RxFiles - Drug Comparison Charts - 7th Edition

Objective, Comparative Drug Information Editors: Brent Jensen, Loren D. Regier

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Evidence Based Medicine (EBM) Overview References

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

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Julius S, et al.; Trial of Preventing Hypertension (**TROPHY**) Study. Feasibility of treating prehypertension with an ARB.(candesartan) N Engl J Med. 2006 Apr 20;354(16):1685-97. Epub 2006 Mar 14. (see also PharmLetter May06.) (InfoPOEMs: This study tells us what we already know (that is, that blood pressure medications reduce blood pressure), but says nothing about what really matters: Does intervention in patients with prehypertension improve patient-oriented outcomes? The choice to study such an expensive drug is also disappointing, but not surprising. Given that the number needed to treat [NNT] to prevent 1 stroke, heart attack, or death in patients with mild hypertension is 140 for 5 years (http://www.jr2.ox.ac.uk/bandolier/index.html), it is likely that the actual clinical benefit of treating prehypertension is even smaller. (LOE = 1b))

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Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of **angioedema** associated with enalapril. Arch Intern Med. 2005 Jul 25;165(14):1637-42. RESULTS: Angioedema occurred in 86 of 12 557 (0.68%) of the subjects.

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McCall KL, Craddock D, Edwards K. Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Type 1 Receptor Blockers on the Rate of **New-Onset Diabetes Mellitus**: A Review and Pooled Analysis. Pharmacotherapy. 2006 Sep;26(9):1297-306.

McDonald MA, Simpson SH, Ezekowitz JA, et al. Angiotensin receptor blockers and risk of **myocardial infarction**: systematic review. BMJ. 2005Oct 15;331(7521):873. Epub 2005 Sep 23. CONCLUSIONS: Treatment with angiotensin receptor blockers was not associated with a significantly increased risk of myocardial infarction. The 95% confidence intervals do, however, not exclude an increase of up to 16% in the risk of myocardial infarction or a reduction in risk of up to 25%. Until further information specifically dealing with this issue is available from large prospective trials, our findings may alleviate recent concerns over the safety of this class of medications.

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Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the **ADVANCE** trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy. (InfoPOEMs: Perindopril (Aceon) plus indapamide (Lozol) is better than placebo in decreasing clinically relevant events in patients with type 2 diabetes who are at high risk of cardiovascular complications. Whether the combination is better than other medications -- like aspirin -- isn't addressed by this study. (LOE = 1b))

Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse Effects of **Combination Angiotensin II Receptor Blockers Plus Angiotensin-Converting Enzyme Inhibitors** for Left Ventricular Dysfunction: A Quantitative Review of Data From Randomized Clinical Trials. Arch Intern Med. 2007 Oct 8;167(18):1930-6. Four studies (N = 17 337; mean follow-up, 25 months [range, 11-41 months]) were selected. Combination ARB plus ACE inhibitor vs control treatment that included ACE inhibitors was associated with significant increases in medication discontinuations because of adverse effects in patients with chronic heart failure (RR, 1.38 [95% CI, 1.22-1.55]) or in patients with acute myocardial infarction with symptomatic left ventricular dysfunction (RR, 1.17 [95% CI, 1.03-1.34]), and for both conditions there were significant increases in worsening renal function (RR, 2.17 [95% CI, 1.59-2.97] and RR, 1.61 [95% CI, 1.31-1.98], respectively), hyperkalemia (RR, 4.87 [95% CI, 2.39-9.94] and RR, 1.33 [95% CI, 0.90-1.98], respectively; the latter was not significant), and symptomatic hypotension (RR, 1.50 [95% CI, 1.09-2.07], and RR, 1.48 [95% CI, 1.33-3.18], respectively).Combination ARB plus ACE inhibitor therapy in subjects with symptomatic left ventricular dysfunction was accompanied by marked increases in adverse effects.

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

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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.

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, Shishehbor M, Magyar WA, Crowe TD, Kapadia S, Nissen SE. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. Ann Intern Med. 2007 Jul 3;147(1):10-8. The analysis demonstrates that beta-blockers can slow progression of coronary atherosclerosis.

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Turnes J, et al. Pharmacological reduction of portal pressure and long-term risk of first **variceal bleeding** in patients with cirrhosis. Am J Gastroenterol. 2006 Mar;101(3):506-12.

van Gestel YR, Hoeks SE, Sin DD, et al. The Impact of Cardioselective Beta-Blockers on Mortality in Patients with **COPD and Atherosclerosis**. Am J Respir Crit Care Med. 2008 Jun 19. [Epub ahead of print] Cardioselective beta-blockers were associated with reduced mortality in COPD patients undergoing vascular surgery. In carefully selected patients with COPD, the use of cardioselective beta-blockers appears to be safe and associated with reduced mortality.

Wax PM, et al. **Beta-blocker ingestion**: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila). 2005;43(3):131-46. http://www.aapcc.org/FinalizedPMGdlns/beta-blocker%20guideline%20for%20AAPCC%202005-3-30.pdf

Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence. Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005 Sep 4; [Epub ahead of print] CONCLUSIONS: Although noninferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, our results indicate that it may be as safe and efficacious to initiate treatment for CHF with bisoprolol as with enalapril. n=1010.

Willenheimer R. Effect on mode and cause of death of initiation of treatment for chronic heart failure with bisoprolol followed by additional enalapril compared to the opposite sequence: results of the randomized **CIBIS III** trial. World Congress of Cardiology 2006; September 6, 2006; Barcelona, Spain.

Wiysonge C, et al. **Beta-blockers for hypertension**. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD002003. The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension. This conclusion is based on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo or no treatment. More importantly, it is based on the trend towards worse outcomes in comparison with calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics. Most of the evidence for these conclusions comes from trials where atenolol was the beta-blocker used (75% of beta-blocker participants in this review). However, it is not known at present whether beta-blockers have differential effects on younger and elderly patients or whether there are differences between the different sub-types of beta-blockers.

Wyse DG, Waldo AL, DiMarco JP, et al. Atrial Fibrillation Follow-up Investigation of Rhythm Management (**AFFIRM**) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 Dec 5;347(23):1825-33. Management of atrial fibrillation with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy. Anticoagulation should be continued in this group of high-risk patients.

CALCIUM CHANNEL BLOCKER (CCB): Comparison Chart

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

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

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[8] Drugs in Pregnancy & Lactation, 8th Ed. Briggs GE,et al. Wilkins;Baltimore, MD.2008.

[9] Micromedex 2008 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.

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Additional articles:

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

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

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-))

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

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

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

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

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

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

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

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

Thiazide Like Diuretics and Miscellaneous Antihypertensives

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

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

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[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.

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48. Barzilay JI, Davis BR, Cutler JA, et al. Fasting Glucose Levels and Incident Diabetes Mellitus in Older NondiabeticAdults Randomized to Receive 3 Different Classes of Antihypertensive Treatment: A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2006 Nov 13;166(20):2191-201. Fasting glucose levels increase in older adults with hypertension regardless of treatment type. For those taking chlorthalidone vs other medications, the risk of developing FG levels higher than 125 mg/dL (6.9 mmol/L) is modestly greater, but there is no conclusive or consistent evidence that this diuretic-associated increase in DM risk increases the risk of clinical events.
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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.
Hooper L, et al. Risks and benefits of **omega 3 fats** for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006 Mar 24; [Epub ahead of print] (Wang C, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006 Jul;84(1):5-17.)
Howard BV, et al. **Low-fat dietary pattern** and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006 Feb 8;295(6):655-66.
Hou FF, Zhang X, Zhang GH, et al. Efficacy & safety of **benazepril** for advanced chronic renal (CKD pts) insufficiency. N Engl J Med. 2006 Jan 12;354(2):131-40. (InfoPOEMs: In a group of nondiabetic patients with serum creatinine levels between 3.0 & 5.0 mg/dL, benazepril slows the progression of renal disease. These pts were carefully monitored for any changes in renal function during the first 8 weeks, and were carefully screened & monitored to detect any early adverse effects on renal function. (LOE = 1b))
Jackson R, Broad J, Connor J, Wells S. **Alcohol** and ischaemic heart disease: probably no free lunch. Lancet. 2005 Dec 3;366(9501):1911-2.
Kaikkonen KS, et al. **Family history** and the risk of sudden cardiac death as a manifestation of an acute coronary event. Circulation. 2006 Oct 3;114(14):1462-7. Epub 2006 Sep 25.
Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. Circulation. 2005 Jun 7;111(22):2906-12. Epub 2005 May 31. (InfoPOEMs: There is no evidence from randomized trials that percutaneous coronary intervention (PCI) improves important clinical outcomes better than careful medical management for patients with chronic stable coronary artery disease (CAD). Although this is the largest study to date, it's still limited by a relatively small number of outcomes of interest. (LOE = 1a))
Khachaturian et al. Antihypertensive Medication Use and Incident **Alzheimer** Disease: The Cache County Study. Arch Neurol. 2006 Mar 13; [Epub ahead of print]
Khan NA, et al. Canadian Hypertension Education Program. The **2006 Canadian Hypertension Education Program** recommendations for the management of hypertension: Part II - Therapy. Can J Cardiol. 2006 May 15;22(7):583-93.
Kim JW, et al. How well do clinic-based **blood pressure measurements** agree with the mercury standard? J Gen Intern Med. 2005 Jul;20(7):647-9. (InfoPOEMs: In this study, usual blood pressure readings in an office were frequently higher a standardized measurement, leading to incorrect labeling of blood pressure control in 1 of 5 patients. Several conclusions can be drawn from this study, which replicates the findings in other studies: First, retrain yourself to take an accurate blood pressure reading (see: http://www.theberries.ns.ca/

SPRING2005a/taking_BP_technique.html). Second, train your office nurses how to do it correctly. Third, retrain them often, since other research has shown high recidivism. Fourth, check any patients with high blood pressure readings yourself, using good technique. (LOE = 1b))

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

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

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

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

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

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

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

Mancia G, De Backer G, Dominiczak A, et al. Management of Arterial Hypertension of the ESH; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (**ESH**) and of the European Society of Cardiology (ESC). J Hypertens. **2007** Jun;25(6):1105-87. Erratum: J Hypertens. 2007 Aug;25(8):1749.

Mancia G, De Backer G, Dominiczak A, et al. **2007** Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (**ESC**). Eur Heart J 2007 Jun;28(12):1462-536.

Martin U, Coleman JJ. Monitoring **renal function** in hypertension. BMJ. 2006 Oct 28;333(7574):896-9.

McDonald MA, Simpson SH, Ezekowitz JA, et al. Angiotensin receptor blockers and risk of **myocardial infarction**: systematic review. BMJ. 2005Oct 15;331(7521):873. Epub 2005 Sep 23. CONCLUSIONS: Treatment with angiotensin receptor blockers was not associated with a significantly increased risk of myocardial infarction. The 95% confidence intervals do, however, not exclude an increase of up to 16% in the risk of myocardial infarction or a reduction in risk of up to 25%. Until further information specifically dealing with this issue is available from large prospective trials, our findings may alleviate recent concerns over the safety of this class of medications.

McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of **ethnic differences** in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ. 2006 May 20;332(7551):1177-81. Epub 2006 May 5.

McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment & **dementia** in patients without apparent prior cerebrovascular disease. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD004034. There was no convincing evidence from the trials identified that blood pressure lowering prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease. There were significant problems identified with analysing the data, however, due to the number of patients lost to follow-up and the number of placebo patients given active treatment. This introduced bias. More robust results may be obtained by analysing one year data to reduce differential drop-out or by conducting a meta-analysis using individual patient data.

Medical Letter. **Aliskiren (Tekturna)** for Hypertension. April 9,2007.

Messerli FH, et al. Dogma disputed: can aggressively **lowering diastolic blood pressure** in hypertensive patients with coronary artery disease be **dangerous**? Ann Intern Med. 2006 Jun 20;144(12):884-93. (InfoPOEMs: Lower is not always better. Despite a push toward lower blood pressure in many populations, bad outcomes (mortality, myocardial infarction, and stroke) are increased in patients with coronary artery disease (CAD) if their blood pressure consistently remains lower than 70 mmHg diastolic. (LOE = 1b))

Messerli FH, Williams B, Ritz E. **Essential hypertension**. Lancet. 2007 Aug 18;370(9587):591-603.

Moolchan ET, Robinson ML, Ernst M, et al. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics 2005;115:407-14. (InfoPOEMs: Approximately 1 in 5 adolescents (20%) given weekly therapy sessions and a nicotine patch will not be smoking 6 months after their quit date. (LOE = 1b-))

Morrow DA, de Lemos JA, Blazing MA, et al.; A to Z Investigators. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. JAMA. 2005 Dec 14;294(22):2866-71. (InfoPOEMs: Serial determination of B-type natriuretic peptide (BNP) during follow-up of patients after an acute coronary syndrome (ACS) helps predict the risk of subsequent death or congestive heart failure (CHF). It remains uncertain whether having this information will lead to a change in clinical management that improves patient-oriented outcomes or simply increases costs without any added benefit. (LOE = 1b))

Moser M, Setaro JF. Clinical practice. **Resistant** or difficult-to-control **hypertension**. N Engl J Med. 2006 Jul 27;355(4):385-92.

Mozaffarian D, Rimm EB. **Fish intake**, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006 Oct 18;296(15):1885-99.

Mozaffarian D, et al. **Trans fatty acids** and cardiovascular disease. N Engl J Med. 2006 Apr 13;354(15):1601-13.

Mueller C, Laule-Kilian K, Frana B, Rodriguez D, Scholer A, Schindler C, Perruchoud AP. Use of **B-type natriuretic peptide** in the management of acute dyspnea in patients with pulmonary disease. Am Heart J. 2006 Feb;151(2):471-7. (InfoPOEMs: In patients with pre-existing pulmonary disease, B-type natriuretic peptide (BNP) testing in the emergency department is effective at distinguishing an exacerbation due to heart failure (HF) from that caused by pulmonary disease. As a result, hospitalizations are fewer, probably because of initiation of more appropriate therapy in the emergency department. Also, the duration of the hospital stay is shorter and the cost is less. (LOE = 1b))

Mukamal KJ, Chiuve SE, Rimm EB. **Alcohol consumption** and risk for coronary heart disease in men with healthy lifestyles. Arch Intern Med. 2006 Oct 23;166(19):2145-50.

Murabito JM, Pencina MJ, Nam BH, et al. **Sibling cardiovascular disease** as a risk factor for cardiovascular disease in middle-aged adults. JAMA. 2005 Dec 28;294(24):3117-23.

Naghavi M, Falk E, Hecht HS, et al. From vulnerable plaque to vulnerable patient: Part III. Introducing a new paradigm for the prevention of heart attack; identification and treatment of the asymptomatic vulnerable patient. Screening for Heart Attack Prevention and Education (SHAPE) task force report. Executive summary. *Am J Cardiol* 2006; DOI: 10.1016/j.amjcard.2006.03.002. Available at http://www.ajconline.org.

National High Blood Pressure Education Program Working Group on High Blood Pressure in **Children and Adolescents**. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004 Aug;114(2 Suppl 4th Report):555-76.

Niiranen TJ, et al. A comparison of **home measurement** and **ambulatory monitoring** of blood pressure in the adjustment of antihypertensive treatment. Am J Hypertens. 2006 May;19(5):468-74.

Ohkubo T, Kikuya M, Metoki H, et al. Prognosis of "masked" hypertension & "white-coat" hypertension detected by 24-h **ambulatory blood pressure monitoring** 10-year follow-up from the Ohasama study. J Am Coll Cardiol.2005 Aug 2;46(3):508-15. (InfoPOEMs: Using 24-hour ambulatory blood pressure monitoring as the standard, some patients will have white-coat hypertension (that is, higher blood pressures in the office than at home) and some will also have masked hypertension as a result of lower blood pressure measurements in the office. White-coat hypertension does not confer added risk, but masked hypertension underestimates a patient's risk. Evidence is accumulating that blood pressure should be measured at home, either with a 24-hour monitor or via self-monitoring (J Am Coll Cardiol 2005;46:743-51), before labeling someone as hypertensive and treating them accordingly. (LOE = 2b))

Okin PM, et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of **new-onset atrial fibrillation** in patients with hypertension. (**LIFE** trial)JAMA. 2006 Sep 13;296(10):1242-8.

Okin PM, et al.; LIFE Study Investigators. **Electrocardiographic strain** pattern and prediction of new-onset congestive heart failure in hypertensive patients: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. Circulation. 2006 Jan 3;113(1):67-73. Epub 2005 Dec 19.

Okin PM, et al. Impact of Diabetes Mellitus on Regression of Electrocardiographic Left Ventricular Hypertrophy and the Prediction of Outcome During Antihypertensive Therapy. The Losartan Intervention For Endpoint (LIFE) eduction in Hypertension Study. Circulation. 2006 Mar 13; [Epub ahead of print]

Østergaard Pedersen J, Heitmann B L, Schnohr P, and Grønbæk M. The combined influence of leisure-time **physical activity and weekly alcohol** intake on fatal ischaemic heart disease and all-cause mortality. Eur Heart J 2008; DOI:10.1093/eurheartj/ehm574.

Osranek M, Bursi F, Bailey KR, et al. **Left atrial volume** predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. Eur Heart J. 2005 Dec;26(23):2556-61. Epub 2005 Sep 1.

Owan TE, et al. Trends in prevalence and outcome of **heart failure** with **preserved ejection fraction**. N Engl J Med. 2006 Jul 20;355(3):251-9.

Panagiotakos DB, et al. The Relation Between Pulse Pressure & Cardiovascular Mortality in 12 763 Middle-aged Men From Various Parts of the World: A 25-Year Follow-up of the Seven Countries Study. Arch Intern Med. 2005 Oct

10;165(18):2142-7. CONCLUSIONS: Pulse pressure followed by diastolic and systolic blood pressures were the best predictors for CVD mortality among other blood pressures, as well as age, physical activity, total serum cholesterol level, anthropometric indexes, and smoking habits. No significant differences were observed among the different populations studied.

Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the **ADVANCE** trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy. (InfoPOEMs: Perindopril (Aceon) plus indapamide (Lozol) is better than placebo in decreasing clinically relevant events in patients with type 2 diabetes who are at high risk of cardiovascular complications. Whether the combination is better than other medications -- like aspirin -- isn't addressed by this study. (LOE = 1b))

Pavy B, et al. Safety of **Exercise Training** for Cardiac Patients: Results of the French Registry of Complications During Cardiac Rehabilitation. Arch Intern Med. 2006 Nov 27;166(21):2329-2334.

Peila R, et al. Reducing the risk of **dementia**: efficacy of long-term treatment of hypertension. Stroke. 2006 May;37(5):1165-70. Epub 2006 Apr 6.

Percutaneous Coronary Intervention: ACC/AHA/SCAI 2005 Guideline Update for (Update of the 2001 PCI Guidelines) (J Am Coll Cardiol, January 3, 2006 issue; Vol/Page Numbers pending) http://www.acc.org/clinical/guidelines/percutaneous/update/index.pdf

Perez M, Musini V. Pharmacological interventions for **hypertensive emergencies**. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003653. There is no RCT evidence demonstrating that anti-hypertensive drugs reduce mortality or morbidity in patients with hypertensive emergencies. Furthermore, there is insufficient RCT evidence to determine which drug or drug class is most effective in reducing mortality and morbidity. There were some minor differences in the degree of blood pressure lowering when one class of antihypertensive drug is compared to another. However, the clinical significance is unknown.

Peripheral Arterial Disease: ACC/AHA Guidelines for the Management of Patients With (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic); A Collaborative Report From the AAVS/SVS, SCAI, SIR, SVMB, and the ACC/AHA Task Force on Practice Guidelines http://www.acc.org/clinical/guidelines/pad/summary.pdf (Abramson BL, et al.; **Canadian Cardiovascular Society**. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease - executive summary. Can J Cardiol. 2005 Oct;21(12):997-1006.)

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Pickering TG, Shimbo D, Haas D. **Ambulatory blood-pressure monitoring**. N Engl J Med. 2006 Jun 1;354(22):2368-74.

Pickering TG, Houston-Miller N, Ogedegbe G, et al. Call to action on use and reimbursement for **home blood pressure monitoring**. Hypertension 2008; DOI: 10.1161/hypertensionaha.107.189010.

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

P**rospective Studies Collaboration**, Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370(9602):1829-1839. This study reinforces what we already know: Higher cholesterol levels and blood pressure are each associated with an increased risk of vascular mortality. Be careful with these results; this kind of study doesn't tell us that lowering cholesterol levels and blood pressure will prevent deaths. For that, we'd need an intervention trial. (LOE = 1a)

Psaty BM, Weiss NS, Furberg CD. Recent trials in hypertension: compelling science or **commercial speech**? JAMA. 2006 Apr 12;295(14):1704-6.

Rastas S, et al. Association Between Blood Pressure and Survival over 9 Years in a General Population **Aged 85 elderly and Older**. J Am Geriatr Soc. 2006 Jun;54(6):912-8.

Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after **maternal placental syndromes** (CHAMPS): population-based retrospective cohort study. Lancet. 2005 Nov 19;366(9499):1797-803.

Rahman M, et al. ALLHAT Collaborative Research Group. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline **glomerular filtration rate**. Ann Intern Med. 2006 Feb 7;144(3):172-80.

Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: A scientific statement from the **American Heart Association Council for High Blood Pressure** Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007; 2007; 115:2761-2788.

Rothenbacher D, Koenig W, Brenner H. Life Time **Physical Activity** Patterns and Risk of Coronary Heart Disease. Heart. 2006 Jul 19; [Epub ahead of print]

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

Salt Info: www.saltinstitute.org;

China Salt Substitute Study Collaborative Group. Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial. J Hypertens. 2007 Oct;25(10):2011-8.

Cohen HW, Hailpern SM, Fang J, Alderman MH. Sodium intake and mortality in the NHANES II follow-up study. Am J Med. 2006 Mar;119(3):275.e7-14.

Parikh NI, Gona P, Larson MG, et al. Plasma renin and risk of cardiovascular disease and mortality: the Framingham Heart Study. Eur Heart J. 2007 Nov;28(21):2644-52. Epub 2007 Sep 25.

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Schuijf JD, et al. Diagnostic accuracy of **64-slice multislice computed tomography** in the noninvasive evaluation of significant coronary artery disease. Am J Cardiol. 2006 Jul 15;98(2):145-8. Epub 2006 May 19.

Schulman SP, et al. **L-arginine** therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. JAMA. 2006 Jan 4;295(1):58-64.

Shlipak MG, et al. **Cystatin C** and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med. 2006 Aug 15;145(4):237-46.

Singer W, et al. **Pyridostigmine** treatment trial in **neurogenic orthostatic hypotension**. Arch Neurol. 2006 Apr;63(4):513-8. Epub 2006 Feb 13.

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Spahr A, et al. **Periodontal infections** & coronary heart disease: role of periodontal bacteria & total pathogen burden in the Coronary Event & Periodontal Disease (CORODONT) study. Arch Intern Med. 2006 Mar 13;166(5):554-9.

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Staessen JA, Li Y, Richart T. Oral renin inhibitors. Lancet. 2006 Oct 21;368(9545):1449-56.

Stone PH, Gratsiansky et al. **ERICA** Investigators. Antianginal efficacy of **ranolazine** when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol. 2006 Aug 1;48(3):566-75. Epub 2006 Jun 15. (InfoPOEMs: Ranolazine (Ranexa), added to maximum dosing of amlodipine, decreases angina episodes and nitroglycerin doses slightly more than placebo does; patients taking ranolazine experienced approximately 1 fewer episode, on average, every 2 weeks. These results occurred in patients with frequent symptoms -- at least 4 anginal episodes per week -- and its effect is likely to be less pronounced in patients with less frequent symptoms. (LOE = 1b)

Strandberg TE, et al. **Multifactorial intervention** to prevent recurrent cardiovascular events in patients **75 years or older**: the Drugs and Evidence-Based Medicine in the Elderly (**DEBATE**) study: a randomized, controlled trial. Am Heart J. 2006 Sep;152(3):585-92. (InfoPOEMs: First, the good news: Researchers were able, without unusual effort, to apply evidence-based guidelines to older elderly patients with cardiovascular disease (CVD) and achieve goal blood pressure and cholesterol levels in the majority. Now, the bad news: These interventions did not decrease the likelihood of the patients experiencing a cardiovascular problem over the next 3.4 years. The treated patients did not live any longer over this period, and the treatment did not delay deaths. (LOE = 1b)))

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

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

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

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

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

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

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

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Kurth T, Barr RG, Gaziano JM, Buring J. Randomised Aspirin Assignment And Risk Of Adult-Onset Asthma In The Women's Health Study. (WHS) Thorax. 2008 Mar 13; [Epub ahead of print] In this large, randomised clinical trial of apparently healthy adult women, assignment of 100 mg of aspirin

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with clinic management: a randomized trial. Ann Intern Med. 2005 Jan 4;142(1):1-10. (InfoPOEMs: Although many patients will not wish to do so, home monitoring of anticoagulation status and subsequent self-adjustment of dosing is safe and effective. Self-monitoring of anticoagulation is a bit trickier than home blood glucose monitoring, and approximately 30% of patients dropped out during the training period. The testing equipment is expensive ($1300 US), a cost-effectiveness analysis has not been done, and there is no evidence that it leads to better clinical outcomes (ie, less bleeding and less recurrent embolic events) . (LOE = 1b))

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Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. (OASIS-5) N Engl J Med. 2006 Mar 14; [Epub ahead of print] Conclusions Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long term mortality and morbidity. (InfoPOEMs: **Fondaparinux** is a safer alternative to enoxaparin in patients with acute coronary syndrome (ACS), and has slightly better long-term efficacy, as well. (LOE = 1b))

136. Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction: The **OASIS-6** Randomized Trial. JAMA. 2006 Mar 14; [Epub ahead of print] CONCLUSION: In patients with STEMI, particularly those not undergoing primary percutaneous coronary intervention, **fondaparinux** significantly reduces mortality & reinfarction without increasing bleeding and strokes. (InfoPOEMs: Fondaparinux (Arixtra) reduces the risk of mortality and reinfarction without increasing the risk of severe bleeding events in patients with acute ST-segment elevation myocardial infarction. Patients undergoing primary percutaneous coronary intervention (PCI) received no additional benefit from fondaparinux compared with unfractionated heparin (UFH). (LOE = 1b-)) Mehta SR, et al.; ASPIRE Investigators. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation (ASPIRE) Pilot Trial. Circulation. 2005 Mar 22;111(11):1390-7.
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absolute annual increases attributable to aspirin were major bleeding: 0.13% (95% CI, 0.08-0.20); major GI bleeding: 0.12% (95% CI, 0.07-0.19), intracranial bleeding: 0.03% (95% CI, 0.01-0.08). No study compared clopidogrel with placebo. One study showed increased major GI bleeding (but not non-GI bleeding endpoints) with aspirin versus clopidogrel (RR=1.45; 95% CI, 1.00-2.10). The absolute annual increase was 0.12% (95% CI, 0.00-0.28). CONCLUSIONS: Low-dose aspirin increases the risk of major bleeding by approximately 70%, but the absolute increase is modest: 769 patients (95% CI, 500-1250) need to be treated with aspirin to cause one additional major bleeding episode annually. Compared with clopidogrel, aspirin increases the risk of GI bleeding but not other bleeding; however, 883 patients (95% CI, 357-infinity) would need to be treated with clopidogrel versus aspirin to prevent one major GI bleeding episode annually at a cost of over 1 million dollars.

