, cannabis; long-term ↓ cognitive performance.}⁵⁸

Substance Abuse in Older Adults⁵⁹: 2005 USA data on treatment programs: Alcohol only (48%), alcohol + 2nd illicit substance (52%); 2nd substance cocaine 40%, marijuana 29%, opiates 16%, stimulants 5%, other 10%.

♦ **Signs:** headache, ↓ cognitive/memory ability; **Unique features** in elderly: tendency to drink smaller quantities more often, DI with ↑ metabolism of other drugs, Δ in sleep patterns. **Clues:** recent losses, psych hx, family hx of abuse.

ALDH=alcohol dehydrogenase 5HT=serotonin fx=function HCV= hepatitis C virus HX=history NIDU= non-injecting drug users Qt=qt interval RR=respiratory rate

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Organ Transplant Facts:

Canada: There were 2083 solid organ transplants in Canada, as compared with 2188 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 initiative 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.

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Drugs in Pregnancy Risk Classification ^{1,2,3,4}

The following are the codes that appear on some of our charts. This table explains the rating system used.

RISK FACTOR	CLASSIFICATION	COMMENTS * Weight risk vs benefit esp. in some diseases eg. diabetes, asthma, hypertension, psychiatry. Benefit of treatment in these conditions, may outweigh the risks of not treating.
A	SAFE	No risk. Considered safe in all trimesters. No evidence of fetal risk in controlled studies in humans.
B	LIKELY SAFE	Minimal risk. Either no evidence of risk in animals or risk found in animal studies not reproduced in humans.
B/D		With higher dose, longer duration of drug exposure or near term the risk becomes D
C	CAUTION	Potential risk. Risk evident from studies in animals and/ or no human studies available. Use only if benefit outweighs risk. May be more or less safe depending on trimester.
C/D		With higher dose, longer duration of drug exposure or near term the risk becomes D
D	EXTREME CAUTION	Positive evidence of risk. Use only if benefit outweighs risk.
X	CONTRAINDICATED	++ Positive evidence of risk. Avoid in women who are or may become pregnant as risk of use outweighs any benefit.
U	UNKNOWN	Risk unknown or untested. Information unavailable / inadequate at this time.

* Rating system has limitations eg. antidepressant frequently used like fluoxetine has a C rating; yet maprotiline (B rating) has less clinical experience

General Info: **Pregnancy Exposure Registries** <http://www.fda.gov/womens/registries/default.htm> **LactMed** ^{Lactation} <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

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3. Individual Drug Product Monographs. 4. Micromedex 2010 {NOTE: for additional Canadian information on drugs in pregnancy & lactation see <http://www.motherisk.org/index.jsp> }

WHO Essential Medicines List <http://www.who.int/medicines/publications/essentialmedicines/en/index.html>

Common RxFiles ABBREVIATIONS & SYMBOLS –most of our charts have footnotes to explain unique abbreviations.

☎ =Exception Drug Status (EDS) in Saskatchewan (1-800-667-2549)

X =non-formulary in Saskatchewan

\$ Retail Cost to Consumer based on acquisition cost, markup & dispensing fee in Saskatchewan. Lowest generic price used where available

BID=twice daily **BP** =blood pressure **Bz** =benzodiazepine **CI** =contraindication

HF =heart failure **HR** =Heart rate **HSR** =Hypersensitivity reaction

SE =side effect **SJS** =Stevens Johnson Sx **Sx** =syndrome/symptom **Sz** =seizure

♻ =indicates strength of tablet is scored ☺ = tastes good

👉 =↓ dose required for **Renal** dysfunction ¹ if 1) ≥ 75% renal excretion 2) toxic if accumulates 3) an active metabolite requiring dose adjustment. [CrCl <60ml/min shows impaired renal function]

CrCl ml/min **Male**= {(140-age) x **ABW** weight in Kg} / {serum creatinine in umol/l x 0.814}

Female= 0.85 x CrCl male

Adjusted body weight in kg (**ABW**) = {Ideal body weight (**IBW**) + 0.4 (Actual body weight-**IBW**)}

IBW (Males)= 50kg + 0.906 (Height in cm - 152.4cm); **IBW** (Females)= 45kg + 0.906 (Height in cm - 152.4cm)

MDRD (eGFR)= accurate, but need PDA with MedCalc to do the calculation. **CKD-EPI** eGFR= new accurate for CKD

☑ =prior approval required by NIHB (Non-Insured Health Benefits) coverage for eligible **First Nations & Inuit** 1-800-580-0950

⊗ =not covered by NIHB http://www.hc-sc.gc.ca/fnih-spni/pubs/nihb-ssna_e.html#drug-med_bull-lebull

▼ =covered by NIHB for the **OTC charts** p70-73 & identified **ONLY** for those drugs which have **Sask.** Formulary restrictions such as **EDS or non formulary status**

CV =cardiovascular **DI** =drug interaction **Dx** =diagnosis/disease **g** =generic avail. **GI** =Gastrointestinal **HA** =headache

LFT =Liver Function tests **M** =Monitoring **OD** =daily **Ⓟ** =a concern if given **Pre-Op** **QID** =four times daily

TID =three times daily **Tx** =treatment **Units** = uses **SI** but can convert (cholesterol x 38.6=mg/dL; glucose x 18=mg/dL)

🇨🇦 = CDN (We are Canadian) ⓧ =Avoid → soybean & peanut allergy ♂ =male ♀ =women

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Newsletters, Charts & **References** are available online at www.RxFiles.ca

RxFiles Academic Detailing Program

Objective comparisons for optimal drug therapy. For more information check our website - www.RxFiles.ca or, contact Loren Regier BSP, BA RxFiles, c/o , Saskatoon City Hospital

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