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Brain Natriuretic Peptide (BNP) has diagnostic value for both types of HF and is recommended where available, when diagnosis in unclear. The use of BNP in non-acute HF and community outpatient practice remains to be clarified.[3]

Table: Brain natriuretic peptide (BNP) and prohormone of BNP (NT-proBNP) assay cut-off points for the diagnosis of heart failure[3]

	Age	HF unlikely	HF possible but consider alternative diagnoses	HF very likely
BNP (pg/mL)	**All**	**<100**	**100-500**	**>500**
NT-proBNP (pg/mL)	**<50**	**<300**	**300-450**	**>450**
	50-75	**<300**	**300-900**	**>900**
	>75	**<300**	**300-1800**	**>1800**

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LIPID LOWERING THERAPY: DYSLIPIDEMIA Comparison Chart

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46. InfoPOEMs July, 2005. More adverse events with rosuvastatin than other statins. Bottom line: The United States Federal Drug Administration (FDA), Health Canada, and European regulators have recently issued advisories to physicians regarding higher doses of rosuvastatin. These data -- though inherently limited by their voluntary nature and the possibility of reporting bias- lend credence to concerns that rosuvastatin is less safe than other statins. It is also the only statin for which we do not have patient-oriented outcome data. (LOE = 2c). *Circulation 2005;111:3051-57.*
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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)

Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of magnitude of lipid lowering on risk of **elevated liver enzymes, rhabdomyolysis, and cancer**. J Am Coll Cardiol 2007; 50:409-418. DOI: 10.1016/j.jacc.2007.02.073. Available at: http://content.onlinejacc.org. Risk of statin-associated elevated liver enzymes or rhabdomyolysis is not related to the magnitude of LDL-C lowering. However, the risk of cancer is significantly associated with lower achieved LDL-C levels.

Amarenco P, et al.; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (**SPARCL**) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006 Aug 10;355(6):549-59. (Kent DM. Stroke--an equal opportunity for the initiation of statin therapy. N Engl J Med. 2006 Aug 10;355(6):613-5.) (InfoPOEMs: High-dose atorvastatin reduces the risk of recurrent stroke, but does not improve mortality rates. A reduction in the risk of transient ischemic attack (TIA) or unclassified stroke was partially offset by an increase in the risk of hemorrhagic stroke. (LOE = 1b)) Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, Hennerici M, Simunovic L, Zivin JA, Welch KM; SPARCL Investigators. Effects of Intense Low-Density Lipoprotein Cholesterol Reduction in Patients With Stroke or Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. Stroke. 2007 Oct 25; [Epub ahead of print] As compared with having no change or an increase in LDL-C, achieving a >/=50% lowering was associated with a greater reduction in the risk of stroke and major coronary events with no increase in brain hemorrhages. Goldstein LB, Amarenco P, Szarek M, Callahan A 3rd, Hennerici M, Sillesen H, Zivin JA, Welch KM; On behalf of the SPARCL Investigators. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology. 2007 Dec 12; [Epub ahead of print] Hemorrhagic stroke was more frequent in those treated with atorvastatin, in those with a hemorrhagic stroke as an entry event, in men, and increased with age. Those with Stage 2 hypertension at the last visit prior to the hemorrhagic stroke were also at increased risk. Treatment did not disproportionately affect the hemorrhagic stroke risk associated with these other factors. There were no relationships between hemorrhage risk and baseline low-density lipoprotein (LDL) cholesterol level or recent LDL cholesterol level in treated patients.

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Arca M. **Atorvastatin** Efficacy in the Prevention of Cardiovascular Events in Patients with **Diabetes** Mellitus and/or Metabolic Syndrome. Drugs. 2007;67 Suppl 1:43-54. (Cards, Ascot-LLA, Greace, TNT, Prove-It, Aspen) In summary, several patient populations, from definitive, large-scale studies, are now available to corroborate the integral place of atorvastatin - in line with various regional and internationally accepted disease management guidelines - in the primary and secondary prevention of cardiovascular events in patients with diabetes and/or metabolic syndrome.

Bader T, Fazili J, Madhoun M, et al. Fluvastatin **Inhibits Hepatitis C** Replication in Humans. Am J Gastroenterol. 2008 Apr 9. [Epub ahead of print] FLV used as monotherapy in vivo showed suppressive effects of HCV clinically that are modest, variable, and often short-lived. These findings support "proof-of-concept" for pilot trials combining fluvastatin with standard therapy. Statins and fluvastatin, in particular, appear to be safe for use in hepatitis C.

Baigent C, Keech A, Kearney PM, et al.; **Cholesterol Treatment Trialists' (CTT)** Collaborators. Efficacy & safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-78. Epub 2005 Sep 27. (InfoPOEMs: Statins reduce 5-year overall mortality, and specifically decrease cardiovascular mortality and morbidity. The patients at highest baseline risk derive the greatest benefit. (LOE = 1a))

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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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QT PROLONGATION and TORSADES DE POINTES: DRUGS and SUDDEN DEATH

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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, pruritius & erythema Serious: rare systemic salicylate toxicity: nausea, vomiting, diarrhea, dizziness, loss of hearing, lethargy, psychic disturbances & hyperpnea ?protect from sun 8-12 weeks for noted improvement	√Used with topical retinoids to treat mild comedonal acne or 2nd line monotherapy agent[3] (also for seborrhea & psoriasis) ☒Not commonly recommended (less potent than equal strength BP) 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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Benzoyl peroxide products: Adasept B.P. .5 acne gel; Clean & Clear Continuous Control = BP 5% lotion = WATER based; CLEAN & CLEAR PERSA-GEL = BP 5% gel = WATER BASED; OVERNIGHT ACNE CONTROL LOTION = BP 3% lotion = WATER based; CLEAR ACNE TREATMENT CREAM = BP 5% cream = WATER based; CLEAR PORE ON-THE SPOT ACNE TREATMENT, VANISHING = BP 2.5% lotion; CLEAR SKIN TREATMENT REPAIRING LOTION = BP 3.7% lotion; CLEAR ZONE ACNE SYSTEM SKIN PURIFYING MOISTURIZER = BP 3.5% lotion; CLEARASIL STAYCLEAR ACNE TREATMENT CREAM BP PLUS - VANISHING = BP 5% cream; CLEARZ - IT = BP 5% lotion; CLINIQUE ACNE SOLUTIONS CLEARING MOISTURIZER = BP 2.5% lotion; CLINIQUE ACNE SOLUTIONS EMERGENCY LOTION = BP 5% lotion; DERMACNE LOTION TRAITMENT 5% = BP 5% lotion; DERMALOGICA SPECIAL CLEARING BOOSTER = BP 5% lotion; LIFE ACNE MEDICATION = BP 5% gel; MEDICATED ACNE GEL 5% = BP 5% gel; NATURE'S CURE ACNE TREATMENT = BP 5% cream; OBAGI CLENZIDERM ACNE GEL = BP 5% gel; OXY 5 COVER UP FORMULA = BP 5% cream; OXY 5 SENSITIVE SKIN VANISHING LOTION = BP 2.5% lotion; OXY 5 VANISHING FORMULA = BP 5% lotion; OXYDERM LOT 20% = BP 20% lotion - Schedule F; OXYDERM LOTION 10% = BP 10% lotion - Schedule F; OXYDERM LOTION 5% = BP 5% lotion; PURE PEFECTION CLASSIC REPLENISHING CLEANSER = BP 2.5% cream; PURE PERFECTION CLASSIC RENEWING CREME = BP 2.5% cream; RODAN & FIELDS/PROACTIV SOLUTION:RENEWING CLEANSER = BP 2.5% lotion; RODAN & FIELDS/PROACTIV SOLUTION:REPAIRING LOTION = BP 2.5% lotion; SPECTRO ACNECARE DEEP PORE VANISHING LOTION = BP 5% lotion; SPECTRO ACNECARE VANISHING LOTION FOR SENSITIVE SKIN = BP 2.5% lotion; CLEAR ZONE ACNE SYSTEM SKIN PURIFYING WASH = BP 3.5% liquid (WASH); PANOXYL CREAMY WASH 4% = BP 4% (WASH)

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Draelos ZD, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol. 2007 Mar;56(3):439.e1-10. Epub 2007 Jan 17. Dapsone gel 5% (Aczone) is marginally more effective than placebo (NNT = 13, 9-23) in the treatment of acne vulgaris. At 12 weeks of treatment, less than half the patients in the treatment group received acne assessment scores of "none" or "minimal". No serious adverse events were reported, but data from follow-up longer than 3 months is forthcoming. (LOE = 1b)

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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).

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/

Medical Letter Nov 20/06. Extended release minocycline od (Solodyn) for acne

March 15, 2007 – InfoPOEMs: Dapsone gel effective for acne vulgaris treatment. Bottom Line: Dapsone gel 5% (Aczone) is marginally more effective than placebo (NNT = 13, 9-23) in the treatment of acne vulgaris. At 12 weeks of treatment, less than half the patients in the treatment group received acne assessment scores of "none" or "minimal". No serious adverse events were reported, but data from follow-up longer than 3 months is forthcoming. (LOE = 1b)

November 8, 2006 -- Medicis and Dow Pharmaceutical Sciences, Inc. announced that the U.S. Food and Drug Administration ("FDA") has approved Ziana(TM) (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel. Ziana(TM) Gel is the first and only combination of clindamycin and tretinoin approved for once daily use for the topical treatment of acne vulgaris in patients 12 years or older.

November 8, 2006 -- QLT Inc. announced positive results of a Phase IV clinical trial of Aczone(TM) dapsone in more than 50 patients with G6PD deficiency that was performed to meet a post-approval commitment requested by the FDA. Mar/08 FDA removes G6PD screening & labeling requirements from the label. June 6/08 /CNW/ - QLT Inc. (NASDAQ: QLTI; TSX: QLT) announced today that Health Canada has completed its review of QLT USA, Inc.'s labeling supplement (SNDS) for Aczone(R) and has removed the glucose-6-phosphate dehydrogenase (G6PD) screening and blood monitoring requirements.

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FDA: Nov/07 Cosmetic Eyelash-Lengthener Seized The FDA says U.S. marshals have seized more than 12,000 applicator tubes of Age Intervention Eyelash, a cosmetic promoted to increase eyelash growth, because of concerns it may cause eye damage. In a press release the agency said that the product is an "adulterated cosmetic" because it contains bimatoprost (Lumigan), used to treat elevated intraocular pressure. In patients taking the prescription drug, the agency said the extra dose of bimatoprost may decrease the treatment's effectiveness, leading to optic nerve damage. Other side effects could include macular edema and uveitis.The cosmetic's maker, Jan Marini Skin Research, responded that no cases of eye damage have been reported. It said it reformulated the product last year to remove bimatoprost and that "several other companies have copied [Marini's] discontinued product and continue to market their competing products with 'drug' claims for eyelash growth."

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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
    - Mannitol – Onset 10-30min; max effect in 1 hour

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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 awoman for testosterone therapy, recommendations are to rule out causes not related to testosterone levels (eg, physical and psychosocial factors, medications) and to ensure that there is a physiologic cause for reduced testosterone levels (eg, bilateral oophorectomy). Laboratory testing of testosterone levels should be used only to monitor for supraphysiologic levels before and during therapy, not to diagnose testosterone insufficiency. Monitoring should also include subjective assessments of sexual response, desire, and satisfaction as well as evaluation for potential adverse effects. Transdermal patches and topical gels or creams are preferred over oral products because of first-pass hepatic effects documented with oral formulations. Custom-compounded products should be used with caution because the dosing may be more inconsistent than it is with government-approved products. Testosterone products formulated specifically for men have a risk of excessive dosing, although some clinicians use lower doses of these products in women. Testosterone therapy is contraindicated in women with breast or uterine cancer or in those with cardiovascular or liver disease. It should be administered at the lowest dose for the shortest time that meets treatment goals. Counseling regarding the potential risks and benefits should be provided before initiating therapy.

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Oral HYPOGLYCEMIC AGENTS (OHA) - Comparison Chart

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Wilcox R, Kupfer S, and Erdmann E. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: Results from Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive 10). Am Heart J 2008; DOI:10.1016/j.ahj.2007.11.029 In patients with advanced type 2 diabetes at high risk for cardiovascular events, pioglitazone treatment resulted in significant risk reductions in MACE composite end points to 3 years.

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(Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. BMJ. 2007 Apr 28;334(7599):882-4.)
(Nathan DM, Berkwits M. Trials that matter: rosiglitazone, ramipril, and the prevention of type 2 diabetes. Ann Intern Med. 2007 Mar 20;146(6):461-3.)

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Farmer A, Wade A, Goyder E, et al. Impact of **self-monitoring of blood glucose** in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 2007; DOI: 10.1136/bmj.39247.447431. Evidence is not convincing of an effect of self monitoring blood glucose, with or without instruction in incorporating findings into self care, in improving glycaemic control compared with usual care in reasonably well controlled non-insulin treated patients with type 2 diabetes. (see also Pharmacist's Letter Sept 2007) (Peel E, Douglas M, Lawton J. Self monitoring of blood glucose in type 2 diabetes: longitudinal qualitative study of patients' perspectives. BMJ. 2007 Sep 8;335(7618):493. Epub 2007 Aug 30.)
O'Kane MJ, Bunting B, Copeland M, Coates VE; on behalf of the **ESMON** study group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. BMJ. 2008 Apr 17; [Epub ahead of print] In patients with newly diagnosed type 2 diabetes self monitoring of blood glucose concentration has no effect on glycaemic control but is associated with higher scores on a depression subscale. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A; on behalf of the Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the **DiGEM** trial. BMJ. 2008 Apr 17; [Epub ahead of print] Self monitoring of blood glucose with or without additional training in incorporating the results into self care was associated with higher costs and lower quality of life in patients with non-insulin treated type 2 diabetes. In light of this, and no clinically significant differences in other outcomes, self monitoring of blood glucose is unlikely to be cost effective in addition to standardised usual care.

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Gilbert C, Valois M, Koren G. **Pregnancy** outcome after first-trimester exposure to **metformin**: a meta-analysis. Fertil Steril. 2006 Sep;86(3):658-63. Epub 2006 Jul 31. On the basis of the limited data available today, there is no evidence of an increased risk for major malformations when metformin is taken during the first trimester of pregnancy. Large studies are needed to corroborate these preliminary results.

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Gulliford MC, Charlton J, Latinovic R. Risk of Diabetes Associated With Prescribed **Glucocorticoids** in a Large Population. Diabetes Care. 2006 Dec;29(12):2728-2729. The researchers found that the adjusted odds ratio for diabetes associated with 3 or more prescriptions for oral glucorticoids was 1.36. Such patients appeared to account for about 2% of incident cases of diabetes.

Gupta AK, Dahlof B, et al. Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. (**ASCOT**) Diabetes Care. 2008 May;31(5):982-8. Epub 2008 Jan 30. Baseline FPG >5 mmol/l, BMI, and use of an atenolol +/- diuretic regimen were among the major determinants of NOD in hypertensive patients. The model developed from these data allows accurate prediction of NOD among hypertensive subjects.

Health Canada Dec/05 Association of **AVANDIA** & **AVANDAMET** with new onset and/or worsening of **macular edema** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/avandia_avandamet_hpc-cps_e.html

Health Canada Jan/06 & July/07 Association of **AVANDIA** & 6 reports of parotid gland enlargement http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n1_e.html#2

Health Canada Apr/07 is warning consumers from The Hong Kong Department of Health found **Lanmei Keili Ji to be adulterated with gliclazide**, a hypoglycaemic agent (lowers blood sugar).

Health Canada May/07 is advising consumers not to use **Xiaokeshuping Jiangtangning Jiaonang** capsules in Hong Kong to contain the undeclared pharmaceutical drugs phenformin, rosiglitazone, and glibenclamide, which may be used in diabetes to lower blood sugar.

Health Canada May& June/07 is advising consumers & health professionals about heart risks with **Avandia** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2007/avandia_pc-cp_3_e.html

Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang, J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.

Health Canada Nov/07 Rosiglitazone (**AVANDIA®**) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated. Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated. Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV).

Health Canada April/08 warns that Singapore's Health Sciences Authority (HSA) advised the public not to use the product **Power 1 Walnut**, because it was found to contain the prescription drugs sildenafil and glibenclamide.

Health Canada April/08 is advising consumers not to use The Hong Kong Department of Health advised the public not to use the product **Tian Sheng Yi Bao** because it was found to contain two pharmaceutical products, glibenclamide and phenformin.

Health Canada June/08 **Nangen Zengzhangsu** (may also be known as Nangen or Nangeng), Sanbianwan, Jiu Bian Wang, Tian Huang Gu Shen Dan, Zui Xian Dan Gong Shi Zi, and Power Up. The Hong Kong Department of Health has warned consumers not to use these herbal/proprietary Chinese medicine products promoted for erectile dysfunction because they have been found to contain sildenafil and/or glibenclamide.

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

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.

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Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of **medication nonadherence** on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med 2006; 166: 1836-1841.

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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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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.

Howard BV, Roman MJ, Devereux RB, et al. Effect of **lower targets for blood pressure and LDL** cholesterol on atherosclerosis in diabetes: The **SANDS** randomized trial. JAMA. 2008;299:1678-1689. Reducing LDL-C and SBP to lower targets resulted in regression of carotid IMT and greater decrease in left ventricular mass in individuals with type 2 diabetes. Clinical events were lower than expected and did not differ significantly between groups. Further follow-up is needed to determine whether these improvements will result in lower long-term CVD event rates and costs and favorable risk-benefit outcomes.

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-))

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

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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

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.

Kanaya AM, Herrington D, Vittinghoff E, et al. Impaired fasting glucose and cardiovascular outcomes in **postmenopausal women** with coronary artery disease. Ann Intern Med. 2005 May 17;142(10):813-20. (Among postmenopausal women with coronary artery

disease, the 2003 definition for impaired fasting glucose was **not** associated with increased risk for new CHD, stroke or TIA, or CHF).

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Kirkman MS, et al. Treating **postprandial hyperglycemia** (**acarbose** 100mg tid vs placebo) does not appear to delay progression of early type 2 diabetes: the early diabetes intervention program. Diabetes Care. 2006 Sep;29(9):2095-101. Ameliorating postprandial hyperglycemia did not appear to delay progression of early type 2 diabetes. Factors other than postprandial hyperglycemia may be greater determinants of progression of diabetes. Alternatively, once FPG exceeds 126 mg/dl, beta-cell failure may no longer be remediable.

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Kleefstra N, et al. Chromium tx has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. Diabetes Care. 2006 Mar;29(3):521-5.

Klein S, Sheard NF, Pi-Sunyer X, et al.Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. Diabetes Care 2004 Aug;27(8):2067-73.

Lambert BL, et al. Diabetes risk associated with use of **olanzapine, quetiapine, and risperidone** in veterans health administration patients with schizophrenia. Am J Epidemiol. 2006 Oct 1;164(7):672-81. Epub 2006 Aug 30.

Landon MB, Thom E, Spong CY, et al. A planned randomized clinical trial of treatment for mild **gestational diabetes** mellitus. J Matern Fetal Neonatal Med. 2002 Apr;11(4):226-31.

Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with **gestational diabetes mellitus**. N Engl J Med. 2000 Oct 19;343(16):1134-8. In women with gestational diabetes, glyburide is a clinically effective alternative to insulin therapy.

Leiter LA, et al.; International Prandial Glucose Regulation Study Group. **Postprandial glucose** regulation: new data and new implications. Clin Ther. 2005;27 Suppl B:S42-56.

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Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for **polycystic ovary syndrome**. Cochrane Database Syst Rev. 2003;(3):CD003053.

Macintosh MC, et al. **Perinatal mortality & congenital** anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ. 2006 Jul 22;333(7560):177. Epub 2006 Jun 16.

Mangione CM, et al. TRIAD Study Group. The association between quality of care and the intensity of diabetes **disease management programs**. Ann Intern Med. 2006 Jul 18;145(2):107-16. Summary for patients in: Ann Intern Med. 2006 Jul 18;145(2):I41.

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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

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EXTRAS Page

Upcoming Trials in Diabetes/CV Risk Prevention:

- **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research); **TRANSCEND** (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease); **RAPSODI** (rimonabant 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.

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 be harmful in RCTs/durations studied so far (e.g. up to 4 year RCTs.) Patients studied and hypoglycemic agents used may affect the benefit/risk potential.
- The UKPDS-33, ~ 10 year trial saw reductions predominantly in the microvascular events (predominantly photocoagulation), with stroke and heart related endpoints not significant, but trending favorably and contributing to the composite endpoint benefit. (Exception: metformin had all-cause death reduction in obese T2DM in UKPDS-34)
- In UKPDS 34,[p860] which noted a mortality benefit for metformin in obese T2DM, there is inconsistency in the association of A1C & outcomes (less A1C difference but more benefit [UKPDS34 VS 33])
- In UKPDS 34 Metformin + Sulfonylurea combination led to a lower A1C than Sulf alone (7.7 vs 8.2) but had higher incidence of DM death and all cause death (perhaps due to design issues and a several year delay in moving to combination therapy) .
- The UKPDS epidemiologic evidence for the 1% drop in A1C did not control for obesity/BMI/waist circumference. [UKPDS 35]
- In ADOPT, rosiglitazone decreased A1C more that metformin or glyburide, but glyburide had the lowest rate of CV outcomes.

There is some disconcordence between randomized trial outcome evidence and the frequently reported "1% A1C..." benefit. One thing that has growing certainty is that the risks and benefits of drug regimens that lower A1C is more complex than what was previously commonly accepted. While a high A1C is not good, some methods of lowering A1C in some patient groups, 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.*}

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

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Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007 Nov 17;370(9600):1706-13. Our findings suggest that 20 mg per day rimonabant increases the risk of **psychiatric adverse events**--ie, depressed mood disorders and anxiety-despite depressed mood being an exclusion criterion in these trials. Taken together with the recent US Food and Drug Administration finding of increased risk of suicide during treatment with rimonabant, we recommend increased alertness by physicians to these potentially severe psychiatric adverse reactions. { InfoPOEMs Jan08: These authors searched several databases for double-blind randomized trials of rimonabant for weight loss in patients with a body mass index higher than 30 (27 if the patient also had an obesity-related comorbid condition such as diabetes). Two reviewers independently assessed the quality of the included studies using the Jadad score. The authors don't describe looking for unpublished studies. Four trials (4105 patients) were included in this analysis. After 1 year, patients taking rimonabant lost an average of 4.7 kg more than did those given placebo. Additionally, 25% of patients taking rimonabant lost at least 10% of their baseline weight compared with 7% of control patients (number needed to treat = 5.3; 95% CI, 4.8 - 6). However, patients taking rimonabant were more likely to have unspecified serious adverse events (4% vs 6%; number needed to treat to harm [NNTH] = 58; 95% CI, 33 - 295). Additionally, 3% of patients taking rimonabant developed depression compared with 1.4% of control patients (NNTH = 63; 95% CI, 41-150). Although it's not formally addressed in this study, the authors mention recent Food and Drug Administration reports of increased suicide risk in patients taking rimonabant.}

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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 ll contained sibutramine. Obat Asam Urat and Asam Urat both contained dexamethasone, phenylbutazone and piroxicam. The Hong Kong Department of Health warned against the use of Slim 3in1 (Xiao Nan zhi Bao) because it was found to contain the undeclared pharmaceutical ingredients sibutramine and phenolphthalein.
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Useful websites:
UK multicentre obesity management project www.counterweight.org
Lifestyle changes week by week plan for patients taking sibutramine www.changeforlifeonline.com
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Cochrane reviews CD:

- TNF-a for induction: data not combined. One RCT indicates single infusion may induce remission. CDP571 may induce remission; no evidence for etanercept. Need longer f/u to assess SE such as TB & lymphoma.
- MTX for induction: data not combined. Evidence from a single large trial suggests benefit of MTX 25 mg IM weekly for induction of remission & complete withdrawal from steroids in refractory disease. No evidence supports lower dose PO MTX.
- CsA for induction: low dose PO CsA does not induce remission. Higher PO or IV doses not adequately evaluated, but ↑risk SE such as nephrotoxicity. One study found clinical improvement on unvalidated scale, but remission not assessed.
- AZA and 6-MP effective for inducing remission (NNT=5); OR increases after 17 weeks of tx; NNT=3 for steroid sparing effect; NNT for SE=14.
- Budesonide: superior to placebo for induction & superior to mesalamine; budesonide was inferior to prednisone/prednisolone, but fewer SE. Note: in disease limited to ileum or ascending colon.
- Natalizumab: superior to placebo for induction, but trials halted after 2 cases fatal progressive multifocal leukoencephalopathy in MS.
- Corticosteroids superior to enteral nutrition therapy for induction.
- 5-ASA not superior to placebo in maintaining remission in CD.
- PO budesonide 6 mg/day not effective in maintaining remission.
- Anti-tubercular tx for maintaining remission: may be effective when remission induced by corticosteroids combined with anti-TB tx; however, this is based on subgroup analyses of 2 trials with small numbers
- Corticosteroids (maintenance): not effective and increased AE.
- Probiotics (maintenance): Lactobacilli GC, E. coli strain Nissle 1917, VSL#3, Saccharomyces boulardii-all not effective, but may be due to small sample size
- AZA (maintenance): effective NNT=7 for maintenance; NNT=3 for steroid sparing; NNH=19.

Cochrane reviews UC:

- 5-ASA superior to placebo to induce remission in UC & trended towards benefit over sulfasalazine (SSZ). However, cost an issue, therefore SSZ generally preferred. 5-ASA has fewer SE than SSZ. 5-ASA not associated with male infertility, but SSZ is.
- 5-ASA superior to placebo in maintaining remission for UC (NNT=6). 5-ASA NOT superior to SSZ (NNT= -19), indicating SSZ superior. HOWEVER, many trials required tolerance of SSZ as part of inclusion criteria (Bergman 2006)
- Transdermal nicotine superior to placebo for inducing remission in UC, however no benefit was seen when compared to standard therapy (oral prednisone or mesalamine). More patients on transdermal nicotine withdrew due to AE then placebo or standard therapy.
- Only 2 small trials identified for CsA; could not be pooled as major differences in design & patients involved. Quick response rates in severe disease appear beneficial, but long-term effects unknown.
- In moderate-severe, refractory disease, infliximab induces remission. NNT=5 at 8 weeks (based on ACT studies alone)

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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 tapered to low doses or off treatment all together. (LOE =))

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))

Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired **Clostridium difficile**-associated disease. JAMA. 2005 Dec 21;294(23):2989-95.

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.

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.

Ford AC, Qume M, Moayyedi P, et al. Helicobacter pylori "**test & treat**" or endoscopy for managing dyspepsia: an individual patient data meta-analysis. Gastroenterology. 2005 Jun;128(7):1838-44 & ACP Journal Club.

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.

Gatta L, Vaira D, Sorrenti G, et al. Meta-analysis: the efficacy of proton pump inhibitors for **laryngeal symptoms** attributed to gastro-oesophageal reflux disease.Aliment Pharmacol Ther. 2007 Feb 15;25(4):385-92. Therapy with a high-dose proton pump inhibitor is no more effective than placebo in producing symptomatic improvement or resolution of laryngo-pharyngeal symptoms. Further studies are necessary to identify the characteristics of patients that may respond to proton pump inhibitor therapy.

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)

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.

Gomollon F, Calvet X. Optimising acid inhibition treatment. Drugs. 2005;65 Suppl 1:25-33.

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.)

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.

Hirano I, Richter JE; Practice Parameters Committee of the American College of Gastroenterology. ACG practice guidelines: **esophageal reflux testing**. Am J Gastroenterol. 2007 Mar;102(3):668-85.

Holtmann G, et al. A placebo-controlled trial of **itopride** in functional dyspepsia. N Engl J Med. 2006 Feb 23;354(8):832-40. (InfoPOEMs: Itopride was somewhat effective for functional dyspepsia, with a number needed to treat of 6 for global improvement but only a small 2-point benefit on a 40-point symptom scale (essentially, an improvement from 12 to 8 with placebo and from 12 to 6 with itopride). The drug appears to be safe on the basis of this small, short study. (LOE = 1b))

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.

Hunt R, Fallone C, Veldhuyzan van Zanten S, et al. CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of Helicobacter pylori--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H pylori infection. Can J Gastroenterol. 2004 Sep;18(9):547-54.

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.

Jarbol DE, et al. **Proton pump inhibitor or testing for Helicobacter pylori** as the first step for patients presenting with dyspepsia? A cluster-randomized trial. Am J Gastroenterol. 2006 Jun;101(6):1200-8. (InfoPOEMs: A test-and-treat strategy is the most cost-effective approach to dyspepsia in the primary care setting. (LOE = 1b))

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.

Kaltenbach T, Crockett S, Gerson LB. Are **lifestyle** measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med. 2006 May 8;166(9):965-71. Neither tobacco nor alcohol cessation was associated with improvement in esophageal pH profiles or symptoms (evidence B). Head of bed elevation and left lateral decubitus position improved the overall time that the esophageal pH was less than 4.0 (evidence B). Weight loss improved pH profiles and symptoms (evidence B). Weight loss and head of bed elevation are effective lifestyle interventions for GERD. There is no evidence supporting an improvement in GERD measures after cessation of tobacco, alcohol, or other dietary interventions. (InfoPOEMs: Decreasing gastroesophageal reflux disease (GERD) symptoms with lifestyle changes requires an empirical approach; the research literature gives very little guidance regarding nondrug approaches. Neither smoking cessation, alcohol avoidance, nor any food avoidances have been shown to make, on average, a difference in symptoms, although existing studies are small and of poor quality. Elevating the head of the bed may be effective. Weight loss may also be effective. Of course, if patients find something that works, encourage them to continue doing it. (LOE = 3a-))

Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. Gut 2005; 54:40-5.

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

Klok RM, Postma MJ, van Hout BA, Brouwers JR. Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use. Aliment Pharmacol Ther. 2003 May 15;17(10):1237-45. (InfoPOEMs: There is no significant difference between equivalent doses of proton pump inhibitors, including equivalent doses of esomeprazole (Nexium) and omeprazole (Prilosec OTC). The decision to choose one over another should be based first on cost and second on individual patient response. (LOE = 1a))

Koek GH, Sifrim D, Lerut T, et al. Effect of the GABA(B) agonist **baclofen** in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. Gut. 2003 Oct;52(10):1397-402.

Lai KC, Lam SK, Chu KM, 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.

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. CONCLUSIONS: Celecoxib was as effective as lansoprazole co-therapy in the prevention of recurrences of ulcer complications in subjects with a history of NSAID-related complicated peptic ulcers. However, celecoxib, similar to lansoprazole co-therapy, was still associated with a significant proportion of ulcer complication recurrences. In addition, more patients receiving celecoxib developed dyspepsia than patients receiving lansoprazole and naproxen.

Laine L, Shah A, Bemanian S. Intragastric 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.

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))

Leontiadis GI, Sharma VK, Dr. Howden CW. Proton pump inhibitor for **acute peptic ulcer bleeding**. The Cochrane Database of Systematic Reviews 2006, Issue 1.

Leung WK, et al. Initial treatment with lansoprazole in young dyspeptic patients with negative urea breath test result: a randomized controlled trial with 12-month follow-up. Am J Gastroenterol. 2007 Jul;102(7):1483-8. Lansoprazole is not effective in the initial management of young dyspeptic patients without H. pylori infection.

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.

Lowe DO, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for **Clostridium difficile**-associated disease: a population-based study. Clin Infect Dis. 2006 Nov 15;43(10):1272-6. Epub 2006 Oct 13. Among community-dwelling older patients, PPI use is not a risk factor for hospitalization with CDAD.

Lundell L, et al. Continued (5-year) followup of a randomized clinical study comparing **antireflux surgery and omeprazole** in gastroesophageal reflux disease. J Am Coll Surg. 2001 Feb;192(2):172-9; discussion 179-81.

Mahadevan U, Kane S. **American gastroenterological association** institute technical review on the use of gastrointestinal medications in **pregnancy**. Gastroenterology. 2006 Jul;131(1):283-311. http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS001650850600864X.pdf

Mahon D, et al. Randomized clinical trial of **laparoscopic Nissen fundoplication compared with proton-pump inhibitors** for treatment of chronic gastro-oesophageal reflux. Br J Surg. 2005 Jun;92(6):695-9.

Marmo R, Rotondano G, Piscopo R, et al. Combination of age and sex improves the ability to predict upper gastrointestinal malignancy in patients with uncomplicated dyspepsia: a prospective multicentre database study. Am J Gastroenterol 2005; 100:784-91. (InfoPOEMs: A cutoff age of over 35 years old for men and 56 years old for women would detect more upper gastrointestinal cancers among patients with uncomplicated dyspepsia than a single cutoff of 45 years for both sexes. Presumably the cost of more endoscopies among younger men would be balanced by the need to do fewer among women aged 45 to 56 years. However, whether this sort of differential sex-based screening is politically possible is another matter. (LOE = 1b))

Mayor S. Proton pump inhibitors match **surgery** in gastroesophageal reflux. BMJ. 2006 Jan 7;332(7532):10.

Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. **On-demand therapy** for gastroesophageal reflux disease. Am J Gastroenterol. 2007 Mar;102(3):642-53. The available data support the use of on-demand therapy for GERD in uninvestigated reflux disease, nonerosive reflux disease, and possibly mild esophagitis as well. On-demand therapy should not be considered for patients with severe esophagitis.

Miura M, Inoue K, Kagaya H, Satoh S, et al. Influence of rabeprazole and lansoprazole on the pharmacokinetics of tacrolimus in relation to CYP2C19, CYP3A5 and MDR1 polymorphisms in renal transplant recipients. Biopharm Drug Dispos. 2007 May;28(4):167-75.

Moayyedi P, Soo S, Deeks J, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD002096.

Nava-Ocampo AA, Velazquez-Armenta EY, Han JY, Koren G. Use of proton pump inhibitors during **pregnancy** and breastfeeding. Can Fam Physician. 2006 Jul;52:853-4.

Oelschlager BK, Quiroga E, Parra JD, et al. CA. Long-Term Outcomes After **Laparoscopic Antireflux Surgery**. Am J Gastroenterol. 2007 Oct 26; [Epub ahead of print] Seven patients (2%) developed a new onset of dysphagia; 32 patients (11%) developed new or increased diarrhea and 27 patients (9%) developed bloating postoperatively. One hundred nineteen patients (41%) were taking some form of antacid medication; 66 (23%) patients were using PPIs and 10 (3%) had undergone reoperation. LARS provides effective long-term relief of GERD. Younger patients, men, and those without dysphagia are predictors of superior outcomes.

Oregon Health Sciences University. Drug class review on PPIs (July 2006) http://www.ohsu.edu/drugeffectiveness/reports/documents/PPIs%20Final%20Report%20u4%20Unshaded.pdf

Pace F, et al. *Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken `**on-demand**`* Aliment Pharmacol Ther. 2007 Jul;26(2):195-204. On the basis of the analysis of 17 studies, we can conclude that on-demand therapy with currently available PPI appears to be effective in the long-term management of patients with NERD or mild and uninvestigated forms of GERD, but not in patients with (severe) erosive oesophagitis.

Pessaux P, Arnaud JP, Delattre JF, Meyer C, Baulieux J, Mosnier H. Laparoscopic **antireflux surgery**: five-year results and beyond in 1340 patients. Arch Surg. 2005 Oct;140(10):946-51.

Pharmacist's Letter Feb 2007. PPI and risk of **hip fracture**.

Pharmacist's Letter Mar 2007. **Update** on PPIs.

Regula J, et al. Prevention of **NSAID-associated** gastrointestinal lesions: a comparison study **pantoprazole versus omeprazole**. Am J Gastroenterol. 2006 Aug;101(8):1747-55. Epub 2006 Jun 30. (InfoPOEMs: This study confirms many other study results (all nicely summarized in Aliment Pharmacol Ther 2003;17:1237-1245) that have found no clinically important differences between proton pump inhibitors. Begin with omeprazole 20 mg per day and, if necessary, increase to 40 mg per day before switching to a much more expensive nongeneric alternative. (LOE = 1b))

Richter JE. Review article: the management of **heartburn in pregnancy**. Aliment Pharmacol Ther. 2005 Nov 1;22(9):749-57.

Rindi G, Fiocca R, Morocutti A, et al.European Rabeprazole Study Group. Effects of **5 years** of treatment with rabeprazole or omeprazole on the gastric mucosa. Eur J Gastroenterol Hepatol. 2005 May;17(5):559-66. This study has confirmed the link between ECL cell hyperplasia and elevated serum gastrin concentrations, but has found no evidence that this progresses to high grades of hyperplasia during 5 years of treatment with rabeprazole or omeprazole.

Rodgers C, van Zanten SV. A meta-analysis of the success rate of **Helicobacter pylori therapy in Canada**. Can J Gastroenterol. 2007 May;21(5):295-300. Both triple therapies consisting of a proton pump inhibitor (PPI), clarithromycin and either amoxicillin or metronidazole performed well, achieving a success rate of 84% and 82%, respectively. The cure rate of PPI-amoxicillin + metronidazole was 76%. Quadruple therapy consisting of a PPI, bismuth, metronidazole and tetracycline, given for seven to 10 days, achieved a success rate of 87%.

Rohss K, Lind T, Wilder-Smith C. Esomeprazole 40 mg provides more effective intragastric acid control than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with gastro-oesophageal reflux symptoms. Eur J Clin Pharmacol. 2004 Oct;60(8):531-9. Epub 2004 Sep 2.

Ronkainen J, et al. Prevalence of **Barrett's esophagus** in the general population: an endoscopic study. Gastroenterology. 2005 Dec;129(6):1825-31.

Sanabria A, Morales C, Villegas M. **Laparoscopic repair** for perforated peptic ulcer disease. Cochrane Database Syst Rev. 2005 Oct 19;4:CD004778. This systematic review suggests that a decrease in septic abdominal complications may exist when laparoscopic surgery is used to correct perforated peptic ulcer. However, it is necessary to develop more randomised controlled trials that include a greater number of patients to confirm such an assumption, guaranteeing a long learning curve for participating surgeons. With the information provided by the available clinical trials it could be said that laparoscopic surgery results are not clinically different from those of open surgery.

Scheiman JM, et al. Prevention of Ulcers by Esomeprazole in At-Risk Patients Using Non-Selective NSAIDs and COX-2 Inhibitors. (**Venus** & **Pluto**) Am J Gastroenterol. 2006 Feb 22; [Epub ahead of print] CONCLUSIONS: For at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors.

Shaheen N, Ransohoff DF. Gastroesophageal reflux, **Barrett** esophagus, and esophageal cancer: clinical applications. JAMA. 2002 Apr 17;287(15):1982-6.

Shannon C, et al. Regimens of misoprostol with mifepristone for early medical **abortion**: a randomised trial. BJOG. 2006 Jun;113(6):621-8. (group I) 400 micrograms of **oral** misoprostol, (group II) 600 micrograms of **oral** misoprostol, and (group III) 800 micrograms of **vaginal** misoprostol. (Neilson J, et al. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2006 Jul 19;3:CD002253.)

Silverstein FE, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1995 Aug 15;123(4):241-9.

Spechler SJ, Long-term outcome(~10yrs) of **medical and surgical therapies for gastroesophageal reflux disease**: follow-up of a randomized controlled trial. JAMA. 2001 May 9;285(18):2331-8.

Spechler SJ. Clinical practice. **Barrett's Esophagus**. N Engl J Med. 2002 Mar 14;346(11):836-42.

Stretta Procedure for GERD. Medical Letter Dec 4/18,2006

Talley NJ, Moore MG, Sprogis A, Katelaris P. Randomised controlled trial of pantoprazole versus ranitidine for the treatment of uninvestigated heartburn in primary care. Med J Aust. 2002 Oct 21;177(8):423-7. Pantoprazole was associated with significantly higher rates of complete control of GORD symptoms than ranitidine at four weeks (40% v 19%; P < 0.001), eight weeks (55% v 33%; P < 0.001), six months (71% v 56%; P = 0.007) and **12 months (77% v 59%; P = 0.001).** CONCLUSIONS: Low-dose pantoprazole is an effective alternative to standard-dose ranitidine for initial and maintenance treatment of patients with symptomatic GORD.

Talley NJ, Vakil NB, Moayyedi P. **American gastroenterological association** technical review on the evaluation of **dyspepsia**. Gastroenterology. 2005 Nov;129(5):1756-80. (Talley NJ; American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. Gastroenterology. 2005 Nov;129(5):1753-5.) Talley NJ, Vakil N; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005 Oct;100(10):2324-37. (InfoPOEMs: Patients with dyspepsia may have gastroesophageal reflux disease (GERD), peptic ulcer, functional (nonulcer) dyspepsia, or (rarely) malignancy. The authors reviewed the world's literature and based their recommendations on the results of the best available evidence. Patients with the onset of dyspepsia at age 56 or older or those with alarm symptoms (bleeding, anemia, early satiety, unexplained weight loss, dysphagia or odynophagia, persistent vomiting, family history of gastrointestinal malignancy, previous documented peptic ulcer, abdominal mass, or lymphadenopathy) at any age should undergo immediate upper endoscopy. Patients with reflux predominant symptoms should be treated as if they have GERD. If the prevalence of Helicobacter pylori (HP) infection in your community is less than 10%, a trial of a proton pump inhibitor (PPI) is recommended. If that fails, a test for HP infection followed by eradication if positive should be pursued. When HP is more common, the test-and-treat strategy should be pursued first, followed by a trial of a PPI. If these strategies fail, upper endoscopy should be considered according to the clinician's judgment. However, the prevalence of ulcer or malignancy in HP- negative patients is quite low in this group.)

Thjodleifsson B, Rindi G, Fiocca R, et al.; European Rabeprazole Study Group. A randomized, double-blind trial of the efficacy and safety of 10 or 20 mg **rabeprazole** compared with 20 mg omeprazole in the maintenance of gastro-oesophageal reflux disease over 5 years. Aliment Pharmacol Ther. 2003 Feb;17(3):343-51.

Thomas T, Abrams KR, De Caestecker JS, Robinson RJ. Meta analysis: cancer risk in Barrett's oesophagus. Aliment Pharmacol Ther 2007;26(11-12):1465-1477. Approximately 7 per 1000 (0.7%) patients with Barrett's esophagus will develop esophageal cancer per year. The low incidence of Barrett's, followed by this low incidence of esophageal cancer, may make routine evaluation of patients with chronic gastroesophageal reflux less important. (LOE = 1b-)

Tolia V, Boyer K. Long-Term Proton Pump Inhibitor Use in **Children**: A Retrospective Review of Safety.Dig Dis Sci. 2008 Feb;53(2):385-393. Epub 2007 Aug 4. Long-term proton pump inhibitor (PPI) therapy (median treatment duration = 35.2 months) appears to be safe for children. Serum gastrin levels remained elevated in nearly 75% of children, but there was no evidence of an increased risk of carcinoid tumor, abnormal vitamin B12 absorption, or any other concerning outcome. (LOE = 1b-)

Vakil N, Moayyedi P, et al. Limited value of **alarm features** in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology. 2006 Aug;131(2):390-401; quiz 659-60.

Valle PC, et al. "Test, score and scope": a selection strategy for safe reduction of upper gastrointestinal endoscopies in young dyspeptic patients referred from primary care. Scand J Gastroenterol. 2006 Feb;41(2):161-9. (InfoPOEMs: For men younger than 45 years, the endoscopic yield is very low for those without Helicobacter pylori infection, nonsteroidal anti-inflammatory drug (NSAID) use, unintended weight loss, or anemia. (LOE = 2b))

van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD002095.

Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, et al. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in Helicobacter pylori negative, primary care patients with dyspepsia: The CADET-HN study. Am J Gastroenterol 2005; 100:1477-88. (InfoPOEMs: Omeprazole (and to a lesser extent, ranitidine) are somewhat effective for patients with Helicobacter pylori (HP) negative dyspepsia, even if patients with a primary complaint of heartburn or reflux are excluded.

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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

CINV Guidelines: 1) MASCC: http://www.mascc.org/content/1.html
2) ASCO: http://www.asco.org/portal/site/ASCO/

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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 C	SE: nausea (↓with time, CR SL tabs);headache, dizziness, sedation, yawning Not affected by food or alcohol	Onset <30min Peak ~1h Duration ~1-2h Safe with nitrates so may be preferred in select cardiac patients Can be used in combination with PDE5 inhibitors for increased effect Limited efficacy compared to PDE5 inhibitors generally [39]	2-3mg 6mg	

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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
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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 **Libidfit** may pose health risks (promoted for sexual enhancement and erectile dysfunction, but contains an undeclared amount of a pharmaceutical ingredient similar to sildenafil) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_02_e.html
Health Canada May/06 is warning consumers not to use the product **Nasutra** because it has been found to contain the undeclared ingredient sildenafil (chemical name for Viagra) that could lead to serious health risks, especially for patients with existing medical conditions such as heart problems, those who may be taking heart medications, or those who may be at risk for strokes.
Health Canada Feb/07 is advising consumers not to use the following product listed in the table below due to concerns about possible side-effects. More info **Power 58; Platinum Power 58; Ehanix; Jolex; Onyo; Deguozonghengtianxia** because they contained acetildenafil. Acetildenafil is an analogue of sildenafil, a prescription medication indicated for treatment of erectile dysfunction.
Health Canada Mar/07 is warning consumers not to use the unauthorized natural health product **XOX For Men**, because it contains an undeclared pharmaceutical ingredient, tadalafil, an ingredient found in the prescription drug Cialis. The use of XOX For Men could pose serious health risks, especially for patients with existing medical conditions such as heart problems, those taking heart medication, or those at risk of stroke.
Health Canada Mar/07 is warning consumers not to use the unauthorized product **Vigorect** Oral Gel Shooter, because it contains an undeclared drug substance tadalafil, which should only be available by prescription.
Health Canada Apr/07 is warning consumers from the United States FDA found **V.MAX and Rhino Max (Rhino V Max) to contain undeclared amounts of aminotadalafil**, an analogue of tadalafil, used to treat erectile dysfunction.
Health Canada May/07 is warning consumers **Urat Madu** capsules are marketed for the treatment of erectile dysfunction. The product is adulterated with **sildenafil**, a prescription drug that has been associated with serious side effects including sudden vision loss, penile tissue damage and urinary tract infection.
Health Canada May/07 is advising consumers that **HS Joy of Love** product is marketed as a dietary supplement and was found to contain piperadino **vardenafil**.
Health Canada May/07 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: **Power 58 Extra, Platinum Power 58 Extra, Enhanix New Extra Men's Formula, Valentino, King Power Oral Solution, and Stretch Up** Capsules are marketed as treatments for erectile dysfunction. The products contain analogues of **sildenafil** and **vardenafil**, which are prescription drugs used for the treatment of erectile dysfunction.
Health Canada June/07 is warning consumers not to use the product **Encore Tabs for Men**, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.
Health Canada July/07 is warning consumers not to use **Zencore** Tabs, a product advertised as a dietary supplement for sexual enhancement, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.
Health Canada July/07 & the US Food and Drug Administration (FDA) found ***Liviro3*** to contain tadalafil, a prescription drug that should only be taken under the guidance of a health professional.
Health Canada Aug/07 via Medsafe, the New Zealand health regulatory authority, advised the public not to use the products **Darling Capsules, Dali Capsules, Spanish Fly** Capsules, and an unnamed product, because they were found to contain sildenafil.
Health Canada Aug/07 Consumers who use **Excite for women or Ultimates for men** may be at risk of serious side effects similar to those associated with sildenafil.
Health Canada Sept/07 is advising consumers not to use **Satis 60 Hours Ever Lasting Formula** is used for the treatment of erectile dysfunction/sexual enhancement. It was found to contain piperidenafil an analogue of vardenafil.. **True Man** and **Energy Max** are used as sexual enhancement/ erectile dysfunction products and were found to contain an analogue of sildenafil or vardenafil.
Health Canada Sept/07 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: **Top Gun for Men Herbal Extracts** has been found to contain a substance similar to tadalafil. **Oyster Plus** has been found to contain tadalafil. **Deguozhanjiang** contains sildenafil and tadalafil, prescription drugs used for the treatment of erectile dysfunction. **Chongcaoliubian Jiaonang** and **Santi Scalper Penis Erection** Capsule contain sildenafil.
Health Canada Nov/07 is advising consumers not to use **Axcil** and **Desirin**, are promoted as natural sexual enhancement/ erectile dysfunction products. Consumers are warned not to use Axcil and Desirin because both products were found to contain the prescription drug sildenafil.
Health Canada Mar/08 is warning consumers not to use **ADAM**, an unauthorized product that contains an undeclared pharmaceutical ingredient similar to the prescription drug sildenafil.
Health Canada Mar/08 is warning consumers not to use **Libidus**, an unauthorized product promoted on the web site of the manufacturer for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the undeclared prescription drug sildenafil.
Health Canada April//08 warns that Singapore's Health Sciences Authority (HSA) advised the public not to use the product **Power 1 Walnut**, because it was found to contain the prescription drugs sildenafil and glibenclamide
Health Canada April//08 is advising consumers not to use 2 foreign health products, **Aspire 36** and **Aspire Lite**, because they were found to contain undeclared sildenafil analogues.
Health Canada April/08 is warning consumers not to use **Vigoureux**, an unauthorized product promoted for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the prescription drug sildenafil

Health Canada April/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **Tian Li** was found to contain tadalafil and hydroxyhomosildenafil. Xian Zhi Wei II was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.

Health Canada May/08 is advising consumers not to use **vpxl No1** Dietary Supplement for Men was found to contain tadalafil

Health Canada May/08 is warning consumers not to use **Desire**, an unauthorized product promoted to enhance male sexual performance as this product may pose serious health risks in certain patients. Lot 0070263 of the product was found to contain the prescription drug phentolamine.

Health Canada June/08 **Nangen Zengzhangsu** (may also be known as Nangen or Nangeng), Sanbianwan, Jiu Bian Wang, Tian Huang Gu Shen Dan, Zui Xian Dan Gong Shi Zi, and Power Up. The Hong Kong Department of Health has warned consumers not to use these herbal/proprietary Chinese medicine products promoted for erectile dysfunction because they have been found to contain sildenafil and/or glibenclamide.

Health Canada June/08 **Zhong Hua Niu Bian**. Zhong Hua Niu Bian is an herbal/proprietary Chinese medicine product promoted for erectile dysfunction. Singapore's Health Sciences Authority has warned against the use of this product because it has been found to contain sildenafil, glibenclamide, tadalafil and sibutramine

Health Canada July/08 Foreign Product Alerts: **Super Shangai,Strong Testis, Shangai Ultra, Shangai Ultra X, Lady Shangai, Shangai Regular (also known as Shangai Chaojimengnan), Actra-Sx, An unknown product containing the plant Lycium barbarum L., Adam Free, NaturalUp, Erextra, Yilishen, Blue Steel, Hero, & Naturalē Super Plus.** These products have been found to contain sildenafil or an unapproved substance similar to sildenafil.

Health Canada July/08 is advising consumers not to use foreign health products due to concerns about possible side-effects: Wodibo. **Wodibo** is promoted as an all-natural Chinese potency-enhancing product for the treatment of erectile dysfunction. The Danish Medicines Agency has warned against the use of Wodibo because it was found to contain sildenafil and tadalafil, prescription drugs authorized for treatment of erectile dysfunction. **Viril-Ity-Power** (VIP) Tabs. The U.S. Food and Drug Administration has warned consumers not to use Viril-Ity-Power (VIP) Tabs because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil.

Health Canada Aug/08 is warning consumers not to use **Rize 2 The Occasion** capsules (Rize2), an unauthorized product promoted for the treatment of erectile dysfunction, because it may pose serious health risks. Rize 2 contains an undeclared pharmaceutical ingredient similar to the prescription drug sildenafil.

Health Canada Aug/08 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: **Oyster Extract** Caps. The Hong Kong Department of Health has recalled Oyster Extract Caps because they were found to contain an undeclared ingredient similar to the prescription drug sildenafil. **Xiadafil** VIP Tabs. At the request of the U.S. Food and Drug Administration, U.S. federal authorities seized all Xiadafil VIP Tabs sold in 8 tablet bottles (Lot #6K029) and blister cards of 2 tablets (Lot #6K029-SEI) because they were found to contain an undeclared ingredient similar to the prescription drug sildenafil. **Herb Vigour, Natural Vigour and China Vigour**. The Netherlands Health Care Inspectorate, the U.K. Medicines and Healthcare Products Regulatory Agency, and the Danish Medicines Agency has warned against the use of Herb Vigour, Natural Vigour and China Vigour because they were found to contain undeclared pharmaceutical ingredients used for the treatment of erectile dysfunction that should only be taken under the supervision of a health care professional.

Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Armstrong Natural Herbal Supplement, Enhanix New Extra Men's Formula, Power 58 Extra, and Platinum Power 58 Extra** were adulterated with tadalafil or unapproved substances with structures similar to tadalafil and vardenafil.

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Extras:

1) ACs, Other: **propantheline** -less effective & ↑ SE than flavoxate & oxybutynin.[11] NICE states not to use[1]; Adult: 7.5mg tid, 7.5-30mg 3-5x/day, 60mg qid; Geriatric: 7.5mg tid; Peds: 7.5-15mg q4-6h;
2) Adrenoreceptor agonists (**phenylpropanolamine** predominantly studied but use extended to **ephedrine**, **pseudoephedrine**): studied for SUI. But cardiac arrhythmias & HTN outweigh benefits [31].
3) **Belladonna & opium suppositories**-used to relieve **pain of uretal spasms** & pain associated with bladder tenesmus that can occur post-op[32]. Some report use in nocturnal diuresis[11]
   dicyclomine -insufficient data to recommend over other agents, dose 20-40mg qid.[11]
4) **Flavoxate**: Not used for OAB currently[1] but may be used in discomfort associated with BPH. Efficacy might be comparable to propantheline according to older, short-term studies[11].
   Dose: Adult: 100-200mg tid-qid. May reduce dose with Sx improvement. One trial found 1200mg to be superior to 600mg/day. May be effective in children from 6-12 y/o experiencing nocturnal enuresis (33% vs 17% response in placebo)[11]. Pediatrics > 12y/o: 100-200mg tid-qid. May reduce dose with Sx improvement[11].
5) **Phenazopyridine**[11]: used strictly as a **urinary analgesic**. The necessity of this medication would suggest pathology different from UI. Dose: Adult: 200mg tid after meals. If renal GFR > 50ml/min 200mg q8-16h. Avoid if GFR < 50ml/min. Geriatrics: ↑risk of accumulation & toxicity. SE: discolor urine
6) **Propiverine** [53]: tertiary amine with anticholinergic & calcium channel antagonist activity; has active metabolites; dose: 15mg IR bid or 30mg ER daily; available United Kingdom [2006].

Oxybutynin (Oxy) vs Tolterodine in OAB

- OBJECT: Oxy ER 10mg daily vs Tolt IR 2mg BID: 12 week; ♂ & ♀; Oxy ER slightly more effective (e.g. Total incontinence episodes/wk: NNT=45); no difference in overall AEs (dry mouth, CNS effects).[52]
- OPERA: Oxy ER 10mg vs Tolt ER 4mg daily; 12 week: ♀ only with severe symptoms; Oxy ER somewhat more effective (e.g. 23 vs 16.8% no UI; NNT=16); but also more dry mouth (Any 29.7% vs 22.3%; NNH=13: mod-severe 7.4% vs 5.0% , NS).[50]
- ACET: Oxy ER 5 or 10mg vs Tolt ER 2 or 4mg daily; 8 week; ♂ & ♀; Tolt 4mg more effective than Oxy 10 70 vs 60% improvement; but lower doses efficacy still ~60% & less dry mouth but similar for Tolt 4 vs Oxy 5 ; open label trial & subjective assessments subject to bias.[51]

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IFIS; however, their relationship to the syndrome is not as definitive. IFIS is a clinical syndrome observed during cataract surgery reported in patients taking systemic alpha1AR antagonists. It has been most strongly linked to use of tamsulosin. Medication washout periods of up to 2 weeks and specific surgical procedures have been attempted to reduce risk of complications from alpha1AR antagonists in the setting of cataract surgery.

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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
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(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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126. April/07 NEJM: In the face of Congressional subpoenas and unfavorable publicity, reviewers at the FDA were warned at a June 2006 meeting by Andrew von Eschenbach, then the acting FDA commissioner, not to discuss **Ketek** outside the agency. By this time, 23 cases of acute severe liver injury and 12 cases of acute liver failure, 4 of them fatal, had been linked to Ketek. By the end of 2006, Ketek had been implicated in 53 cases of hepatotoxic effects. The FDA did not relabel Ketek to indicate its possible severe hepatotoxicity until 16 months after the first liver-failure cases became public. The withdrawal of approval for two indications, acute bacterial sinusitis and acute exacerbation of chronic bronchitis, for which Ketek's efficacy had never been demonstrated, did not occur until February 12, 2007 — only a day before the Congressional hearing on Ketek.
127. Wilson W, Taubert KA, Gewitz M, et al. **Prevention of infective endocarditis guidelines** from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007. DOI:10.1161/CIRCULATIONAHA.106.183095. Available at: http://circ.ahajournals.org. (see also Pharmacist's Letter. May 2007. Guidelines for infective endocarditis. Recommended if: artificial heart valve, history of infective endocarditis, specific congenital heart conditions, or if a heart transplant that develops a problem in a heart valve)
128. Medical Letter: Treatment Guidelines. **Choice of Antibacterial Drugs**. May 2007.
129. Health Canada Sept/07 Sanofi-aventis Canada, Inc. is informing Canadians that the antibiotic Ketek (telithromycin), should no longer be used to treat sinusitis, bronchitis, tonsillitis or pharyngitis. Ketek can still be used to treat certain types of pneumonia. (only for CAP)
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2007 Oct 17;298(15):1772-8. In the years following introduction of PCV7, a strain of S pneumoniae has emerged in the United States as an otopathogen that is **resistant** to all FDA-approved antibiotics for treatment of AOM in children.

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133. Ramakrishnan K, Sparks RA, Berryhill WE. Diagnosis and treatment of **otitis media**. Am Fam Physician. 2007 Dec 1;76(11):1650-8.
134. Slapak I, Skoupá J, et al Efficacy of **isotonic nasal seawater wash** in the treatment & prevention of rhinitis in children. Arch Otolaryngol Head Neck Surg. 2008 Jan;134(1):67-74.
135. Monaghan T, Boswell T, Mahida YR. Recent advances in **Clostridium difficile**-associated disease. Gut. 2008 Feb 5; [Epub ahead of print]
136. Young J, De Sutter A, Merenstein D, et al. Antibiotics for adults with clinically diagnosed **acute rhinosinusitis**: a meta-analysis of individual patient data. Lancet. 2008 Mar 15;371(9616):908-14. Common clinical signs and symptoms cannot identify patients with rhinosinusitis for whom treatment is clearly justified. Antibiotics are not justified even if a patient reports symptoms for longer than 7-10 days.
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Extras

Combos to Avoid: Early virologic failure: abacavir + lamivudine (or emtricitabine) + tenofovir ; didanosine + lamivudine (or emtricitabine) + tenofovir; didanosine + tenofovir + NNRTI; lamivudine/emtricitabine + tenofovir + nevirapine[66]

↑SE: Didanosine + stavudine (peripheral neuropthy, pancreatitis & lactic acidosis); ATV + IDV ↑bilirubin; 2 NNRTI regimen Antagonism: stavudine + zidovudine

- Oral contraceptives + non-ritonavir boosted atazanavir (may ↑ hormone levels; ⇨use lowest dose OC)[67] or indinavir (will maintain hormone levels)

{Refractory large volume diarrhea, HIV related: octreotide (50-500mcg sc tid)$$$ }[68,69]

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Bhat N, Wright JG, Broder KR, et al. Influenza-Associated Deaths among Children in the United States, 2003-2004. N Engl J Med. 2005 Dec 15;353(24):2559-2567. RESULTS: One hundred fifty-three influenza-associated deaths among children were reported by 40 state health departments

Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet. 2005 Oct 1;366(9492):1175-81. Epub 2005 Sep 22. FINDINGS: More than 7000 influenza A field isolates were screened for specific aminoacid substitutions in the M2 gene known to confer drug resistance. During the decade of surveillance a significant increase in drug resistance was noted, from 0.4% in 1994-1995 to 12.3% in 2003-2004. This increase in the proportion of resistant viruses was weighted heavily by those obtained from **Asia** with 61% of resistant viruses isolated since 2003 being from people in Asia. INTERPRETATION: Our data raise concerns about the appropriate use of adamantanes & draw attention to the importance of tracking the emergence and spread of drug-resistant influenza A viruses.

Bright RA, et al. Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. JAMA. 2006 Feb 22;295(8):891-4. Epub 2006 Feb 2. RESULTS: A total of 209 influenza A(H3N2) viruses isolated from patients in 26 states were screened, of which 193 (92.3%) contained a change at amino acid 31 (serine to asparagine [S31N]) in the M2 gene known to be correlated with adamantane resistance. Two of 8 influenza A(H1N1) viruses contained the same mutation. Drug-resistant viruses were distributed across the United States. CONCLUSIONS: The high proportion of influenza A viruses currently circulating in the United States demonstrating adamantane resistance highlights the clinical importance of rapid surveillance for antiviral resistance. Our results indicate that these drugs should not be used for the treatment or prophylaxis of influenza in the United States until susceptibility to adamantanes has been reestablished among circulating influenza A isolates.

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FDA Acts to Protect Public from **Fraudulent Avian Flu Therapies** Dec/05 http://www.fda.gov/bbs/topics/NEWS/2005/NEW01274.html

FDA April /08 GlaxoSmithKline informed healthcare professionals of changes to the WARNINGS AND PRECAUTIONS sections of prescribing information for **Relenza** regarding information from postmarketing reports (mostly from Japan) of **delirium and abnormal behavior** leading to injury in patients with influenza who are receiving neuraminidase inhibitors, including Relenza. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of Relenza to these events has not been established. Influenza can be associated with a variety of neurologic and behavioral symptoms which can include seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

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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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Primaquine 26.3mg tab (= 15mg base) ✗ ▼ 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 July06 [2].

- **Chloroquine/doxycycline/mefloquine prophylaxis**: primaquine taken in conjunction with the last 2 wks of post-exposure prophylaxis, but may be taken immediately after.
- **Atovaquone/proguanil prophylaxis:** primaquine is taken during atovaquone/ proguanil post-exposure prophylaxis & then for an additional 7-14 days after.

Pediatric Dosing

Prophylaxis: 0.5 mg(base)/kg/day
Terminal Prophylaxis: 0.5 mg/kg/day x14d

Adult Dosing

Prophylaxis: 52.6 mg (30 mg base) OD $9
Terminal Proph.: 30 mg base/d x 14d $9

For prophylaxis: begin 1-2d prior to entering MRZ, continue during stay, & 1 wk after leaving

Primaquine eradicates latent parasites in the liver.

Comments

Second-line for chloroquine resistant areas

- 85- 95% effective against P. *falciparum* & P. *vivax*
- **Only therapy to prevent relapse from P. vivax & P.ovale** due to dormant hypnozoites in liver (relapse may occur within 5 years of exposure)

CI: **G6PD deficiencies**, 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**

{Recent historical resistance trends: {choroquine sensitive areas: travel to **Caribbean** including Haiti and rural areas of Dominican Republic; travelers visiting resort areas not generally at risk; travel to Central America except Panama, Mexico, Argentina; parts of China / Middle east; geographic risk and resistance trends change over time.}

Approximate malaria risk (1 month stay without chemoprophylaxis): (source: CCDR 2000 Malaria Recommendations, p.3)

-	Oceania (Papua New Guinea, Irian Jaya, Solomon Islands, and Vanuatu)	1:30 or higher
-	Sub-Saharan Africa	1:50
-	Indian Subcontinent	1:250
-	Southeast Asia	1:1000
-	South America	1:2,500
-	Central America	1:10,000

- Risk also ↑'d with >6month stay, in part due to underuse of protection measures.
- Stand-By Emergency Treatment (self-admin) may be recommended in select cases.

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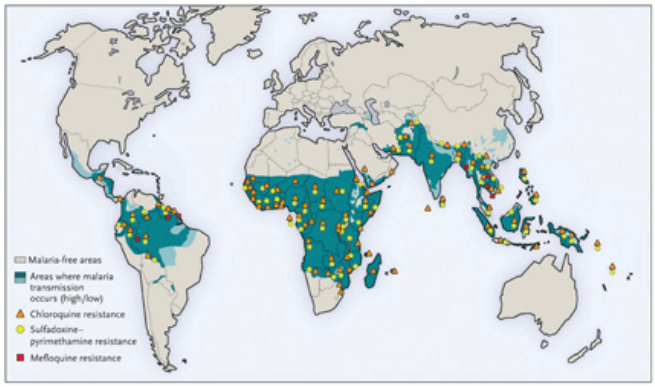

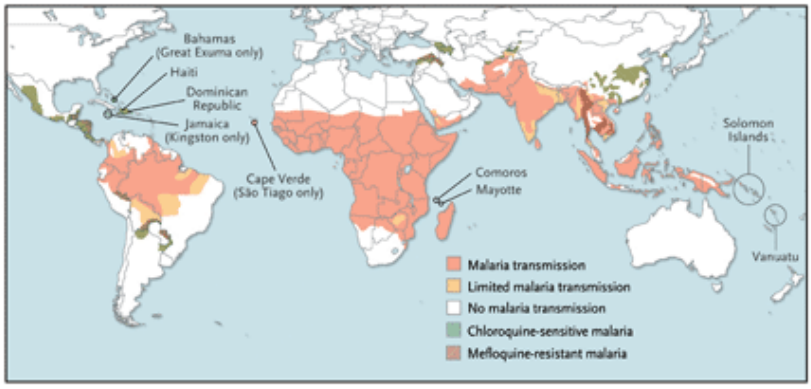

Thumbnails: Areas of Malaria Transmission and Antimalarial Drug Resistance. Data on malaria transmission are for 2007 and are from the World Health Organization. Data on drug resistance are for 2004 and are from the Roll Back Malaria partnership.**NEJM** June 5,2008. 2nd Map Thumbnail: NEJM Aug 7, 2008.

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Hydroxychloroquine PLAQUENIL,g 200mg tab **{Not used very often!** Licensed for malaria in USA**}** Second-line: chloroquine sensitive malaria **C** - Only in chloroquine-sensitive P. *falciparum* malaria prevention {Opthalmological exam periodically if used weekly low dose long term; risk very low in first 5yrs; if >5yrs (BMJ,CDC), or high risk (ACP)}.	Pediatric: 5 mg base/kg weekly (200 mg tab = 155 mg base) (Do not exceed adult dose) •Adult: 400 mg **weekly** ◆Begin **2 wks prior** to entering MRZ, continue during stay & **8 wks after** leaving MRZ	19	• **Caution**: pts with hepatic failure, **G6PD** deficiency, pre-existing auditory damage; psoriasis, prophyria {Pregnancy: considered safe} • **SE**: N/V/D(↓ by giving with food or milk), pruritus, fatigue, seizures, headache & dizziness. Uncommon: alopecia, hair depigmentation, skin eruptions & seizures. • **DI**: antacids, cimetidine, digoxin (increase dig level) • Vaccine Interaction[17]: Assume same as chloroquine

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COMMUNITY ACQUIRED PNEUMONIA – Empiric Antibiotic Selection

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URINARY TRACT INFECTIONS (UTI), ADULT – TREATMENT OPTIONS

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Pharmacist's Letter: Treatment of Uncomplicated UTI June 2006

Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003237. DOI: 10.1002/14651858.CD003237.pub2. {Cochrane Summary: Severe urinary tract infection (UTI) is a common infection in adults and children, causing acute disease with a variety of symptoms such as fever and flank pain. This may lead to kidney damage, kidney failure or hypertension. Standard therapy involves antibiotics given at least initially by injection. This review identified 15 studies (1743 participants). The results of this review suggest oral therapy is equally effective in treating UTI and preventing long-term damage. This might reduce costs but also inconvenience for the patient.}

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in most patients. (LOE = 2b))
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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)-

Back Pain Treatment Options: REFERENCES

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Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, Owens DK; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. **Diagnosis and treatment of low back pain**: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. **2007** Oct 2;147(7):478-91. 1: Clinicians should conduct a focused history and physical examination to help place patients with low back pain into 1 of 3 broad categories: nonspecific low back pain, back pain potentially associated with radiculopathy or spinal stenosis, or back pain potentially associated with another specific spinal cause. The history should include assessment of psychosocial risk factors, which predict risk for chronic disabling back pain (strong recommendation, moderate-quality evidence). RECOMMENDATION 2: Clinicians should not routinely obtain imaging or other diagnostic tests in patients with nonspecific low back pain (strong recommendation, moderate-quality evidence). RECOMMENDATION 3: Clinicians should perform diagnostic imaging and testing for patients with low back pain when severe or progressive neurologic deficits are present or when serious underlying conditions are suspected on the basis of history and physical examination (strong recommendation, moderate-quality evidence). RECOMMENDATION 4: Clinicians should evaluate patients with persistent low back pain and signs or symptoms of radiculopathy or spinal stenosis with magnetic resonance imaging (preferred) or computed tomography only if they are potential candidates for surgery or epidural steroid injection (for suspected radiculopathy) (strong recommendation, moderate-quality evidence). RECOMMENDATION 5: Clinicians should provide patients with evidence-based information on low back pain with regard to their expected course, advise patients to remain active, and provide information about effective self-care options (strong recommendation, moderate-quality evidence). RECOMMENDATION 6: For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy (strong recommendation, moderate-quality evidence). For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs. RECOMMENDATION 7: For patients who do not improve with self-care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits-for acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation (weak recommendation, moderate-quality evidence).

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European Evidence Based Guidelines: 2005 http://www.backpaineurope.org/web/files/WG2_Guidelines.pdf

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Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: **Botulinum** neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 May 6;70(19):1707-14. Botulinum neurotoxin (BoNT) should be offered as a treatment option for the treatment of axillary hyperhidrosis and detrusor overactivity (Level A), should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia after spinal cord injury (Level B), and may be considered for gustatory sweating and low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B). There is presently no consistent or strong evidence to permit drawing conclusions on the efficacy of BoNT in chronic daily headache (mainly transformed migraine) (Level U). While clinicians' practice may suggest stronger recommendations in some of these indications, evidence-based conclusions are limited by the availability of data.

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88 Jüni P, Reichenbach S, Trelle S, et al. Swiss Viscosupplementation Trial Group. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. Arthritis Rheum. 2007 Nov;56(11):3610-9. We found no evidence for a difference in efficacy between hylan and HAs. In view of its higher costs and potential for more local adverse events, we see no rationale for the continued use of hylan in patients with knee OA. {Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: A systematic review and meta-analysis. Arthritis Rheum. 2007 Nov 29;57(8):1410-1418 [Epub ahead of print] Given the likely lack of a superior effectiveness of hylan over hyaluronic acids and the increased risk of local adverse events associated with hylan, we discourage the use of intraarticular hylan in patients with knee osteoarthritis in clinical research or practice.

Additonal articles:

Arnold LM, Rosen A, et al. A randomized, double-blind, placebo-controlled trial of **duloxetine** in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005 Dec 15;119(1-3):5-15. Epub 2005 Nov 17. InfoPOEMs: 26Apr2006. **Duloxetine** (Cymbalta, Xeristar, Yentreve) is effective in some women with fibromyalgia, whether or not they are depressed. The average decrease in pain score as compared with placebo is small -- 1.31 to 1.44 of a possible 10 -- and many women will discontinue treatment (35% - 39% in this study). However, a significant proportion of women will experience a 50% or greater drop in average pain scores. The number needed to treat is 6 for 3 months. (LOE = 1b-)

Bandolier: InfoPOEMs: 03May2006. **Avocado/soybean** unsaponifiables reduce pain, NSAID use in knee OA. The limited data to date support the safety and possible efficacy of ASU for osteoarthritis of the knee. More and longer studies are needed before we can recommend this to our patients without hesitation. (LOE = 1b-)

Berry JD, Petersen KL. A single dose of **gabapentin** reduces acute pain and allodynia in patients with **herpes zoster**. Neurology. 2005 Aug 9;65(3):444-7.

Boureau F, Legallicier P, Kabir-Ahmadi M. **Tramadol in post-herpetic neuralgia**: a randomized, double-blind, placebo-controlled trial. Pain. 2003 Jul;104(1-2):323-31.

Busch AJ, Barber KAR, Overend TJ, Peloso PMJ, Schachter CL. Exercise for treating **fibromyalgia** syndrome. **Cochrane** Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003786. DOI: 10.1002/14651858.CD003786.pub2

Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005522. Review.

{Tramadol or tramadol/paracetamol decreases pain intensity, produces symptom relief, and improves function in patients with OA, but these benefits are small}

Chandra K, et al. **Gabapentin versus nortriptyline** in **post-herpetic neuralgia** patients: a randomized, double-blind clinical trial--the GONIP Trial. Int J Clin Pharmacol Ther. 2006 Aug;44(8):358-63. Gabapentin was shown to be equally efficacious but was better tolerated compared to nortriptyline and can be considered a suitable alternative for the treatment of PHN.

Clegg DO, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808. InfoPOEMs: 03May2006. **Glucosamine** HCl and **chondroitin** provides modest if any symptomatic benefit for patients with mild osteoarthritis of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (LOE = 1b)

Carville SF, Arendt-Nielsen S, Bliddal H, et al. **EULAR** evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2008;7:536-541. {InfoPOEMs: Antidepressants, pramipexole (Mirapex and Sifrol), pregabalin (Lyrica), tramadol (Ultram), tropisetron (Navoban), and heated pool treatments have been shown to have short-term effectiveness in the treatment of fibromyalgia pain. (LOE = 1a-)}

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33. Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ. 2005 Apr 12;172(8):1039-43. (InfoPOEMs: The evidence that intra-articular

hyaluronic acid helps patients with knee osteoarthritis is of poor quality. Improvements in pain at rest and pain during exercise is seen in a minority of studies, and those studies were of lower quality than those showing no benefit. There is no evidence of functional improvement. Injections like this have a potentially powerful placebo effect, so any benefit seen in unblinded studies without concealed allocation is likely represent the placebo effect rather than any effect of the drug. (LOE = 1a-)) Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol. 2006 May;33(5):951-6.

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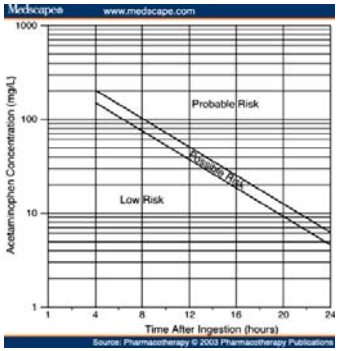
35. Sudbo J, Lee JJ, Lippman SM, et al. Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study. Lancet. 2005 Oct 15-21;366(9494):1359-66.
Long-term use of NSAIDs is associated with a reduced incidence of oral cancer (including in active smokers), but also with an increased risk of death due to cardiovascular disease. These findings highlight the need for a careful risk-benefit analysis when the long-term use of NSAIDs. (Jan/06 The Norwegian daily newspaper Dagbladet reports that a number of **statistical improbabilities** were found in the data set of the cancer trial, published in the Lancet in October last year. Lancet editor Dr Richard Horton told the BBC he would be speaking to the coauthors of the study to seek their permission to retract the paper. One example of the improbabilities" is the fact that of the 908 people in the trial, 250 shared the same birthday.)

36. **Acetaminophen Overdose**: Medscape article: http://www.medscape.com/viewarticle/459187_4 ; Merck Manual's Online Medical Manual: http://www.merck.com/mmpe/sec21/ch326/ch326c.html {Rumack-Matthew nomogram for predicting (Caution with units of measure!) } (10ug/ml = 66.2umol/L) {Acetaminophen level: 4hrs post ingestion & repeat in 4hrs; if ≥150mg/kg and 8hr post, may start **n-acetylcysteine** while awaiting levels; TOXIC levels: 4hr level >993umol/L; 6hr >728umol/L; 8hr >496.5umol/L; 24hr >29.8umol/L } {LFTs: AST usually ↑ first} Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med. 2008 Jul 17;359(3):285-92.



ADAPT Research Group. Cognitive Function Over Time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): Results of a Randomized, Controlled Trial of Naproxen and Celecoxib. Arch Neurol. 2008 May 12. [Epub ahead of print] Use of naproxen or celecoxib did not improve cognitive function. There was weak evidence for a detrimental effect of naproxen.

Al-Sukhun J, Koivusalo A, Tornwall J, Lindqvist C. COX-2 inhibitors and early **failure of free vascular flaps**. N Engl J Med. 2006 Aug 3;355(5):528-9.

Amin AK, et al. Does **obesity** influence the clinical outcome at five years following total **knee replacement** for osteoarthritis? J Bone Joint Surg Br. 2006 Mar;88(3):335-40**.** (InfoPOEMs: In this study, obese patients undergoing primary knee arthroplasty had comparable long-term outcomes with nonobese patients. (LOE = 1b-))

Amin SB, Sinkin RA, Glantz JC. Metaanalysis of the effect of antenatal **indomethacin** on **neonatal outcomes**. Am J Obstet Gynecol. 2007 Nov;197(5):486.e1-10. Antenatal indomethacin may be associated with an increased risk of periventricular leukomalacia and necrotizing enterocolitis in premature infants and therefore should be used judiciously for tocolysis.

Andersohn F, et al. Cyclooxygenase-2 Selective Nonsteroidal Anti-Inflammatory Drugs and the **Risk of Ischemic Stroke**. A Nested Case-Control Study. Stroke. 2006 May 25; [Epub ahead of print] Current use of rofecoxib (OR=1.71; 95% CI, 1.33 to 2.18), etoricoxib (OR=2.38; 95% CI, 1.10 to 5.13), but not of celecoxib (OR=1.07; 95% CI, 0.79 to 1.44) was associated with a significantly increased risk of ischemic stroke. For rofecoxib and etoricoxib, ORs tended to increase with higher daily dose and longer duration of use and were also elevated in patients without major stroke risk factors. "From the non-selective NSAIDs, diclofenac, but not ibuprofen or naproxen, was also associated with a slightly increased risk of ischemic stroke," Dr. Andersohn said.

Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs & risk of **acute myocardial infarction**. Circulation. 2006 Apr 25;113(16):1950-7. Epub 2006 Apr 17. Current use of etoricoxib was associated with a 2.09-fold (95% confidence interval [CI], 1.10 to 3.97) risk of AMI compared with no use of NSAIDs during the prior year. Current use of rofecoxib (RR=1.29; 95% CI, 1.02 to 1.63), celecoxib (RR=1.56; 95% CI, 1.22 to 2.00), and diclofenac (RR=1.37; 95% CI, 1.17 to 1.59) also significantly increased the AMI risk. For current use of valdecoxib, the RR was 4.60 (95% CI, 0.61 to 34.51). RRs appeared to increase with higher daily doses of COX-2 inhibitors and were also increased in patients without major cardiovascular risk factors.

Andrew T. Chan, MD, MPH; Edward L. et al. Long-term Use of Aspirin and Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Cancer JAMA. 2005;294:914-923. CONCLUSIONS: Regular, long-term aspirin use reduces risk of colorectal cancer. Nonaspirin NSAIDs appear to have a similar effect. However, a significant benefit of aspirin is not apparent until more than a decade of use, with maximal risk reduction at doses greater than 14 tablets per week. These results suggest that optimal chemoprevention for colorectal cancer requires long-term use of aspirin doses substantially higher than those recommended for prevention of cardiovascular disease, but the dose-related risk of gastrointestinal bleeding must also be considered. (InfoPOEMs: Regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), especially more than 14 doses per week for at least 10 years, reduces the risk of colon cancer while also increasing the risk of a major gastrointestinal bleeding event. All-cause mortality is not affected by regular use. We need additional methods (gene testing?) to determine who is at high risk of colorectal cancer before making specific recommendations for prevention. (LOE = 2b))

Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs. An update for clinicians. A scientific statement from the **American Heart Association**. Circulation 2007; DOI:10.1161/CIRCULATIONAHA.106.181424. Available at: http://circ.ahajournals.org.

Bandolier. Avocado/soybean unsaponifiables for OA. April 2004;122-23. Web site: http://www.jr2.ox.ac.uk/bandolier/band122/b122-3.html. The limited data to date support the safety and possible efficacy of ASU for osteoarthritis of the knee. More and longer studies are needed before we can recommend this to our patients without hesitation. (LOE = 1b-)

Barkhuizen A, et al. Celecoxib is efficacious and well tolerated in treating signs and symptoms of **ankylosing spondylitis**. J Rheumatol. 2006 Sep;33(9):1805-12.

Baron JA, et al. A randomized trial of **aspirin to prevent colorectal adenomas**. N Engl J Med. 2003 Mar 6;348(10):891-9.

Bavbek S, et al. Safety of **Meloxicam** in Aspirin-**Hypersensitive** Patients with Asthma and/or Nasal Polyps. A Challenge-Proven Study. Int Arch Allergy Immunol. 2006 Oct 2;142(1):64-69 [Epub ahead of print]

Bellamy N, et al. **Viscosupplementation** for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD005321.

Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. **Reye's syndrome** in the United States from 1981 through 1997. N Engl J Med. 1999 May 6;340(18):1377-82.

Berman BM, et al. Effectiveness of **acupuncture** as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. Ann Intern Med. 2004 Dec 21;141(12):901-10. Summary for patients in: Ann Intern Med. 2004 Dec 21;141(12):I20.

Bingham CO 3rd, Eet al. Efficacy and safety of **etoricoxib** 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. Rheumatology (Oxford). 2006 Aug 27.

Biswal S, Medhi B, Pandhi P. Longterm efficacy of **topical nonsteroidal antiinflammatory** drugs in knee osteoarthritis: metaanalysis of randomized placebo controlled clinical trials. J Rheumatol. 2006 Sep;33(9):1841-4.

Butler GJ, Neale R, Green AC, Pandeya N, Whiteman DC. Nonsteroidal anti-inflammatory drugs and the risk of **actinic keratoses and squamous cell** cancers of the skin. J Am Acad Dermatol. 2005 Dec;53(6):966-72. Epub 2005 Oct 19.

Cannon CP, et al.; **MEDAL** Steering Committee. Clinical trial design and patient demographics of the Multinational **Etoricoxib and Diclofenac** Arthritis Long-term (MEDAL) study program: cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. Am Heart J. 2006 Aug;152(2):237-45.

Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with **etoricoxib and diclofenac** in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (**MEDAL**) programme: a randomised comparison. Lancet 2006: DOI:10.1016/S0140-6736(06)69666-9. Rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib are similar to those in patients on diclofenac with long-term use of these drugs.

Capone ML, Sciulli MG, Tacconelli S, Grana M, Ricciotti E, Renda G, Di Gregorio P, Merciaro G, Patrignani P. Pharmacodynamic interaction of **naproxen with low-dose aspirin** in healthy subjects. J Am Coll Cardiol. 2005 Apr 19;45(8):1295-301.

Cardiovascular and Cerebrovascular Events in the Randomized, Controlled **Alzheimer's** Disease Anti-Inflammatory Prevention Trial (**ADAPT**). PLoS Clin Trials. 2006 Nov 17;1(7):e33 [Epub ahead of print] For celecoxib, ADAPT data do not show the same level of risk as those of the APC trial. The data for **naproxen**, although not definitive, are suggestive of increased cardiovascular and cerebrovascular risk. (Nissen SE. ADAPT: The Wrong Way to Stop a Clinical Trial. PLoS Clin Trials. 2006 Nov 17;1(7):e35 [Epub ahead of print])

Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. **Cyclooxygenase inhibitors and the antiplatelet effects of aspirin**. N Engl J Med. 2001 Dec 20;345(25):1809-17**.**

Chan 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 AT, et al. Nonsteroidal Antiinflammatory Drugs, Acetaminophen, and the Risk of **Cardiovascular Events**. Circulation. 2006 Mar 13; [Epub ahead of print]

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.

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.

Corman SL, Fedutes BA, Ansani NT. Impact of **nonsteroidal antiinflammatory drugs on the cardioprotective effects of aspirin**. Ann Pharmacother. 2005 Jun;39(6):1073-9. Epub 2005 May 3.

Cox-2 inhibitors & NSAIDS: **Drug Class Review Nov 2006** Oregon Health & Science University http://www.ohsu.edu/drugeffectiveness/reports/documents/NSAIDS%20Final%20Report%20Update%203.pdf

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

Diener HC, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalagia. 2006 May;26(5):537-47.

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)

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**.

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.

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.

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.

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.

Health Canada Prohits sale of Bextra http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_134_e.html

Health Canada June/06 two documents as part of its ongoing evaluation of COX-2-selective drugs: its official comments on the advice provided by the COX-2 Expert Advisory Panel and a report on the Department's scientific review of certain COX-2s. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-consult/cox2/index_e.html

Health Canada Aug/07 reports that the Therapeutic Goods Administration (TGA), the federal regulatory authority in Australia, recently withdrew market authorization for **Prexige due to eight reports of serious liver adverse events** in Australia linked to the drug, including two deaths and two liver transplants. These adverse events were primarily with use of 200 mg and 400 mg doses daily.

Health Canada Sept/07 reports that **Qiangli Zhuanggutongbiling** has reportedly been used for joint pain and stiffness. It was found to contain the undeclared prescription drugs prednisolone acetate, cortisone acetate, piroxicam, and diclofenac.

Health Canada Sept/07: **Khun-Phra** is a health product promoted for pain relief that has been found to contain the undeclared drugs dexamethasone, prednisolone, phenylbutazone, diazepam, cyproheptadine and mebhydrolin.. **Asam Urat Flu Tulang, PJ Dewandaru** is a health product promoted to treat joint pain, rheumatism and arthritis. It has been found to contain the undeclared drugs dexamethasone, diclofenac and acetaminophen.

Health Canada Oct/07 Foreign Product Alerts: ***Zhen Feng Da Brand Xi Tong Wan*** is promoted as a pain reliever. Lot #060908 has been found to contain undeclared indomethacin, a prescription anti-inflammatory drug that should only be taken under the guidance of a health professional. ***Wellring Brand Yin Qiao Jie Du*** is a health product promoted to treat cold and flu symptoms. Lot#51005 has been found to contain undeclared acetaminophen. ***Gu Ci Dan*** and ***Xu Log Bou*** are promoted as pain relievers and have been found to contain indomethacin.

Health Canada Oct/07 is advising consumers that it has stopped the sale of the anti-inflammatory drug **Prexige** (lumiracoxib) in Canada and will cancel the drug's market authorization due to the potential for serious liver-related adverse events. (2 new severe cases in Canada)

Health Canada July/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **3rd Generation In Homoeopathy Arthrit Indica Tablet**. The product is labelled for "intense joint pain." The Health Sciences Authority of Singapore has warned consumers not to use the product because it contains **nimesulide**, a pharmaceutical ingredient that has been associated with liver damage.

Health Canada Aug/08 is advising consumers not to use foreign health products due to concerns against the use of **AA Qu Feng Shu Jin Wan** because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. **Obat Asam Urat** and **Asam Urat** both contained dexamethasone, phenylbutazone and piroxicam.

Helin-Salmivaara A, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. Eur Heart J. 2006 Jul;27(14):1657-63. Epub 2006 May 26.

Huerta C, Varas-Lorenzo C, Castellsague J, Garcia Rodriguez LA. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for **heart failure** in the general population. Heart. 2006 Nov;92(11):1610-5. Epub 2006 May 22.

Hill KP, Ross JS, Egilman DS, Krumholz HM. The **ADVANTAGE seeding trial**: a review of internal documents. (Vioxx marketing trial) Ann Intern Med. 2008 Aug 19;149(4):251-8.

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.

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.

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.

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.

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.

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Lane NE. Clinical practice. **Osteoarthritis of the hip**. N Engl J Med. 2007 Oct 4;357(14):1413-21.

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hepatic tests in alcoholic patients--a multicenter randomized study. BMC Med. 2007 May 30;5:13. Alcoholic patients treated with the maximum recommended daily dose of acetaminophen for 3 consecutive days did not develop increases in serum transaminase or other measures of liver injury. Treatment of pain or fever for 3 days with acetaminophen appears safe in newly-abstinent alcoholic patients, such as those presenting for acute medical care.) (Heard K, Green JL, Bailey JE, Bogdan GM, Dart RC. A randomized trial to determine the change in alanine aminotransferase during 10 days of paracetamol (acetaminophen) administration in subjects who consume moderate amounts of alcohol. Aliment Pharmacol Ther. 2007 Jul 15;26(2):283-90. Therapeutic dosing of paracetamol administered for 10 days appears to elevate serum ALT in moderate drinkers, but does not produce clinically evident liver injury.)

Levesque LE, Brophy JM, Zhang B. Time variations in the risk of **myocardial infarction** among elderly users of COX-2 inhibitors. CMAJ. 2006 May 23;174(11):1563-9. Epub 2006 May 2. A small proportion of patients using rofecoxib for the first time had their first MI shortly after starting the drug. This risk did not increase with the length of treatment and returned to baseline shortly after treatment was discontinued. More research is needed to identify those most susceptible to cardiotoxicity mediated by COX-2 inhibitor therapy.

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Mamdani M, Warren L, Kopp A, Paterson JM, Laupacis A, Bassett K, Anderson GM. Changes in rates of upper gastrointestinal hemorrhage after the introduction of **cyclooxygenase-2 inhibitors** in British Columbia and Ontario. CMAJ. 2006 Dec 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))

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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Rebordosa C, Kogevinas M, Horváth-Puhó E,et al. **Acetaminophen use during pregnancy**: effects on risk for congenital abnormalities. Am J Obstet Gynecol. 2008 Feb;198(2):178.e1-7. Acetaminophen is not associated with an increased prevalence of congenital abnormalities overall or with any specific group of major abnormalities.

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Roddy E, Zhang W, Doherty M. **Aerobic walking or strengthening exercise** for osteoarthritis of the knee? A systematic review. Ann Rheum Dis. 2005 Apr;64(4):544-8 & ACP Journal Club .

Rostom A, et al; U.S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for **primary prevention of colorectal cancer**: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007 Mar 6;146(5):376-89. Review. Summary for patients in: Ann Intern Med. 2007 Mar 6;146(5):I35. Cyclooxygenase-2 inhibitors and NSAIDs reduce the incidence of colonic adenomas. Nonsteroidal anti-inflammatory drugs also reduce the incidence of CRC. However, these agents are associated with important cardiovascular events and gastrointestinal harms. The balance of benefits to risk does not favor chemoprevention in average-risk individuals. (InfoPOEMs: The US Preventive Services Task Force recommends against routine use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent colorectal cancer. The beneficial decrease in colorectal adenoma, cancer incidence, and possibly cancer-related mortality is more than offset by the harm associated with their use. Ulcers leading to gastrointestinal bleeding, renal impairment, and an increase in cardiovascular events are the main problems. (LOE = 1a))

Rostom A, Muir K, Dube C, Jolicoeur E, Boucher M, Joyce J, Tugwell P, Wells GW. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. Clin Gastroenterol Hepatol. 2007 Jul;5(7):818-28, 828.e1-5; quiz 768. Epub 2007Jun 6. **COX-2s appear to offer greater upper GI safety** and are better tolerated than nonselective NSAIDs. The co-administration of acetylsalicylic acid might reduce the safety advantage of COX-2s over that of nonselective NSAIDs.

Roumie CL, Mitchel EF Jr, Kaltenbach L, Arbogast PG, Gideon P, Griffin MR. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. Stroke. 2008 Jul;39(7):2037-45. Epub 2008 Apr 24. Our results indicate an increased risk of stroke with current use of two highly selective coxibs, rofecoxib and valdecoxib, also shown to increase cardiovascular risk. These results also provide some reassurance about other specific NSAIDs regarding stroke risk.

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Scheiman JM, et al. Prevention of Ulcers by Esomeprazole in At-Risk Patients Using Non-Selective NSAIDs and COX-2 Inhibitors. (**Venus** & **Pluto**) Am J Gastroenterol. 2006 Feb 22; [Epub ahead of print] CONCLUSIONS: For at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors.

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). Fourteen 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.}

Silverstein FE, et al. **Misoprostol** reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1995 Aug 15;123(4):241-9.

Soininen H, West C, Robbins J, Niculescu L. Long-Term Efficacy and Safety of **Celecoxib** in **Alzheimer's** Disease. Dement Geriatr Cogn Disord. 2006 Oct 26;23(1):8-21 [Epub ahead of print] Celecoxib 200 mg bid did not slow the progression of AD in this study, and the occurrence of adverse events was as expected for an elderly population with a complex chronic medical condition.

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Solomon SD, Wittes J, Finn PV, et al.; for the Cross Trial Safety Assessment Group. Cardiovascular Risk of Celecoxib in 6 Randomized Placebo-Controlled Trials. The Cross Trial Safety Analysis. Circulation. 2008 Mar 31; [Epub ahead of print] We observed evidence of differential cardiovascular risk as a function of celecoxib dose regimen and baseline cardiovascular risk. By further clarifying the extent of celecoxib-related cardiovascular risk, these findings may help guide treatment decisions for patients who derive clinical benefit from selective cyclooxygenase-2 inhibition.

Sotoudehmanesh R, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after **ERCP**. Am J Gastroenterol. 2007 May;102(5):978-83. Epub 2007 Mar 13. n=490.

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Strand V. Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin? Lancet 2007; 370:2138-2151. Mortality associated with gastrointestinal events is less frequent than with cardiovascular events, but asymptomatic ulcers can result in severe complications. Data support the conclusion that COX-2 inhibitors are preferable to non-selective NSAIDs in patients with chronic pain and cardiovascular risk needing low-dose aspirin, but relative risks and benefits should be assessed individually for each patient.

Tannenbaum H, Bombardier C, Davis P, Russell AS; **Third Canadian Consensus** Conference Group. An evidence-based approach to prescribing nonsteroidal antiinflammatory drugs. Third Canadian Consensus Conference. J Rheumatol. 2006 Jan;33(1):140-57. Epub 2005 Dec 1.

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Wilcox CM, Allison J, Benzuly K, Borum M, Cryer B, Grosser T, Hunt R, Et al. Consensus development conference on the use of nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 enzyme inhibitors and aspirin. Clin Gastroenterol Hepatol. 2006 Sep;4(9):1082-9. Epub 2006 Jul 31.

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Zhang W, Doherty M, Arden N, et al. EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). EULAR evidence based recommendations for the management of **hip osteoarthritis**: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2005 May;64(5):669-81. Epub 2004 Oct 7 & ACP Journal Club .

Zhang J, Ding EL, Song Y. Adverse Effects of Cyclooxygenase 2 Inhibitors on Renal and Arrhythmia Events: Meta-analysis of Randomized Trials. JAMA. 2006 Sep 12; [Epub ahead of print] In this comprehensive analysis of 114 randomized trials with 116 094 participants, **rofecoxib** was associated with increased renal and arrhythmia risks. A COX-2 inhibitor class effect was not evident.

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

[1] Ballantyne JC, Mao J. Opioid Therapy for Chronic Pain. N Engl J Med. 2003 Nov 13;349(20):1943-1953.

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[3] Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2008.

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[5] Morrison, R. Sean, Meier, Diane E., Palliative Care. N Engl J Med 2004 350: 2582-2590.

[6] Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005 Mar 31;352(13):1324-34. (InfoPOEMs: The combination of gabapentin & morphine provides a small but clinically unimportant benefit over either drug alone. Tricyclic antidepressants have been shown in other studies to be as effective as gabapentin & much less expensive, but were not studied in this trial. (LOE = 1b))

[7] Health Canada Aug 2005 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_84_e.html (Long-Acting Opioids and a New Type of **Alcohol Warning**. Pharmacit's Letter. Dec 2005).

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

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Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005 Jun 22;293(24):3043-52. CONCLUSIONS: Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrate significant efficacy of opioids over placebo for neuropathic pain, which is likely to be clinically important. Reported adverse events of opioids are common but not life-threatening. Further RCTs are needed to establish their long-term efficacy, safety (including addiction potential), and effects on quality of life.

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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 $_{\text{diphenhydramine}}$ +/- H2 $_{\text{ranitiidine}}$ blocker.
  - Flushing, itching, hives, sweating, and/or mild hypotension
  - Itching, flushing or hives at injection site only
- **Potential true opioid allergy** (**RARE**! - would require change to non-opioid or opioid from different chemical class – see below)
  - Severe hypotension
  - Skin reaction other than (Flushing, itching, hives)
  - Breathing, speaking, swallowing difficulties
  - Swelling of the face, lips, mouth, tongue, pharynx or larynx

Opioid Chemical Class

1. **Phenylpiperidines**: meperidine, fentanyl, sufentanil, remifentanil

2. **Diphenylheptanes**: methadone, propoxyphene
3. **Morphine group**: morphine, codeine, hydromorphone, nalbuphine, butorphanol, levorphanol, pentazocine

New Drugs {Not yet in Canada 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

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 1 g) will cover & anesthetize an area of up to 30cm^2 (6×5 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 kg —100 sq cm {~ 2.5x area of a credit card};10 to 20 kg — 600 sq cm; Greater than 20 kg — 2000 sq cm ; causes vasoconstriction.

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

- **Benzocaine** –in NG tube placement controversial[10] Causes methemoglobinemia!!! AVOID!
- **Lidocaine iontophoresis** {Numby Stuff}: mild electric current penetrates skin more quickly; effective in 10-20min.[59] 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.uihealthcare.com/topics/medicaldepartments/urology/catheterization/index.html)
- **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 Emerg.: A Review of Clinical Outcomes and Economic Evaluation http://cadth.ca/media/pdf/O0428_Short-Acting-Procedural-Sedation_to_e.pdf

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Pain Intensity Scoring:

- Chose 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. 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

FLACC SCALE – for assessing postop pain in very young children

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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http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_63_e.html (Singh S, Wooltorton E. Increased mortality among elderly patients with dementia using atypical antipsychotics. CMAJ. 2005 Aug 2;173(3):252.) (Medical Letter August 1,2005 -Atypical antipsychotics in the Elderly FDA n=5106 17 RCTs mortality rate of 4.5% with atypical antipsychotic therapy vs 2.6% with placebo, most deaths were due to cardiovascular & infectious causes such as pneumonia.) Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005 Oct 19;294(15):1934-43. (InfoPOEMs: The use of atypical antipsychotic drugs for even short periods (less than 8 to 12 weeks) is associated with a significantly increased risk of death. Antipsychotic drugs should be used only in individual situations of an identifiable risk of harm and when alternate therapies have failed. (LOE = 1a)){15 trials (9 unpublished) of atypical antipsychotics vs placebo for ~10-12weeks n=5110; 3.5 vs 2.3% death rate}(Wang PS et al. Risk of Death in Elderly Users of Conventional vs Atypical Antipsychotic Medications. N Engl J Med 2005;353:2335-41. Conclusion: If confirmed, these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should no be used to replace atypical agents discontinued in response to the FDA warning. (InfoPOEMs: It seems reasonable to conclude that conventional and atypical antipsychotic agents are both associated with an increased risk of death in elderly pts. The limitations of this study do not allow us to confidently conclude that older agents are less safe than newer agents, though. (LOE = 2b))) (Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ. 2007 Feb 27;176(5):627-32. Among elderly patients, the risk of death associated with conventional antipsychotic medications is comparable to and possibly greater than the risk of death associated with atypical antipsychotic medications. Until further evidence is available, physicians should consider all antipsychotic medications to be equally risky in elderly patients.) (Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N, Gurwitz JH, Rochon PA. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007 Jun 5;146(11):775-86. Atypical antipsychotic use is associated with an increased risk for death compared with nonuse among older adults with dementia. The risk for death may be greater with conventional antipsychotics than with atypical antipsychotics.)
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Rochon PA, Normand SL, et al. Antipsychotic therapy and short-term **serious events** in older adults with dementia. Arch Intern Med. 2008 May 26;168(10):1090-6. Relative to those who received no antipsychotic therapy, community-dwelling older adults newly dispensed an atypical antipsychotic therapy were 3.2 times more likely (95% confidence interval, 2.77-3.68) and those who received conventional antipsychotic therapy were 3.8 times more likely (95% confidence interval, 3.31-4.39) to develop any serious event during the 30 days of follow-up. The pattern of serious events was similar but less pronounced among older adults living in a nursing home. Serious events, as indicated by a hospital admission or death, are frequent following the short-term use of antipsychotic drugs in older adults with dementia. Antipsychotic drugs should be used with caution even when short-term therapy is being prescribed.
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Useful Web sites:

Alzheimer Society Canada www.alzheimer.ca

Alzheimer Association USA www.alz.org

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Essential Tremor (ET) & Restless Legs Syndrome (RLS) - Treatment Options

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Miyasaki JM, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: evaluation and treatment of **depression, psychosis, and dementia** in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):996-1002. http://www.neurology.org/cgi/reprint/66/7/996 Screening tools are available for depression and dementia in patients with PD, but more specific validated tools are needed. There are no widely used, validated tools for psychosis screening in Parkinson disease (PD). Clozapine successfully treats psychosis in PD. Cholinesterase inhibitors are effective treatments for dementia in PD, but improvement is modest and motor side effects may occur.

Pahwa R, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: treatment of Parkinson disease with **motor fluctuations and dyskinesia** (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):983-95. http://www.neurology.org/cgi/reprint/66/7/983 1. Entacapone and rasagiline should be offered to reduce off time (Level A). Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B). Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C). 2. The available evidence does not establish superiority of one medicine over another in reducing off time (Level B). Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C). 3. Amantadine may be considered to reduce dyskinesia (Level C). 4. Deep brain stimulation of the STN may be considered to improve motor function and reduce off time, dyskinesia, and medication usage (Level C). There is insufficient evidence to support or refute the efficacy of DBS of the GPi or VIM nucleus of the thalamus in reducing off time, dyskinesia, or medication usage, or to improve motor function. 5. Preoperative response to levodopa predicts better outcome after DBS of the STN (Level B).

Suchowersky O, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: **neuroprotective strategies and alternative** therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):976-82. http://www.neurology.org/cgi/reprint/66/7/976 1. Levodopa does not appear to accelerate disease progression. 2. No treatment has been shown to be neuroprotective. 3. There is no evidence that vitamin or food additives can improve motor function in PD. 4. Exercise may be helpful in improving motor function. 5. Speech therapy may be helpful in improving speech volume. 6. No manual therapy has been shown to be helpful in the treatment of motor symptoms, although studies in this area are limited. Further studies using a rigorous scientific method are needed to determine efficacy of alternative therapies.

Suchowersky O, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: diagnosis and prognosis of **new onset Parkinson** disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):968-75. http://www.neurology.org/cgi/reprint/66/7/968 1. Early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor, and early autonomic dysfunction are probably useful in distinguishing other parkinsonian syndromes from Parkinson disease (PD). 2. Levodopa or apomorphine challenge and olfactory testing are probably useful in distinguishing PD from other parkinsonian syndromes. 3. Predictive factors for more rapid motor progression, nursing home placement, and shorter survival time include older age at onset of PD, associated comorbidities, presentation with rigidity and bradykinesia, and decreased dopamine responsiveness. Future research into methods for earlier and more accurate diagnosis of the disease and identification and clarification of predictive factors of rapid disease progression is warranted.

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Heiss G, Wallace R, Anderson GL, et al. WHI Investigators. Health risks and benefits **3 years after stopping** randomized treatment with estrogen and progestin. JAMA. 2008 Mar 5;299(9):1036-45. The increased cardiovascular risks in the women assigned to CEE plus MPA during the intervention period were not observed after the intervention. A greater risk of fatal & nonfatal malignancies occurred after intervention in the CEE plus MPA group & the global risk index was 12% higher in women randomly assigned to receive CEE plus MPA compared with placebo.

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statistically significantly more effective than placebo in reducing the number of moderate and severe hot flushes, with a 41% responder rate, supporting the concept of the lowest effective dose. Many women complaining of menopausal hot flushes will get relief from ultra-low-dose hormone therapy patches, so it makes sense to start low in the effort to minimize dosing. (LOE = 1b)

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Canonico M, Oger E, Plu-Bureau G, et al; Estrogen and Thromboembolism Risk (**ESTHER**) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study.Circulation. 2007 Feb 20;115(7):840-5. **Oral but not transdermal estrogen** is associated with an increased **VTE risk**. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. If confirmed, these findings could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogens.

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Haimov-Kochman R, et al. **Gradual discontinuation** of hormone therapy does not prevent the reappearance of climacteric symptoms: a randomized prospective study. Menopause. 2006 May 25; [Epub ahead of print]

Haimov-Kochman R, Hochner-Celnikier D. Hot flashes revisited: pharmacological and herbal options for hot flashes management. What does the evidence tell us? Acta Obstet Gynecol Scand. 2005 Oct;84(10):972-9. CONCLUSIONS: A critical review of the literature shows that progesterone may have an independent effect on relieving hot flashes. New nonhormonal agents such as selective serotonin-uptake-inhibitor anti-depressants and a new anti-convulsant gabapentin yielded promising results on small well-conducted studies. Isoflavone's effect on hot flashes is variable and inconsistent, and only modest and delayed improvement of symptoms could be expected by BC and vitamin E. There are insufficient data on the other herbal alternative therapies at this time. Well-designed large studies are needed to further explore new modalities of treatment.

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

He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of **soybean** protein on blood pressure: a randomized, controlled trial. Ann Intern Med. 2005 Jul 5;143(1):1-9. Summary for patients in: Ann Intern Med. 2005 Jul 5;143(1):I11.

Health Canada Dec/05 Notice to Discontinue **Climacteron** http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/climacteron_hpc-cps_e.pdf

Health Canada Aug/06 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 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.

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.

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.

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**.

Lyytinen H, Pukkala E, Ylikorkala O. **Breast cancer** risk in postmenopausal women using **estrogen-only** therapy. Obstet Gynecol. 2006 Dec;108(6):1354-60. Estradiol for 5 years or more, either orally or transdermally, means 2-3 extra cases of breast cancer per 1,000 women who are followed for 10 years. Oral estradiol use for less than 5 years, oral estriol, or vaginal estrogens were not associated with a risk of breast cancer.

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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.

Motivala A, Pitt B. **Drospirenone** for oral contraception and hormone replacement therapy : are its cardiovascular risks and benefits the same as other progestogens? Drugs. 2007;67(5):647-55. Our review of the literature suggests that because of its anti-mineralocorticoid effects, drospirenone in conjunction with estrogen may prevent the development of cardiovascular disease in both pre- and post-menopausal women.

National Institutes of Health. National Institutes of Health State-of-the-Science Conference statement: **management of menopause-related** symptoms. Ann Intern Med. 2005 Jun 21;142(12 Pt 1):1003-13. Epub 2005 May 27.

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Nelson HD, et al. **Nonhormonal therapies for menopausal hot flashes: systematic review** and meta-analysis. JAMA. 2006 May 3;295(17):2057-71. The SSRIs or SNRIs, clonidine, and gabapentin trials provide evidence for efficacy; however, effects are less than for estrogen, few trials have been published and most have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict use for many women. These therapies may be most useful for highly symptomatic women who cannot take estrogen but are not optimal choices for most women. (InfoPOEMs: Evidence supports the nonhormonal treatment of menopausal hot flashes with paroxetine (Paxil), clonidine (Catapres), gabapentin (Neurontin), and soy isoflavone extract. The overall effect size of all nonhormonal treatments is less than that of estrogen. Treatment should be individualized according to symptom severity and risk profiles. (LOE = 1a-)) (Reddy SY, et al. Gabapentin, Estrogen, and Placebo for Treating Hot Flushes: A Randomized Controlled Trial. Obstet Gynecol. 2006 Jul;108(1):41-48. Despite the small scale of this study, (12 week n=60) gabapentin appears to be as effective as estrogen in the treatment of postmenopausal hot flushes. (InfoPOEMs: In this small study, high-dose gabapentin (Neurontin) was as effective as the usual dose of conjugated equine estrogens (Premarin) for the treatment of menopausal vasomotor symptoms. Larger studies are needed to confirm this result. (LOE = 1b))) (Loprinzi CL, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol. 2006 Mar 20;24(9):1409-14. Epub 2006 Feb 27.)(Butt DA, Lock M, Lewis JE, Ross S, Moineddin R. Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause. 2007 Oct 2; [Epub ahead of print])

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. 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. 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.

Osmers R, Friede M, et al. Efficacy and safety of isopropanolic **black cohosh** extract for climacteric symptoms. Obstet Gynecol 2005; 105:1074-83. (InfoPOEMs: This study reports that isopropanolic black cohosh extract (Remifemin) at a dose of 20 mg twice daily is statistically more effective than placebo for the treatment of menopausal vasomotor symptoms. These results will probably be used to promote its use. However, the authors did not supply sufficient data to determine the extent of benefit or the number needed to treat. This evidence is insufficient to determine whether black cohosh has a clinically relevant effect in treating menopausal symptoms. (LOE = 1b-)) CONCLUSION: This isopropanolic extract of black cohosh root stock is effective in relieving climacteric symptoms, especially in early climacteric women.

Ouyang P, et al.; for the Estrogen And Graft Atherosclerosis Research (**EAGAR**) investigators. Randomized trial of hormone therapy in women after coronary bypass surgery Evidence of differential effect of hormone therapy on angiographic progression of disease in saphenous vein grafts and native coronary arteries. Atherosclerosis. 2006 Jan 23; [Epub ahead of print]

Pandya KJ, Morrow GR, Roscoe JA, et al. **Gabapentin** for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. Lancet. 2005 Sep 3-9;366(9488):818-24. Gabapentin is effective in the control of hot flashes at a dose of 900 mg/day, but not at a dose of 300 mg/day. This drug should be considered for treatment of hot flashes in women with breast cancer. (InfoPOEMs: Women with a history of breast cancer may obtain some relief from hot flashes with 900 mg gabapentin daily. The 300 mg daily dose was not effective. (LOE = 1b-))

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.

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.

Rosenberg L, Palmer JR, Wise LA, Adams-Campbell LL. A prospective study of female **hormone use** and breast cancer among **black women**. Arch Intern Med. 2006 Apr 10;166(7):760-5.

Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M. **Soy** Protein, Isoflavones, and Cardiovascular Health. An **American Heart Association** Science Advisory for Professionals From the Nutrition Committee. Circulation. 2006 Jan 17; [Epub ahead of print]

Salpeter SR, et al. Brief report: **Coronary heart disease** events associated with hormone therapy in **younger and older** women. A meta-analysis. J Gen Intern Med. 2006 Apr;21(4):363-6. Hormone therapy reduces the risk of CHD events in younger postmenopausal women. In older women, HT increases, then decreases risk over time.(Alexandersen P, et al. The long-term impact of 2-3 years of hormone replacement therapy on cardiovascular mortality and atherosclerosis in healthy women. Climacteric. 2006 Apr;9(2):108-18.)

Samsioe G, et al. Estalis 50/140 Study Group. **Endometrial safety**, overall safety and tolerability of transdermal continuous combined hormone replacement therapy over 96 weeks: a randomized open-label study. Climacteric. 2006 Oct;9(5):368-79. Continuous combined transdermal HRT with E2/NETA shows no evidence of an increased endometrial hyperplasia or endometrial cancer risk over a 96-week period.

Schabath MB, Hernandez LM, Wu X, Pillow PC, Spitz MR. Dietary **phytoestrogens** and lung cancer risk. JAMA. 2005 Sep 28;294(12):1493-504.

Sestak I, et al. Influence of hormone replacement therapy on **tamoxifen-induced vasomotor** symptoms. J Clin Oncol. 2006 Aug 20;24(24):3991-6.

Shah NR, Jones JB, Aperi J, Shemtov R, Karne A, Borenstein J. **Selective Serotonin Reuptake Inhibitors** for Premenstrual Syndrome and Premenstrual Dysphoric Disorder: A Meta-Analysis. Obstet Gynecol. 2008 May;111(5):1175-1182. Selective serotonin reuptake inhibitors were found to be effective in treating premenstrual symptoms, with continuous dosing regimens favored for effectiveness.

Star Trial (Study of Tamoxifen and Raloxifene) for Breast Cancer Prevention Medical Letter May 8, 2006 & Pharmacist's Letter May 2006. InfoPOEMs: Tamoxifen (Nolvadex, Tamofen) and raloxifene (Evista) are similarly effective for reducing the risk of invasive breast cancer in postmenopausal women. Although women taking tamoxifen are at an increased risk of thromboembolic events and cataracts, they report improved sexual function compared with women taking raloxifene. All-cause mortality and overall quality-of-life were similar in both treatment groups. (LOE = 1b-).

Stefanick ML, et al. WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006 Apr 12;295(14):1647-57. (InfoPOEMs: Estrogen therapy alone does not increase the risk of breast cancer in postmenopausal women with prior hysterectomy. Women receiving estrogen are more likely to require further testing as a result of questionably abnormal mammogram results, potentially leading to heightened anxiety and a reduced quality of life. The decision to use estrogen in postmenopausal women after hysterectomy should be individualized on the basis of overall potential risks and benefits. Women most likely to benefit from estrogen therapy include those with disabling hot flashes and an increased risk of osteoporotic fractures. Treatment should be limited whenever possible to the first 5 years (or less) after menopause. (LOE = 1b))

Shah NR, Borenstein J, Dubois RW. Postmenopausal hormone therapy and **breast cancer**: a systematic review and meta-analysis. Menopause. 2005 Nov-Dec;12(6):668-78. (InfoPOEMs: This meta-analysis of 13 large observational studies found that combined estrogen and progestin hormone therapy (CHT) for postmenopausal women is more likely than estrogen-only hormone therapy (ET) to be associated with breast cancer. This result is concondant with clinical trial data from the Women's Health Initiative (WHI). There is still uncertainty about whether ET increases the risk of breast cancer, based on the heterogeneity found in this meta-analysis and the discordance of these results with those from the WHI. (LOE = 2a))

Somunkiran A, Erel CT, Demirci F, Senturk ML. The effect of **tibolone** versus 17beta-estradiol on climacteric symptoms in women with surgical menopause: A randomized, cross-over study. Maturitas. 2006 Jul 8; [Epub ahead of print]

Stearns V, Slack R, Greep N, et al. **Paroxetine** is an effective treatment **for hot flashes**: results from a prospective randomized clinical trial. J Clin Oncol. 2005 Oct 1;23(28):6919-30.

Steinauer JE, Waetjen LE, Vittinghoff E, Subak LL, Hulley SB, Grady D, Lin F, Brown JS. Postmenopausal hormone therapy: does it cause incontinence? Obstet Gynecol. 2005 Nov;106(5 Pt 1):940-5.

Suckling J, Lethaby A, Kennedy R. **Local oestrogen for vaginal atrophy** in postmenopausal women. Cochrane Database Syst Rev. 2003;(4):CD001500. (see also Pharmacist's Letter May 2006)

Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA. Combined **estrogen and testosterone** use and risk of breast cancer in postmenopausal women. Arch Intern Med. 2006 Jul 24;166(14):1483-9.

Trock BJ, Meta-analysis of **soy intake and breast cancer risk**. J Natl Cancer Inst. 2006 Apr 5;98(7):459-71. Soy intake may be associated with a small reduction in breast cancer risk. However, this result should be interpreted with caution due to potential exposure misclassification, confounding, and lack of a dose response. Given these caveats and results of some experimental studies that suggest adverse effects from soy constituents, recommendations for high-dose isoflavone supplementation to prevent breast cancer or prevent its recurrence are premature. (InfoPOEMs: If the existing research results are true, high soy intake is associated with a small protective effect against breast cancer. However, the published studies have enough flaws to make me question this effect. (LOE = 3a-))

Uebelhack R, et al. **Black cohosh and St. John's wort** for climacteric complaints: a randomized trial. (n=301 16weeks) Obstet Gynecol. 2006 Feb;107(2 Pt 1):247-55.

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))

Vogel VG, Costantino JP, Wickerham DL, et al. (NSABP). Effect of **tamoxifen vs raloxifene** on the risk of developing invasive breast cancer and other disease outcomes. The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA 2006;295:2727-2741 (InfoPOEMs: Tamoxifen (Nolvadex, Tamofen) and raloxifene (Evista) are similarly effective for reducing the risk of invasive breast cancer in postmenopausal women. Although women taking tamoxifen are at an increased risk of thromboembolic events and cataracts, they report improved sexual function compared with women taking raloxifene. All-cause mortality and overall quality-of-life were similar in both treatment groups. (LOE = 1b-))

Waetjen LE, Brown JS, Vittinghoff E, et al. The Effect of Ultralow-Dose Transdermal Estradiol on **Urinary Incontinence** in Postmenopausal Women. Obstet Gynecol. 2005 Nov;106(5):946-952.

Welton AJ, Vickers MR, Kim J, et al. for the **WISDOM** team. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ. 2008 Aug 21;337:a1190. doi: 10.1136/bmj.a1190. Combined HRT started many years after the menopause can improve health related quality of life.

Yaffe K, Vittinghoff E, Ensrud KE, Johnson KC, Diem S, Hanes V, Grady D. Effects of ultra-low-dose transdermal estradiol on **cognition** and health-related quality of life. Arch Neurol. 2006 Jul;63(7):945-50.

Zhu X, Proctor M, Bensoussan A, Wu E, Smith CA. **Chinese herbal medicine** for primary dysmenorrhoea. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005288. The review found promising evidence supporting the use of Chinese herbal medicine for primary dysmenorrhoea; however, results are limited by the poor methodological quality of the included trials.

Osteoporosis:

Aloia JF, Talwar SA, Pollack S, Yeh J. A randomized controlled trial of **vitamin D3** supplementation in African American women. Arch Intern Med. 2005 Jul 25;165(14):1618-23.

Alonso-Coello P, García-Franco AL, Guyatt G, Moynihan R. Drugs for **pre-osteoporosis: prevention or disease mongering**? BMJ. 2008 Jan 19;336(7636):126-9.

Amin S, et al. **Estradiol, testosterone**, and the risk for hip fractures in **elderly men** from the Framingham Study. Am J Med. 2006 May;119(5):426-33.

Armingeat T, et al. **Intravenous pamidronate** for **pain relief** in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. Osteoporos Int. 2006 Aug 8; [Epub ahead of print]

Avenell A, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD000227& ACP Journal Club . AUTHORS' CONCLUSIONS: Frail older people confined to institutions may sustain fewer hip and other non-vertebral fractures if given vitamin D with calcium supplements. Effectiveness of vitamin D alone in fracture prevention is unclear. There is no evidence of advantage of analogues of vitamin D compared with vitamin D. Calcitriol may be associated with an increased incidence of adverse effects. Dose, frequency, and route of administration of vitamin D in older people require further investigation.

Barrett-Connor E, Grady D, et al.; **MORE** Investigators (Multiple Outcomes of Raloxifene Evaluation). Raloxifene and **cardiovascular** events in osteoporotic postmenopausal women: four-year results from the MORE randomized trial. JAMA. 2002 Feb 20;287(7):847-57.

Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, et al. Upper gastrointestinal tract safety profile of **alendronate**: the Fracture Intervention Trial. Arch Intern Med 2000;160:517-25.

Baxter NN, Habermann EB, Tepper JE, Durham SB, eta l. Risk of pelvic fractures in older women following **pelvic irradiation**. JAMA. 2005 Nov 23;294(20):2587-93. (InfoPOEMs: Pelvic irradiation significantly increases the risk of pelvic fractures in older women. Treatment for anal cancer is associated with the highest risk of pelvic fracture. (LOE = 2b-))

Bean GR, Kimler BF, Seewaldt VL. Long-term **raloxifene** in a woman at high risk for **breast cancer**. N Engl J Med. 2006 Oct 12;355(15):1620-2.

Berger C, Langsetmo L, Joseph L, Hanley DA, et al. Canadian Multicentre Osteoporosis Study Research Group. Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. CMAJ. 2008 Jun 17;178(13):1660-8. (CaMos) The period of accelerated loss of bone mineral density in the hip bones occurring among women and men older than 65 may be an important contributor to the increased incidence of hip fracture among patients in that age group. The extent of bone loss that we observed in both sexes indicates that, in the absence of additional risk factors or therapy, repeat testing of bone mineral density to diagnose osteoporosis could be delayed to every 5 years.

Berry SD, Samelson EJ, Hannan MT, et al. **Second hip fracture** in older men and women: the framingham study. Arch Intern Med. 2007 Oct 8;167(18):1971-6. Following a first hip fracture, 2.5% of subjects experienced a second hip fracture within 1 year, and 8.2% of subjects (9.7% of women) experienced a second hip fracture within 5 years. One-year mortality following an initial hip fracture was 15.9% compared with 1-year mortality following a second hip fracture of 24.1%.Among survivors of an initial hip fracture, the incidence of a second hip fracture is substantial. Older age and functional status may be important predictors of a second hip fracture.

Berry S, Waldron T, Winquist E, Lukka H. The use of **bisphosphonates** in men with hormone-refractory **prostate cancer**: a systematic review of randomized trials. Can J Urol. 2006 Aug;13(4):3180-8.

Bilezikian JP. **Osteonecrosis of the jaw**--do bisphosphonates pose a risk? N Engl J Med. 2006 Nov 30;355(22):2278-81.

Bingham CO 3rd, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with **medial compartment osteoarthritis** of the knee: Results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum. 2006 Oct 30;54(11):3494-3507 [Epub ahead of print]

Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005 May 11;293(18):2257-64 & ACP Journal Club . (Oral vitamin D supplementation between 700 to 800 IU/d appears to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons. An oral vitamin D dose of 400 IU/d is not sufficient for fracture prevention.)(InfoPOEMs: Supplementation with calcium 1000 mg and vitamin D3 800 IU daily decreases the likelihood that older people will experience a first hip fracture or other nonvertebral fracture. The dose of calcium is lower than the 1500 mg daily that is recommended and usually used; the vitamin D dose is higher than the dose usually used in comparison studies with other drugs. These results conflict with 2 large studies in patients at high risk or with a previous osteoporotic fracture for whom these doses did not decrease the rate of fracture (BMJ 2005; 330:1003-06 and Lancet 2005; 365:1621-28). (LOE = 1a))

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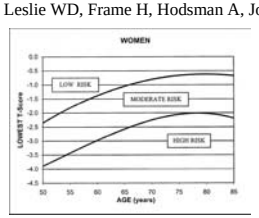

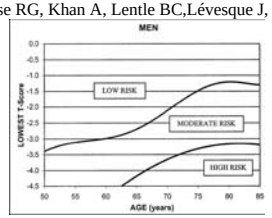

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HERBAL DRUG INTERACTION CHART

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Clegg et al . National Institutes of Health (NIH) Glucosamine/Chondroitin Arthritis Intervention Trial (**GAIT**) Clegg DO, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808. CONCLUSIONS: Glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. Exploratory analyses suggest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain. (The 1,538-pts GAIT trial compared the effectiveness & safety of these supplements taken alone and in combination in patients with painful knee osteoarthritis (WOMAC Pain 125-400 mm) treated at 16 academic medical centers in the U.S. The response rate for all patients was 60.1% in a placebo group, 64% in a glucosamine hydrocholoride arm (500 mg TID); 65.4% in a chondroitin alone arm (400 mg TID); & 66.6% in a glucosamine-plus-chondroitin arm (500 mg/400mg TID) (p=0.09), according to a study results reported at the American College of Rheumatology meeting in San Diego Nov/05). http://nccam.nih.gov/news/19972000/121100/qa.htm (InfoPOEMs: Glucosamine HCl and chondroitin provides modest if any symptomatic benefit for patients with mild osteoarthritis of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (LOE = 1b))

Complementary and alternative medicine-what people ≥50 are using & discussing with their doctor Jan/07 Nearly two-thirds of older people in the U.S. use complimentary or alternative therapies, but less than a third of the users discuss the practice with their physicians, according to a survey commissioned by the NIH and the AARP. The survey was based on interviews last year with about 1600 people aged 50 and older. The leading reason people said they don't discuss alternative therapies -- which include herbal and dietary supplements, massage, and chiropractic manipulation -- is that physicians never ask. Others said, among other reasons, that they did not know they should or they did not have enough time during the office visit. In addition, nearly 75% of respondents report taking one or more prescription medications, and nearly 60% said they take over-the-counter medications. http://assets.aarp.org/rgcenter/health/cam_2007.pdf

Connor KM, Payne V, Davidson JR. **Kava** in generalized anxiety disorder: three placebo-controlled trials. Int Clin Psychopharmacol. 2006 Sep;21(5):249-53. No evidence of hepatotoxicity was found with kava, and all of the treatments were well tolerated. Findings from these three controlled trials do not support the use of kava in DSM-IV generalized anxiety disorder.

Cox MC, et al. Influence of **garlic** (Allium sativum) on the pharmacokinetics of docetaxel. Clin Cancer Res. 2006 Aug 1;12(15):4636-40. This study indicates that garlic does not significantly affect the disposition of docetaxel. However, it cannot be excluded that garlic decreases the clearance of docetaxel in patients carrying a CYP3A5*1A allele.

De Smet PA. **Herbal remedies**. N Engl J Med. 2002 Dec 19;347(25):2046-56.

Dhiman RK, Chawla YK. Herbal medicines for liver diseases. Dig Dis Sci. 2005 Oct;50(10):1807-12. (InfoPOEMs: There is insufficient evidence to recommend most commonly used herbal medicines for the treatment of liver disease. Of the 4 products evaluated in this review -- Phyllanthus, Silybum marianum (milk thistle), **glycyrrhizin** (licorice root extract), and Liv 52 (a mixture of herbs) -- available evidence supports only the use of the **licorice root extract** in the treatment of subacute liver failure and the prevention of hepatocellular carcinoma in patients with chronic hepatitis C. (LOE = 2a))

Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of ginkgo biloba for the prevention of cognitive decline. Neurology. 2008 Feb 27; [Epub ahead of print] n=118 42 month In unadjusted analyses, **ginkgo biloba** extract (GBE) neither altered the risk of progression from normal to Clinical Dementia Rating (CDR) = 0.5, nor protected against a decline in memory function. Secondary analysis taking into account medication adherence showed a protective effect of GBE on the progression to CDR = 0.5 and memory decline.

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Draves AH, Walker SE. Parthenolide content of Canadian commercial **feverfew** preparations (Label claims are misleading in most cases). CPJ Dec 2003/Jan 2004, Vol. 136, No. 10, p23-30.

Effect of **Gamma-Linolenic Acid** on the Transcriptional activity of the Her- 2/neu (erbB-2) oncogene. Journal of the National Cancer Institute, Vol. 97, No. 21, November 2, 2005, p. 1611-1615.

Ernst E. **Cardiovascular adverse effects of herbal medicines**: a systematic review of the recent literature. Can J Cardiol. 2003;19:818-27.

Fava M, Alpert J, et al. A Double-blind, Randomized Trial of **St John's Wort**, Fluoxetine, and Placebo in Major Depressive Disorder. J Clin Psychopharmacol. 2005 Oct;25(5):441-447.

FDA May 2007 FDA chemical analysis revealed that **Energy Max** contains thione analog of sildenafil, a substance with a structure similar to sildenafil, the active ingredient in Viagra, an FDA-approved drug for ED.Substances like this are called analogs because they have a structure similar to another drug and may cause similar side effects and drug interactions. **True Man** contains a thione analog of sildenafil or piperadino vardenafil, an analog of vardenafil, the active ingredient in Levitra, another FDA-approved prescription drug for ED. Neither the thione analog of sildenafil nor piperadino vardenafil are components of approved drug products.

FDA Feb/08 Palo Alto Labs and FDA notified consumers and healthcare professionals of a voluntary nationwide recall of two dietary supplements, **Aspire36** and **Aspire Lite**. The products were recalled because they were found to contain Aildenafil in trace amounts and Dimethyl sildenafil thione, an analog of Sildenafil, a drug used to treat erectile dysfunction.

FDA Mar/08 The U.S. Food and Drug Administration is advising consumers not to purchase or use "**Blue Steel**" or "**Hero**" products, marketed nationally as dietary supplements, because these products contain undeclared ingredients similar to sildenafil.

FDA April/08 **Herbal Science International**, Inc. and FDA informed consumers and healthcare professionals of a nationwide recall of twelve dietary supplements that contain ephedra, aristolochic acid or human placenta because they may present a serious health hazard to consumers. FDA has long regarded dietary supplements containing ephedra, a botanical that contains ephedrine alkaloids, as a potential health hazards because the alkaloid raises blood pressure and otherwise stress the circulatory system.

FDA May/08 is requesting that the manufacturer of **Xiadafil** — an "all natural" dietary supplement sold to treat erectile dysfunction — recall all its stock from natural food stores & discontinue marketing it on the Web since it contains an analog of sildenafil.

FDA May/08 notified consumers and healthcare professionals that supplement products sold under the brand name of **Viril-ity Power** (VIP) Tablets is being recalled because one lot was found to contain a potentially harmful undeclared ingredient, hydroxyhomosildenafil, an analog of sildenafil.

FDA May/08 The US Food and Drug Administration advised consumers not to use the products **Total Body Formula** in Tropical Orange and Peach Nectar flavours, and **Total Body Mega Formula** in Orange/Tangerine flavour, because they contain high doses of selenium and chromium.

FDA July/08 Jack Distribution, LLC issued a voluntary nationwide recall of selected lots of **Rize 2 The Occasion Capsules** and **Rose 4 Her Capsules**, marketed as dietary supplements. The products were recalled because certain lots contained thiomethisosildenafil, an undeclared analog of sildenafil, a FDA-approved drug used for Erectile Dysfunction.

FDA July/08 not to buy or use **Viapro** 375mg Capsules because one lot of the product was found to contain a potentially harmful undeclared ingredient, thio-methisosildenafil, an analog of sildenafil.

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.

Gardner CD, Lawson LD, Block E, et al. Effect of raw garlic versus commercial **garlic** supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia. Arch Int Med 2007; 167:346-353. None of the forms of garlic used in this study, including raw garlic, when given at an approximate dose of a 4-g clove per day, 6 d/wk for 6 months, had statistically or clinically significant effects on LDL-C or other plasma lipid concentrations in adults with moderate hypercholesterolemia.

Gastpar M, et al. Comparative Efficacy and Safety of a Once-Daily Dosage of **Hypericum** Extract STW3-VI and Citalopram in Patients with Moderate Depression: A Double-Blind, Randomised, Multicentre, Placebo-Controlled Study.Pharmacopsychiatry. 2006 Mar;39(2):66-75.

Genistein: Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2007 Aug;92(8):3068-75. Epub 2007 May 22. These results suggest that 54mg genistein plus calcium, vitamin D(3), and a healthy diet was associated with favorable effects on both glycemic control and some cardiovascular risk markers in a cohort of osteopenic, postmenopausal women. D'Anna R, Cannata ML, Atteritano M, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause. 2007 Jul-Aug;14(4):648-55. The phytoestrogen genistein has been shown to be effective on vasomotor symptoms without an adverse effect on endometrium. Marini H, Minutoli L, Polito F, et al. Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):839-47. Summary for patients in: Ann Intern Med. 2007 Jun 19;146(12):I34. Twenty-four months of tx with genistein has positive effects on BMD in osteopenic postmenopausal women.

Gertsch JH, Basnyat B, et al. Randomised, double blind, placebo controlled comparison of **ginkgo biloba** and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT). BMJ. 2004 Apr 3;328(7443):797. Epub 2004 Mar 11.

Grossman E, et al. **Melatonin** reduces night blood pressure in patients with nocturnal hypertension. Am J Med. 2006 Oct;119(10):898-902. n=38 4weeks

Guo R, Canter PH, Ernst E. A systematic review of randomised clinical trials of individualised herbal medicine in any indication. Postgrad Med J. 2007 Oct;83(984):633-7. There is a sparsity of evidence regarding the effectiveness of individualised herbal medicine & **no convincing evidence to support the use of individualised herbal medicine in any indication**.

Gunton JE, Cheung NW, et al. **Chromium** Supplementation Does Not Improve Glucose Tolerance, Insulin Sensitivity, or Lipid Profile: A randomized, placebo-controlled, double-blind trial of supplementation in subjects with impaired glucose tolerance. Diabetes Care. 2005 Mar;28(3):712-3.

Hadley S, Petry JJ. **Valerian**. Am Fam Physician. 2003 Apr 15;67(8):1755-8.

Health Canada is warning consumers: Jan/06 African herbal products **M2 Formula** & **Energy 2000** pose potential health risks http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_01_e.html

Health Canada is warning Aril/06 consumers not to not to use advises consumers not to use unauthorized products containing **anabolic steroids** (Five products containing illegal anabolic steroids, as they can potentially cause serious health issues such as liver disorders and heart problems. The five products are: Anabolic Xtreme Superdrol, Methyl-1-P, Ergomax LMG, Prostanozoland, and FiniGenX Magnum Liquid.)

Health Canada is warning consumers not to not to use **Kaizen Ephedrine HCL tablets for weight loss Dec/05** http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_138_e.html

Health Canada is warning consumers not to ingest the herb **chaparral** in the form of loose leaves, teas, capsules or bulk herbal products because of the risk of liver and kidney problems. Dec/05 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_135_e.html

Health Canada is warning consumers not to use certain **Ayurvedic medicinal** products because they contain high levels of heavy metals such as lead, mercury and/or arsenic. July/05 http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_80.html

Health Canada Jan/06 Natural health product **Libidfit** may pose health risks (promoted for sexual enhancement and erectile dysfunction, but contains an undeclared amount of a pharmaceutical ingredient similar to sildenafil) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_02_e.html

Health Canada is warning consumers Feb/06: Not to use the Chinese medicinal product White Peony Scar-repairing pills, manufactured in Hong Kong by White Peony Pharmaceuticals Limited, due to high levels of lead. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_05_e.html

Health Canada is warning consumers Feb/06 not to use 13 Chinese herbal products manufactured by the Hong Kong Chi Chun Tang Herbal Factory due to bacterial contamination that could lead to serious health risks. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_08_e.html

Health Canada advises consumers April/06 not to use Super Fat Burning and LiDa Daidaihua Slimming Capsules for weight loss because they have been found to contain sibutramine http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_15_e.html

Health Canada is advising consumers Apr/06 not to use unapproved products containing **yohimbine or yohimbe bark**, including Strauss Energy SIX capsules. Yohimbine is a prescription substance that can pose serious health risks for people with underlying risk factors. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_16_e.html

Health Canada is advising consumers Apr/06 not to use unapproved Miracle Bion products as it could be contaminated with bacteria such as *E. coli*. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_23_e.html

Health Canada May/06 is warning consumers not to use the product **Nasutra** because it has been found to contain the sildenafil (chemical name for Viagra) that could lead to serious health risks, especially for patients with existing medical conditions such as heart problems, those who may be taking heart medications, or those who may be at risk for strokes.

Health Canada May/06 is advising consumers not to use Ocean Plasma **Isotonic Living Water and Ocean Plasma Hypertonic Living Water** because they are unapproved products that contain unacceptable amounts of aerobic bacteria.

Health Canada June/06 is advising consumers not to use four unapproved **Ayurvedic medicinal products** from India because they contain high levels of lead and/or mercury. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_46_e.html

Health Canada July/06 is advising Fat Rapid Loss Capsules (Xin Yan Zi Pai Mei Zi Jiao Nang) because may contain sibutramine http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_55_e.html

Health Canada July/06 is advising consumers not to use 4 foreign health products due to concerns about possible side-effects: **Zhuifeng Tougu Wan** & **Fufang LuHui Jiaonang**, two traditional Chinese medicines that contain toxic levels of mercury; **Safi**, a herbal product manufactured in India and Pakistan that contains toxic levels of arsenic; and **Baike Wan**, a herbal product from Malaysia that contains the prescription drugs piroxicam and frusemide, and the over-the- counter drug chlorpheniramine.

Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well Dietary Supplement** because a sample has been found to contain **estazolam.**

Health Canada Warns Consumers August 04, 2006 Not To Use **Neophase** Formula For Men Due To Potential Health Risks which has been found to contain an undeclared ingredient similar to the active pharmaceutical ingredient found in Viagra. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_67_e.html

Health Canada Aug/06 is reminding consumers not to use Miracle II Miracle Neutralizer or any other products exported or sold by Tedco, Inc. of Louisiana because they could contain harmful bacteria. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_68_e.html

Health Canada Aug/06 is advising consumers about a possible link between health products containing the herbal medicine **black cohosh and liver damage**. There have been a number of international case reports of liver damage suspected to be associated with the use of black cohosh, including three case reports in Canada and one published case of death in the United States. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html

Health Canada Aug/06 is advising consumers not to use four foreign health products due to concerns about possible side-effects: **Reduce Weight**, a proprietary Chinese Medicine marketed as a weight-loss product. Contains the prescription drug sibutramine (the generic name for Meridia) **Yixinjiaonang**, a proprietary Chinese medicine marketed as a sexual enhancement & erectile dysfunction product, contains the prescription drug tadalafil (the generic name for Cialis) **Meng Rong**, a proprietary Chinese medicine marketed as a sexual enhancement and erectile dysfunction product, contains the prescription drug sildenafil (the generic name for Viagra) **VG**, a proprietary Chinese medicine marketed as a sexual enhancement and erectile dysfunction product, contains the prescription drug sildenafil (the generic name for Viagra) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/index_e.html

Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well** Dietary Supplement because a sample analyzed by Health Canada has been found to contain the undeclared drug Estazolam. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_82_e.html

Health Canada Aug/06 is advising consumers not to use two foreign health products due to concerns about possible side-effects: **Chao Nongsu Qingzhi Jiaonang** (OPC Care) is promoted as a weight-loss product. The product is adulterated with sibutramine and mazindol, two prescription medications used to suppress appetite. **Conting Qianweisu Slimming Herbs** Capsule is marketed as a weight-loss product. The product is adulterated with sibutramine, a prescription medication used to suppress appetite. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/2006/2006_84_e.html http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/2006/2006_83_e.html

Health Canada Sept/06 advises against use of the **Ayurvedic medicinal product Jambrulin** due to lead content http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_89_e.html

Health Canada Sept/06 is warning consumers not to use the natural health product **Libidus** because it contains an undeclared pharmaceutical ingredient, a modified form of vardenafil.

Health Canada Oct/06 is advising consumers not to use the unauthorized natural health products **Emperor's Tea Pill (Tian Huang Bu Xin Wan)** and **Hepatico Extract (Shu Gan Wan)** because certain lots of these products contain high levels of lead and mercury. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_98_e.html

Heath Canada Nov/ 06 is warning Canadians not to use the unauthorized product **Embrun de mer** promoted for the treatment of skin irritation in newborns and adults because it contains unacceptable amounts of harmful bacteria.

Health Canada Dec/06 is advising consumers not to use a product called **Eden Herbal Formulations Sleep Ease Dietary Supplement**, because it was found to contain an undeclared drug estazolam http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_127_e.html

Health Canada Dec/06 is advising consumers not to use two foreign health products due to concerns about possible side-effects: **Slim & Detox Peptide**, which are weight-loss products. Containing the prescription drug sibutramine (the generic name for Meridia) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/index_e.html

Health Canada Jan/07 is advising consumers not to use **Kang Da** and **four unlabelled products** are marketed as herbal sexual enhancements and treatments for erectile dysfunction. The products are adulterated with a prescription medication used in the treatment of sexual dysfunction. **Qing Zhi** and one unlabelled product are marketed as herbal weight-loss products. The products are adulterated with sibutramine, a prescription medication used to suppress appetite.

Health Canada Feb/07 is advising consumers not to use a product called **Sleepees**, because it was found to contain an undeclared drug **estazolam**, which can be habit-forming when used for as little as a few months. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_16_e.html

Health Canada Feb/07 is updating Canadians about adverse reaction reports it has received concerning the use of **EMPowerplus**, a vitamin mineral supplement, for serious medical conditions. Health Canada has received nine case reports of serious adverse reactions associated with the use of EMPowerplus. Most of the adverse reactions relate to worsening of psychiatric symptoms in those patients with serious underlying mental health problems, such as bipolar disorder and depression.

Health Canada Feb/07 is advising consumers not to use the following product listed in the table below due to concerns about possible side-effects. More info **Power 58; Platinum Power 58; Ehanix; Jolex; Onyo; Deguozonghengtianxia** because they contained acetildenafil. Acetildenafil is an analogue of sildenafil, a prescription medication indicated for treatment of erectile dysfunction.

Health Canada Mar/07 is Health Canada is advising consumers not to use **MIAOZI Slimming Capsules** because they have been found to contain sibutramine, a prescription medication that should only be taken under medical supervision.

Health Canada Mar/07 is warning consumers not to use the unauthorized natural health product **XOX For Men**, because it contains an undeclared pharmaceutical ingredient, tadalafil, an ingredient found in the prescription drug Cialis. The use of XOX For Men could pose serious health risks, especially for patients with existing medical conditions such as heart problems, those taking heart medication, or those at risk of stroke.

Health Canada Mar/07 is warning consumers not to use the unauthorized product **Vigorect** Oral Gel Shooter, because it contains an undeclared drug substance tadalafil.

Health Canada Apr/07 is warning consumers about **Bitter orange** & cardiovascular reactions in the Canadian Adverse Reactions April 2007 Newsletter.

Health Canada Apr/07 is warning consumers from The Hong Kong Department of Health found **Lanmei Keili Ji to be adulterated with gliclazide**, a hypoglycaemic agent (lowers blood sugar). The Hong Kong Department of Health found **Lexscl Fat Rapid Loss capsules to be adulterated with sibutramine** and thyroid hormones. The United States Food and Drug Administration found **V.MAX and Rhino Max (Rhino V Max) to contain undeclared amounts of aminotadalafil**, an analogue of tadalafil, used to treat erectile dysfunction.

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

Health Canada April/07is advising consumers not to use a product **FiberChoice plus Multivitamins** is marketed as a fibre supplement. The product is contaminated with **fish gelatin**, a known allergen that could cause life-threatening reactions in some sensitive individuals.

Health Canada May/07 is warning consumers **Urat Madu** capsules are marketed for the treatment of erectile dysfunction. The product is adulterated with **sildenafil**, a prescription drug that has been associated with serious side effects including sudden vision loss, penile tissue damage and urinary tract infection.

Health Canada May/07 is advising consumers not to use **Xiaokeshuping Jiangtangning Jiaonang** capsules in Hong Kong to contain the undeclared pharmaceutical drugs phenformin, rosiglitazone, and glibenclamide, which may be used in diabetes to lower blood sugar.

Health Canada May/07 is advising consumers that **HS Joy of Love** product is marketed as a dietary supplement and was found to contain piperadino **vardenafil**.

Health Canada May/07 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: **Power 58 Extra, Platinum Power 58 Extra, Enhanix New Extra Men's Formula, Valentino, King Power Oral Solution, and Stretch Up** Capsules are marketed as treatments for erectile dysfunction. The products contain analogues of sildenafil and vardenafil, which are prescription drugs used for the treatment of erectile dysfunction.

Health Canada June/07 is advising consumers not to use **Optimum Health Care SleePlus TCM** or **BYL SleePlus**, because the products contain the undeclared drug **clonazepam.**

Health Canada June/07 is warning consumers not to use the product **Encore Tabs for Men**, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.

Health Canada July/07 is warning Canadians not to use the dietary supplement **MdMt**, or any other supplements containing the synthetic steroids methyl-1-testosterone or methyldienolone that are obtained without a prescription, due to potentially serious health risks including reduced fertility and liver disorders.

Health Canada July/07 is warning consumers not to use **Zencore** Tabs, a product advertised as a dietary supplement for sexual enhancement, because it contains an undeclared pharmaceutical ingredient similar to the approved drug tadalafil.

Health Canada July/07 & the US Food and Drug Administration (FDA) found ***Liviro3*** to contain tadalafil, a prescription drug that should only be taken under the guidance of a health professional.

Health Canada July/07 is advising consumers not to use the sleep supplement product **Optimum Health Care Sleep Easy**, because it contains the undeclared drug clonazepam.

Health Canada July/07 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: **Jie Jie Pills** and **Chuan Xiong Cha Tiao Wan** are proprietary Chinese medicines that have been found to contain aristolochic acid, a natural toxin known to cause kidney failure and cancer in humans. Medsafe, the New Zealand health regulatory authority, advised the public not to use the products **Darling Capsules**, **Dali Capsules**, **Spanish Fly Capsules**, and an unnamed product, because they were found to contain sildenafil. Medsafe also advised the public not to use the product **Dai Dai Hua Jiao Nang** because it was found to contain sibutramine. The Hong Kong Department of Health [HKDH] found batch #WA00030 of the product K**ui Hua Chut Lee San Bird's Nest & Pearl** to exceed the acceptable limit for microbiological contaminants set out by the HKDH. Further investigation revealed that this product also exceeded the limit for bacterial contamination in Natural Health Products in Canada.

Health Canada Aug/07 Consumers who use **Excite for women or Ultimates for men** may be at risk of serious side effects similar to those associated with sildenafil.

Health Canada Aug/07 is advising Canadians of a recall in the United States of one lot of **Metaboslim Apple Cider Vinegar**, which is marketed as a dietary supplement, because it has been found to contain **sibutramine**, a prescription medication that should only be taken under medical supervision.

Health Canada Sept/07 is advising consumers not to use 13 foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang, J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada. **Satis 60 Hours Ever Lasting Formula** is used for the treatment of erectile dysfunction/sexual enhancement. It was found to contain piperidenafil an analogue of vardenafil, a drug that should only be used under the supervision of a health professional. **Qiangli Zhuanggutongbiling** has reportedly been used for joint pain and stiffness. It was found to contain the undeclared prescription drugs prednisolone acetate, cortisone acetate, piroxicam, and diclofenac. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional. **Endopile Capsules** is used for the treatment of hemorrhoids and piles, and related symptoms and was found to contain potentially toxic levels of lead and mercury. **BuXie PaiDu XiaoDou Su** is used as an acne treatment and was found to contain the prescription drug rifampicin (rifampin). **True Man** and **Energy Max** are used as sexual enhancement/ erectile dysfunction products and were found to contain an analogue of sildenafil or vardenafil which are prescription medications.

Health Canada Sept/07 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: **Top Gun for Men Herbal Extracts** has been found to contain a substance similar to tadalafil. **Oyster Plus** has been found to contain tadalafil. **Deguozhanjiang** contains sildenafil and tadalafil, prescription drugs used for the treatment of erectile dysfunction. **Chongcaoliubian Jiaonang** and **Santi Scalper Penis Erection** Capsule contain sildenafil.

Health Canada Sept/07: **Khun-Phra** is a health product promoted for pain relief that has been found to contain the undeclared drugs dexamethasone, prednisolone, phenylbutazone, diazepam, cyproheptadine and mebhydrolin.. **Asam Urat Flu Tulang, PJ Dewandaru** is a health product promoted to treat joint pain, rheumatism and arthritis. It has been found to contain the undeclared drugs dexamethasone, diclofenac and acetaminophen.

Health Canada Oct/07 Foreign Product Alerts: ***Zhen Feng Da Brand Xi Tong Wan*** is promoted as a pain reliever. Lot #060908 has been found to contain undeclared indomethacin, a prescription anti-inflammatory drug that should only be taken under the guidance of a health professional. ***Wellring Brand Yin Qiao Jie Du*** is a health product promoted to treat cold and flu symptoms. Lot#51005 has been found to contain undeclared acetaminophen. ***Gu Ci Dan*** and ***Xu Log Bou*** are promoted as pain relievers and have been found to contain undeclared indomethacin. Indomethacin is a prescription anti-inflammatory drug that should only be taken under the guidance of a health professional.

Health Canada Oct/07 is advising, especially pregnant & breastfeeding women, not to use **Calabash chalk** because of the potential health risk due to high levels of lead.

Health Canada Oct/07: Foreign Product Alerts: **Red Yeast Rice, Red Yeast Rice/Policosonal Complex and Cholestrix, and Xie Gan Wan**. Red Yeast Rice, Red Yeast Rice/Policosonal Complex and Cholestrix are promoted as dietary supplements for the treatment of high cholesterol. These products may contain **lovastatin**, a prescription medication for the treatment of high cholesterol that should only be taken under the guidance of a health professional. Xie Gan Wan is a Proprietary Chinese Medicine with unknown indication for use. Xie Gan Wan, was found to contain **Aristolochia** plant species.

Health Canada Oct/07: **Royal Medic No.1 Chinese Caterpillar Fungus** is a proprietary Chinese medicine promoted as a general health tonic, but Health Canada advises Canadians not to use this product due to microbial contamination. **Steripaste Medicated Paste Bandages** may not be sterile therefore there is a possibility the bandage may cause a wound infection.

Health Canada Nov/07 is advising consumers not to use **Axcil** and **Desirin**, are promoted as natural sexual enhancement/ erectile dysfunction products. Consumers are warned not to use Axcil and Desirin because both products were found to contain the prescription drug **sildenafil**.

Health Canada Dec/07 is advising Canadians not to use unauthorized products manufactured by **Wild Vineyard** because of the potential health risk to consumers. Wild Vineyard is not authorized to manufacture, package, label or import natural health products in Canada.

Health Canada Jan/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **Baby's Bliss Gripe Water** (apple flavour), code 26952V, a natural health product given to infants to ease stomach discomfort and gas, was found to contain the parasite cryptosporidium. Cryptosporidium may cause severe, chronic or even fatal effects, especially in infants. **Zhong Ti Xiao Er Jian Pi San** is a natural health product. Batch number JPS0704 has been recalled due to microbial contamination.

Health Canada Jan/08 is warning Canadians not to use the unauthorized product **Yeniujyn** because the product contains heavy metal contaminants and may pose a serious health risk. Yeniujyn is advertised as a natural health product, for adults and children, to be used "to cure involuntary passage of urine diseases." The product was found to contain high levels of **lead and arsenic**.

Health Canada Jan/08 is warning Canadians not to use the unauthorized product 1- ZhenZhu HouFengSan Penji; Vyling Cornu Saigae Tataricae Cooling Tea; Natorny Kwek's Herb 106; Chinese Herbal Heritage Herbal Slimming Tea; Vyling Urticaria Itch-Killer A; Vyling Water- Melon Pearls Powder; Phoenix Brand Tea For Sore Throat And Fever; Qing Yin Bai Hua Tea; and Yinqiao Flu & Fever Tea. **Nine specific batches** of Chinese medicines and teas manufactured in Singapore that have been recalled due to microbial (bacterial) and/or yeast and mould **contamination**.

Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules (batch number 28012007 / expiration date: Jan 2009). This product is promoted for weight loss and has been found to contain a derivative of the prescription drug **sibutramine**.

RGC-RMC Rheumax Capsule (batch number REM1-SI93016N). This batch of RGC-RMC Rheumax Capsule has been found to contain **progesterone**, a steroid hormone that can have adverse effects on the brain, breast and skin and should only be taken if prescribed by a health professional.

Health Canada Feb/08 warning Canadians not to use Foreign Products: 1) **Jingzhi Kesou Tanchuan; Guanxin Suhe capsules**; **Qing Re An Cang Wan**; & **Guan Xin Su He** 2) **Xiao Qin Long Capsules** 3) **Xiao Qin Long Wan**; **Chuan Xiong Cha Tiao Wan Tablets**; **Bai Tou Weng Wan**

4) **Wannianqing Pai Danggui Niantong Tang** (batch number 050401) These products have been found to contain aristolochic acid, a toxin associated with serious and potentially fatal health effects.

Health Canada Feb/08 warning Canadians not to **use VPX 'No Shotgun' and BSN 'Cell Mass' Body Building Powders** These products have been found to contain coumarin.

Health Canada Feb/08 warning Canadians not to use 1) Ding Lu Brand Guipi Wan (batch number 060401); Ding Lu Brand Bushen Yijing Wan (batch number 060401); Ding Lu Brand Shiquan Dabu Wan (batch number 060401); **Ding Lu Brand Xiangsha Liujun Wan** (batch number 060401); Ding Lu Brand Xiaoyao Wan (batch number 060401); Medco Brand Vitality Essence Extract Of Deer Fetus (batch number 61007); Plasmin (batch number 20060102) 2) **Yogaraja Gulgulu Pills** (batch number GK039) and Pilsol Capsule 3) **Conforer Global Yang Tonic-2** (batch number 060117) 4) **Liang Gel San Concentrated Powder** (batch number G3238913) and **Qing Xin Lian Zi Yin Concentrated** Powder (batch number G3239274) These products were found to contain excessive amounts of heavy metals.

Health Canada Mar/08 is warning consumers not to use **Libidus**, an unauthorized product promoted on the web site of the manufacturer for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the undeclared prescription drug sildenafil.

Health Canada April/08 is warning consumers not to use Foreign Product Alert: **Tetrasil, Genisil, Aviralex, OXi-MED, Beta-mannan Micronutrient, Qina** and **SlicPlus**. They are marketed for the prevention or treatment of a variety of sexually transmitted diseases.

Health Canada April//08 is advising consumers not to use 2 foreign products, **Aspire 36** & **Aspire Lite**, because they were found to contain undeclared sildenafil analogues.

Health Canada April/08 is warning consumers not to use **Vigoureux**, an unauthorized product promoted for the treatment of erectile dysfunction. The product may pose serious health risks, as it was found to contain the prescription drug sildenafil

Health Canada April/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: **Tian Li** was found to contain tadalafil and hydroxyhomosildenafil, and should only be taken under the guidance of a healthcare professional. **Xian Zhi Wei II** was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.

Health Canada April/08 is advising consumers not to use The Hong Kong Department of Health advised the public not to use the product **Tian Sheng Yi Bao** because it was found to contain two pharmaceutical products, glibenclamide and phenformin

Health Canada April/08 is advising consumers about The Health Sciences Authority (HSA) of Singapore recalled **Qili Brand Tongbianling Jiaonang, Sincere Brand ChuanXinLian Jiaonang, Xiangyao Brand Xiangyao Weian Jiaonang, Biflora Brand Fufang Danshen Pian (film-coated), Biflora Brand 306 Xiaoyan Jiedu capsules, and Xiang Sha Liu Jun Wan** as they were found to contain high levels of arsenic and/or mercury that exceeded the permissible limits outlined by the HSA standards of safety and quality.

Health Canada May/08 is advising consumers not to use **vpxl No1** Dietary Supplement for Men was found to contain tadalafil

Health Canada May/08 is reminding consumers who choose to use unapproved Ayurvedic medicinal products that some of these products may contain high levels of heavy metals. Consumption of excessive amounts of heavy metals, such as lead, mercury, and arsenic, pose serious health risks.

Health Canada May/08 is warning consumers not to use **Trophic Kelp & Glutamic Acid HCl** due to the health risk posed by exposure to high levels of iodine.

Health Canada May/08 is warning consumers not to use **Desire**, an unauthorized product promoted to enhance male sexual performance as this product may pose serious health risks in certain patients. Lot 0070263 of the product was found to contain the prescription drug phentolamine.

Health Canada June/08 is advising that **Desire** contains Phentolamine, which should only be used under the supervision of a health care professional.

Health Canada June/08 **6-OXO**, which contains the compound 4-androstene-3,6,17-trione, is an unauthorized natural health product in Canada. **1-AD** contains 1-androstenediol, an anabolic steroid that is regulated as a controlled substance in Canada

Health Canada July/08 Foreign Product Alerts: **Super Shangai,Strong Testis, Shangai Ultra, Shangai Ultra X, Lady Shangai, Shangai Regular (also known as Shangai Chaojimengnan), Actra-Sx, An unknown product containing the plant Lycium barbarum L., Adam Free, NaturalUp, Erextra, Yilishen, Blue Steel, Hero, & Naturalë Super Plus.** These products have been found to contain sildenafil or an unapproved substance similar to sildenafil.

Health Canada July/08 is advising consumers not to use 4 foreign health products due to concerns about possible side-effects: Wodibo. **Wodibo** is promoted as an all-natural Chinese potency-enhancing product for the treatment of erectile dysfunction. The Danish Medicines Agency has warned against the use of Wodibo because it was found to contain sildenafil and tadalafil, prescription drugs authorized for treatment of erectile dysfunction. Both of these medications should only be used under the supervision of a health care professional. **Viril-Ity-Power** (VIP) Tabs. The U.S. Food and Drug Administration has warned consumers not to use Viril-Ity-Power (VIP) Tabs because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil. The product has been recalled by the manufacturer in the U.S. **Therma Power** (red and blue varieties) and **Grenade Fat Burner**. The U.K. Medicines and Healthcare products Regulatory Agency (MHRA) warned consumers not to use the ephedrine-containing products Therma Power (red variety) and Grenade Fat Burner after the products were associated with serious adverse reactions. The MHRA also warned consumers to not use the ephedrine-free Therma Power (blue variety) because it contains synephrine and caffeine, a combination that has been associated with cardiovascular adverse reactions.

Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Dan Bai Shou Shen Su** was found to contain undeclared thyroid hormones and sibutramine. **Karntien and Karntien Easy to Slim** were adulterated with sibutramine and a compound that is similar in structure to sibutramine (N-desmethylsibutramine). **Armstrong Natural Herbal Supplement, Enhanix New Extra Men's Formula, Power 58 Extra, and Platinum Power 58 Extra** were adulterated with tadalafil or unapproved substances with structures similar to tadalafil and vardenafil. **More Slim** was found to contain the undeclared pharmaceutical ingredient sibutramine. **Soloslim** was found to contain an undeclared substance similar in structure to the prescription drug sibutramine. It also contains the prescription drug L-carnitine, as well as synephrine, which is not authorized for sale in weight loss products in Canada.

Health Canada Aug/08 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of Natural (Xin Yi Dai) and Lasmi because Natural (Xin Yi Dai) was found to contain sibutramine and phenolphthalein, and Lasmi was found to contain sibutramine and spironolactone. The Hong Kong Department of Health warned against the use of AA Qu Feng Shu Jin Wan because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. Apisate contained fenfluramine and Energy ll contained sibutramine. Obat Asam Urat and Asam Urat both contained dexamethasone, phenylbutazone and piroxicam. The Hong Kong Department of Health warned against the use of Slim 3in1 (Xiao Nan zhi Bao) because it was found to contain the undeclared pharmaceutical ingredients sibutramine and phenolphthalein.

Health Canada Sept/08 is advising consumers not to use any unauthorized health products sold under the brand names **Life Choice, Healthy Choice, Doctor's Choice and Your Choice** as well as other products without a brand name. All of these unauthorized health products have the same identifying image on their label.

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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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Conclusions The data from this large trial indicated that **600 IU of natural-source vitamin E** taken every other day provided no overall benefit for major cardiovascular events or cancer, did not affect total mortality, and decreased cardiovascular mortality in healthy women. These data do **not support** recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women. (InfoPOEMs: Vitamin E does not reduce the risk of cardiovascular disease, cancer, or total mortality among healthy women 45 years or older. (LOE = 1b))
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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.

References: ADHD Treatment Chart

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Health Canada Aug/06 Lamictal warning with non-syndromic oral clefts. Emerging data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry suggest an association between LAMICTAL® (lamotrigine) and an increased risk of non-syndromic oral clefts over the reference population for the registry (ie. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston, USA)1. Recently published data from the Registry report three cases of isolated, non syndromic cleft palate and two cases of isolated, non syndromic cleft lip without cleft palate in infants from 564 first trimester lamotrigine monotherapy exposures giving a rate of 8.9 per 1,000, as compared to 0.37 per 1000 in the reference population for that registry. The prevalence of oral clefts noted in the NAAED registry is also higher than the background prevalence of non-syndromic oral clefts reported in the literature, including studies from the United States, Australia and Europe. While different studies have differing results due to geographic and case ascertainment variations, the reported range is 0.50 to 2.16/1000 3-17. To assist with the assessment of risk, analysis of data from additional pregnancy registries, with approximately 2200 additional lamotrigine monotherapy first trimester exposures has been conducted, and 4 additional non-syndromic cases of oral cleft have been identified.
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Cohen LS, et al. Relapse of major depression during **pregnancy** in women who maintain or discontinue antidepressant treatment. JAMA. 2006 Feb 1;295(5):499-507. CONCLUSIONS: Pregnancy is not "protective" with respect to risk of relapse of major depression. Women with histories of depression who are euthymic in the context of ongoing antidepressant therapy should be aware of the association of depressive relapse during pregnancy with antidepressant discontinuation.{InfoPOEMs Mar 2006: Nearly 50% of women currently receiving antidepressant medication will experience a relapse of major depression during pregnancy. The risk is highest for those discontinuing their medication (68% relapse rate). It is likely that this study sample consists of patients with a higher severity of illness than those found in a routine community practice, so the findings may not generalize to other settings. (LOE = 1b). Women maintaining their medication during pregnancy relapsed significantly less often than those who discontinued medication (26% vs 68%; number needed to treat (NNT)= 2; 95% CI, 1.8 - 4).}
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Depression scales The PHQ-9 is the 9 item depression scale of the Patient Health Questionnaire. The PHQ-9 is a powerful tool for assisting primary care clinicians in diagnosing depression as well as selecting and monitoring treatment. http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/ **PHQ-2 Patient Health Questionnaire 2** about depressed mood and anhedonia: http://www.aafp.org/afp/20040915/1101.html
Deshauer D, Moher D, Fergusson D, et al. Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic **long-term randomized controlled trials**. CMAJ. 2008 May 6;178(10):1293-301. There is a lack of classic randomized controlled trials of serotonin reuptake inhibitors lasting more than 1 year for the treatment of depression. The results of our systematic review support current recommendations for 6-8 months of antidepressant treatment following initial recovery but provide no guidance for longer treatment.
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Elderly

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Pinquart M, Duberstein PR, Lyness JM. Treatments for later-life depressive conditions: a meta-analytic comparison of pharmacotherapy and psychotherapy. Am J Psychiatry. 2006 Sep;163(9):1493-501. Given that psychotherapy and pharmacotherapy did not show strong differences in effect sizes, treatment choice should be based on other criteria, such as contraindications, treatment access, or patient preferences.
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Wilson K, Mottram P. A comparison of side effects of selective serotonin reuptake inhibitors and tricyclic antidepressants in older depressed patients: a meta-analysis. Int J Geriatr Psychiatry. 2004 Aug;19(8):754-62.]

Ensrud KE, et al. for Study of Osteoporotic Fractures Research Gp. Use of **selective serotonin reuptake inhibitors** and **sleep** disturbances in community-dwelling older women. J Am Geriatr Soc 2006 Oct;54(10):1508-15.
Fava M, et al. Efficacy and safety of **sildenafil** in men with **serotonergic antidepressant-associated erectile dysfunction**: results from a randomized, double-blind, placebo-controlled trial.J Clin Psychiatry.2006Feb;67(2):240-6.
Fava M, Rush AJ, Wisniewski SR, et al. A Comparison of Mirtazapine and Nortriptyline Following Two Consecutive Failed Medication Treatments for Depressed Outpatients: A **STAR*D** Report. Am J Psychiatry. 2006 Jul;163(7):1161-72. Following lack of remission or an inability to tolerate an initial trial of citalopram for up to 12 weeks (first step) and a second trial with either monotherapy involving another antidepressant or augmentation of citalopram with bupropion or buspirone (second

step), adult outpatients (N=235) with nonpsychotic major depressive disorder were randomly assigned to 14 weeks of treatment with mirtazapine (up to 60 mg/day) (N=114) or nortriptyline (up to 200 mg/day) (N=121). For mirtazapine, remission rates were 12.3% and 8.0% per the Hamilton and QIDS-SR(16) scores, respectively. For nortriptyline, remission rates were 19.8% and 12.4%, respectively

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Gilbody S, House A, Sheldon T, Gilbody S. **Screening** and case finding instruments for depression. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD002792. AUTHORS' CONCLUSIONS: There is substantial evidence that routinely administered case finding/screening questionnaires for depression have minimal impact on the detection, management or outcome of depression by clinicians. Practice guidelines and recommendations to adopt this strategy, in isolation, in order to improve the quality of healthcare should be resisted. The longer term benefits and costs of routine screening/case finding for depression have not been evaluated. A two stage procedure for screening/case finding may be effective, but this needs to be evaluated in a large scale cluster randomised trial, with a prospective economic evaluation.

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Guaiana G, Barbui C, Hotopf M. **Amitriptyline for depression**. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004186. This present systematic review indicates that amitriptyline is at least as efficacious as other tricyclics or newer compounds. However, the burden of side-effects in patients receiving it was greater. In comparison with selective serotonin reuptake inhibitors amitriptyline was less well tolerated, and although counterbalanced by a higher proportion of responders, the difference was not statistically significant.

Hansen RA, Gartlehner G, Lohr KN, et al. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann Intern Med. 2005 Sep 20;143(6):415-26. CONCLUSIONS: Overall, second-generation antidepressants probably do not differ substantially for treatment of major depressive disorder. Choosing the agent that is most appropriate for a given patient is difficult. (InfoPOEMs: When it comes to the new, nontricyclic antidepressants, the medical literature does not give us any clear guidance as to which one is more effective, of faster onset, safer, or better tolerated. Sexual side effects are lower with bupropion and nausea seems to occur more often with venlafaxine. Other research has shown these new drugs to be no more effective or better tolerated than tricyclic antidepressants. For now, start your patient on your favorite antidepressant, with the realization that most patients will need to switch to another drug at least once. (LOE = 1a))

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Johnson EM, et al. **Cardiovascular changes** associated with **venlafaxine** in the treatment of late-life depression. Am J Geriatr Psychiatry. 2006 Sep;14(9):796-802.

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Kim H, et al. **Monoamine transporter gene polymorphisms** and antidepressant response in Koreans with late-life depression. JAMA. 2006 Oct 4;296(13):1609-18.

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Lam RW, et al. The Can-SAD study: a randomized controlled trial of the effectiveness of **light therapy** and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry. 2006 May;163(5):805-12. (InfoPOEMs: Light therapy and fluoxetine (Prozac) are equally effective treatment options for patients with seasonal affective disorder (SAD). Patient preference and an individual assessment of risks and benefits should guide treatment selection. (LOE = 1b))

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Medical Letter, **Duloxetine** for Diabetic Neuropathic pain. Vol 47 (Issue 1215/1216) Aug 15/29,2005. p.67-68.
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Moja P, Cusi C, Sterzi R, Canepari C. Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002919. CONCLUSIONS: Over 2 months of treatment, SSRIs are no more efficacious than placebo in patients with migraine. In patients with chronic TTH, SSRIs are less efficacious than tricyclic antidepressants. In comparison with SSRIs, the burden of adverse events in patients receiving tricyclics was greater. These results are based on short-term trials and may not generalise to longer-term treatment.
Montgomery SA, Baldwin DS, Blier P, et al. Which antidepressants have demonstrated superior efficacy? A review of the evidence. Int Clin Psychopharmacol. 2007 Nov;22(6):323-329. Only escitalopram was found to have definite superiority in the treatment of severe depression; probable superiority was identified for venlafaxine and possible superiority for milnacipran and clomipramine.
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Reynolds CF 3rd, et al. Maintenance treatment of major depression in **old age**. N Engl J Med. 2006 Mar 16;354(11):1130-8. CONCLUSIONS: Patients elderly 70 years of age or older with major depression who had a response to initial treatment with paroxetine and psychotherapy were less likely to have recurrent depression if they received two years of maintenance therapy with paroxetine. Monthly maintenance psychotherapy did not prevent recurrent depression. (InfoPOEMs: Prolonged treatment with paroxetine (Paxil) reduces the risk of recurrence of major depression in elderly patients. (LOE = 1b))
Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the **risk of fracture**. Arch Intern Med. 2007 Jan 22;167(2):188-94. Daily SSRI use in adults 50 years and older remained associated with a 2-fold increased risk of clinical fragility fracture after adjustment for potential covariates. Depression and fragility fractures are common in this age group, and the elevated risk attributed to daily SSRI use may have important public health consequences.
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Hegel M, Arndt S. Escitalopram and problem-solving therapy for prevention of **poststroke depression**: a randomized controlled trial. JAMA. 2008 May 28;299(20):2391-400. In this study of nondepressed patients with recent stroke, the use of escitalopram or problem-solving therapy resulted in a significantly lower incidence of depression over 12 months of treatment compared with placebo, but problem-solving therapy did not achieve significant results over placebo using the intention-to-treat conservative method of analysis.
Rosen R, et al.; Vardenafil Study Site Investigators. Efficacy and tolerability of **vardenafil** in men with mild depression and erectile dysfunction: the depression-related improvement with vardenafil for erectile response study. Am J Psychiatry. 2006 Jan;163(1):79-87.
Rush AJ, et al. **STAR*D** Study. **Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs** (citalopram) for depression. n=727 N Engl J Med. 2006 Mar 23;354(12):1231-42. CONCLUSIONS: After unsuccessful treatment with an SSRI, approximately **one in four patients** had a **remission** of symptoms after switching to another antidepressant. Any one of the medications in the study provided a reasonable second-step choice for patients with depression. (InfoPOEMs: Bupropion SR (~283mg/d), sertraline(~136mg/d) & venlafaxine XR (~194mg/d) are equally effective at inducing remission or response in patients with persistent symptoms of depression despite initial treatment with citalopram (Celexa ~41mg/d). Most patients will not go into remission, though, and this study lacked a placebo control group. (LOE = 1b))
Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A **STAR*D** Report. Am J Psychiatry. 2006 Nov;163(11):1905-17. The QIDS-SR(16) remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively. The overall cumulative remission rate was 67%.
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Trivedi MH. **STAR*D** Selecting among **second-step antidepressant** medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry. 2008 Aug;65(8):870-80. Clinical, demographic, and treatment history were of little value in recommending 1 medication vs another as a second-step treatment for major depressive disorder. Participants most likely to remit in the second step had less Axis I psychiatric disorder comorbidity, less social disadvantage, and at least a response to citalopram in the first step.
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Saarto T, et al. Antidepressants for **neuropathic pain**. **Cochrane** Database Syst Rev. 2007 Oct 17;(4):CD005454.
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Shah NR, Jones JB, Aperi J, Shemtov R, Karne A, Borenstein J. Selective Serotonin Reuptake Inhibitors for **Premenstrual Syndrome** and Premenstrual Dysphoric Disorder: A Meta-Analysis. Obstet Gynecol. 2008 May;111(5):1175-1182. Selective serotonin reuptake inhibitors were found to be effective in treating premenstrual symptoms, with continuous dosing regimens favored for effectiveness.
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ANTIPSYCHOTIC COMPARISON CHART

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SEDATIVE COMPARISON CHART

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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

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Dalhousie Academic Detailing Service Resources: Update on COPD. http://cme.medicine.dal.ca/files/COPD.pdf ; Summary http://cme.medicine.dal.ca/files/COPD%20Summary.pdf

de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. **Oral or IV Prednisolone** in the Treatment of COPD Exacerbations: A Randomized, Controlled, Double-blind Study. Chest. 2007 Dec;132(6):1741-7. Epub 2007 Jul 23. Therapy with oral prednisolone is not inferior to IV treatment in the first 90 days after starting therapy. Oral steroids are as effective as intravenous (IV) steroids for nonsevere exacerbations of chronic obstructive pulmonary disease (COPD). Because they are cheaper and less invasive, oral steroids should be the preferred treatment option. (LOE = 1b)

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

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Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in **chronic obstructive pulmonary disease** and the risk of hospitalization for **pneumonia**. Am J Respir Crit Care Med. 2007 Jul 15;176(2):162-6. Epub 2007 Mar 30. The use of inhaled corticosteroids is associated with an excess risk of pneumonia hospitalization and of pneumonia hospitalization followed by death within 30 days, among elderly patients with COPD. (InfoPOEMs: In this well-conducted case-control study, elderly patients with chronic obstructive pulmonary disease (COPD) hospitalized for pneumonia were more likely to have been prescribed inhaled corticosteroids. Even though there was a dose response, we still cannot ascertain if this was cause or effect.)

Esposito-Festen J, et al. Aerosol Therapy by Pressured Metered-Dose Inhaler-**Spacer** in Sleeping Young Children: To Do or Not to Do? Chest. 2006 Aug;130(2):487-492.

Feuillet-Dassonval C, et al. [Written asthma **action plans**: a useful tool for self-management] Arch Pediatr. 2005 Dec;12(12):1788-96. Epub 2005 Aug 26.

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FitzGerald JM, et al. Canadian Asthma Exacerbation Study Group. **Doubling the dose of budesonide** vs maintenance treatment in asthma exacerbations. Thorax. 2004Jul;59(7):550-6.

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Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. Chest. 2000 Feb;117(2):440-6. This study demonstrates that when patients with moderate asthma had reached a stable clinical condition with a high dose of budesonide, a low dose of budesonide (200 microg/d) is as effective as the standard dose (800 microg/d) in the control of symptoms and lung function over a period of several months. Furthermore, results showed that the addition of inhaled budesonide (800 microg/d) at onset of an asthmatic exacerbation has a beneficial clinical effect.

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6. Epub 2008 Jun 16. Using two simple predictive factors (baseline parent reported exercise induced wheeze and a history of atopic disorders), it is possible to estimate the likelihood of future asthma in children presenting with preschool wheeze. The absence of baseline exercise induced wheeze and a history of atopic disorders reduces the likelihood of subsequent asthma by a factor of five.

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Gibson PG, Powell H, Coughlan J, et al. **Self-management** education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev. 2003;(1):CD001117.

Graeme P Currie, Graham S Devereux, Daniel K C Lee, and Jon G Ayres. Recent developments in asthma management. BMJ, Mar 2005; 330: 585 - 589.

Granger R, et al. Injectable vaccines for preventing **pneumococcal** infection in patients with COPD. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD001390. There is no evidence from randomised controlled trials that injectable pneumococcal vaccination in persons with COPD has a significant impact on morbidity or mortality. Further large randomised controlled trials would be needed to ascertain if the small benefits suggested by individual studies are real.

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Hahn PY, Morgenthaler TY, Lim KG. Use of **exhaled nitric oxide** in predicting response to **inhaled corticosteroids for chronic cough**. Mayo Clin Proc. 2007 Nov;82(11):1350-5.

Haidl P, Schmidt F, Wiese C, Koehler D. Peak inspiratory flow rate after **methacholine challenge** in asthmatic patients and its impact on the effect of **formoterol** via different inhalers. J Aerosol Med. 2006 Fall;19(3):364-71. If patients fail to generate a PIMF of 30 l/min, 6 microg formoterol via Turbuhaler may provide inadequate relief in a severe asthma attack.

Haland G, et al. ORAACLE. Reduced **lung function** at birth and the risk of asthma at **10 years** of age. N Engl J Med. 2006 Oct 19;355(16):1682-9.Reduced lung function at birth is associated with an increased risk of asthma by 10 years of age. For some measures of lung mechanics, a reading below the median at birth was also associated with severe bronchial hyperresponsiveness (9.1% v 4.9%, P = 0.05) and use of inhaled corticosteroids at 10 years (5.9% v 2.4%, P = 0.02).

Halterman JS, et al. Improved preventive care for asthma: a randomized trial of **clinician prompting** in pediatric offices. Arch Pediatr Adolesc Med. 2006 Oct;160(10):1018-25.

Harrison TW, et al. **Doubling the dose of inhaled corticosteroid** to prevent asthma exacerbations: randomised controlled trial. Lancet. 2004 Jan 24;363(9405):271-5.

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Irvin CG, et al. Clinical Trial of Low-Dose **Theophylline and Montelukast** in Patients with Poorly Controlled Asthma. Am J Respir Crit Care Med. 2006 Sep 22. Neither montelukast nor low-dose theophylline lowered the event-rate of poor asthma control in patients with poorly-controlled asthma despite improved lung function. For patients not using ICS, low-dose theophylline improved asthma symptom control more than montelukast or placebo and provides a safe and low-cost alternative asthma treatment.

Jarjour NN, et al. Control of airway inflammation maintained at a lower steroid dose with 100/50 ug of fluticasone propionate/salmeterol. J Allergy Clin Immunol. 2006 Jul;118(1):44-52.Epub 2006 Jun 2.

Jat GC, et al. 400 µg of inhaled **budesonide** vs 200 µg of inhaled **budesonide and oral montelukast** in children with moderate persistent asthma: randomized controlled trial . Ann Allergy Asthma Immunol. 2006 Sep;97(3):397-401. The overall control of asthma with 5 mg of oral montelukast and 200 microg of inhaled budesonide is inferior to that with 400 microg of inhaled budesonide in children with moderate persistent asthma.

Jenkins C, et al. Efficacy and safety of **high-dose budesonide/formoterol (Symbicort)** compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006 May;11(3):276-86.

Johansson SG, Oman H, Nopp A, Pettersson S. The importance of **IgE antibody** levels in anti-IgE treatment. Allergy. 2006 Oct;61(10):1216-9.

Johnston SL, et al. TELICAST Investigators. The effect of **telithromycin** in acute exacerbations of asthma. N Engl J Med. 2006 Apr 13;354(15):1589-600.(InfoPOEMs: Telithromycin may add a small benefit of questionable clinical significance for adult patients with acute asthma. This comes at the price of high drug cost, increased nausea and diarrhea, and a theoretical increased risk of drug resistance in the community. Given this balance of benefits and harms, as well as recent reports of catastrophic liver failure in a small number of patients taking telithromycin, physicians should resist the temptation to prescribe this drug for asthma. (LOE = 1b))

Jonkers RE, et al. Onset of relief of dyspnoea with **budesonide/formoterol or salbutamol** following **methacholine-induced** severe bronchoconstriction in adults with asthma: a double-blind, placebo-controlled study. Respir Res. 2006 Dec 4;7(1):141 [Epub ahead of print] Budesonide/formoterol and salbutamol both provided rapid relief of dyspnoea and reversal of airway obstruction in patients with asthma with experimentally induced bronchoconstriction. The perception of relief, as confirmed by objective lung function assessment, provides further evidence that budesonide/formoterol can be used as reliever medication in asthma.

Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC; CAMP Research Group. Effect of long-term corticosteroid use on **bone mineral** density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics. 2008 Jul;122(1):e53-61. Multiple oral corticosteroid bursts over a period of years can produce a dosage-dependent reduction in bone mineral accretion and increased risk for osteopenia in children with asthma. Inhaled corticosteroid use has the potential for reducing bone mineral accretion in male children progressing through puberty, but this risk is likely to be outweighed by the ability to reduce the amount of oral corticosteroids used in these children.

Kerstjens HA, Bantje TA, Luursema PB, Sinninghe Damste HE, de Jong JW, Lee A, Wijker SP, Cornelissen PJ. Effects of short-acting bronchodilators added to maintenance tiotropium therapy. Chest. 2007 Nov;132(5):1493-9. Epub 2007 Sep 21. In conclusion, both short-acting bronchodilator classes were effective when added to maintenance treatment with tiotropium. The addition of the beta2-adrenergic fenoterol provided greater additional bronchodilatation than the short-acting anticholinergic ipratropium.

Kiljander TO, et al. Effects of **esomeprazole** 40 mg twice daily on asthma: a randomized placebo-controlled trial. Am J Respir Crit Care Med. 2006 May 15;173(10):1091-7. Epub 2005 Dec 15. n=770 16weeks Esomeprazole improved PEF in subjects with asthma who presented with both GERD and NOC. In subjects without both GERD and NOC, no improvement could be detected. (InfoPOEMs: In this study, esomeprazole (Nexium) was no better than placebo in improving peak expiratory flow, asthma symptoms, or quality of life in patients with stable asthma. Furthermore, esomeprazole was no better than placebo in pts with reflux, either. (LOE = 2b-))

Konikoff MR, et al. A randomized, double-blind, placebo-controlled trial of fluticasone for pediatric **eosinophilic esophagitis**. Gastroenterology. 2006 Nov;131(5):1381-91. Epub 2006 Aug 16.

Koopmans JG, Lutter R, Jansen HM, van der Zee JS. Adding salmeterol to an ICS: long term effects on bronchial inflammation in asthma. Thorax. 2006 Apr;61(4):306-12. Epub 2006 Jan 31.

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Lange P, et al. Inhaled corticosteroids and decline of **lung function** in community residents with asthma. Thorax. 2006 Feb;61(2):100-4.

Laude EA, et al. The effect of helium and oxygen on exercise performance in COPD: a randomized crossover trial. Am J Respir Crit Care Med. 2006 Apr 15;173(8):865-70. Epub 2006 Jan 26. (InfoPOEMs: Inhaling a combination of 72% helium and 28% oxygen during exertion increases the comfortable walking distance and reduces the perception of exertional difficulty in patients with stable chronic obstructive pulmonary disease (COPD). (LOE = 2b))

Levalbuterol (Xopenex HFA) Medical Letter Mar 13,2006.

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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Lundback B, Ronmark E, Lindberg A, et al. Control of mild to moderate asthma over 1-year with the **combination** of salmeterol and fluticasone propionate. Respir Med. 2005 Oct 20

Macie C, Wooldrage K, Manfreda J, Anthonisen NR. Inhaled **Corticosteroids** and **Mortality** in COPD. Chest. 2006 Sep;130(3):640-6.

Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community **pulmonary rehabilitation** after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. BMJ. 2004 Nov 20;329(7476):1209. Epub 2004 Oct 25.

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Masoli M, et al. Inhaled fluticasone and **adrenal effects** in adult asthma: systematic review & meta-analysis. Eur Respir J. 2006 May 31; [Epub ahead of print]

Marks GB, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. J Allergy Clin Immunol. 2006 Jul;118(1):53-61. Epub 2006 May 30. House dust mite avoidance measures and dietary fatty acid modification, as implemented in this trial during infancy and early childhood, did not prevent the onset of asthma, eczema, or atopy in high-risk children.

Marra F, et al. Does **antibiotic exposure** during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006 Mar;129(3):610-8. Exposure to at least one course of antibiotics in the first year of life appears to be a risk factor for the development of childhood asthma.

Matsuyama W, Mitsuyama H, Watanabe M, et al. Effects of **omega-3 polyunsaturated fatty acids** on inflammatory markers in COPD. Chest. 2005 Dec;128(6):3817-27. (InfoPOEMs: This small study found that a diet rich in omega-3 fatty acids causes small improvements in chronic obstructive pulmonary disease (COPD) symptoms. (LOE = 1b))

McCarney RW, et al. An overview of two Cochrane reviews of complementary treatments for chronic asthma: **acupuncture** & **homeopathy**. Respir Med. 2004 Aug;98(8):687-96.

Medical Letter. **Arformoterol (Brovana)** for COPD). Jyly 2, 2007.

Medical Letter. Treatment Guidelines: Drugs for **Chronic Obstructive Pulmonary Disease**. Nov 2007.

Mometasone (Asmanex twisthaler) For Asthma. Med Letter Dec 2005;47:98-99. FDA: age ≥12 220-440ug bid or 440ug od (Fardon TC, Lee DK, Haggart K, et al. Adrenal suppression with dry powder formulations of fluticasone propionate & mometasone furoate. Am J Respir Crit Care Med. 2004 Nov 1;170(9):960-6. Epub 2004 Jun 7; Corren J, Berkowitz R, Murray JJ, Prenner B. Comparison of once-daily mometasone furoate versus once-daily budesonide in patients with moderate persistent asthma. Int J Clin Pract. 2003 Sep;57(7):567-72; Mortimer KJ, Harrison TW, Tattersfield AE. Effects of inhaled corticosteroids on bone. Ann Allergy Asthma Immunol. 2005 Jan;94(1):15-21; quiz 22-3, 79.)

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Mortimer KJ, et al. Oral and inhaled corticosteroids and **adrenal insufficiency**: a case-control study. Thorax. 2006 May;61(5):405-8. Epub 2006 Mar 3.

Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined **corticosteroid and long-acting** beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006829. Combination therapy was more effective than long-acting beta-agonists in reducing COPD exacerbation rates, although the evidence for the effects on hospitalisations was mixed, and requires further exploration. No significant impact on mortality was found even with additional information from the TORCH trial. The superiority of combination inhalers should be viewed against the increased risk of side-effects, particularly pneumonia.

Ni CM, Greenstone IR, Ducharme FM. Addition of inhaled **long-acting beta2-agonists to inhaled steroids** as first line therapy for persistent asthma in steroid-naive adults. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD005307.

Ni CM, Greenstone I, Danish A, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD005535.

Niewoehner DE, et al. Prevention of exacerbations of COPD with **tiotropium**, a once-daily inhaled anticholinergic bronchodilator -an RCT. Ann Intern Med. 2005 Sep 6;143(5):317-26. (InfoPOEMs: Daily treatment with tiotropium for 6 months slightly decreases the number of patients experiencing a chronic obstructive pulmonary disease (COPD) exacerbation, though it doesn't decrease the number of patients who will be hospitalized for an exacerbation. (LOE = 1b-))

O'byrne PM, et al. Budesonide/Formoterol combination therapy as both **maintenance and reliever** medication in asthma (**STAY** trial). Am J Respir Crit Care Med. 2005 Jan 15;171(2):129-36.

O'Byrne PM, et al. Low dose inhaled budesonide & formoterol in mild persistent asthma: the **OPTIMA** randomized trial. Am J Respir Crit Care Med. 2001 Oct 15;164(8 Pt 1):1392-7.

O'byrne PM, et al. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. Chest. 2006 Jun;129(6):1478-85. Long-term, once-daily treatment with low-dose budesonide improved both prebronchodilator and postbronchodilator FEV(1) in patients with recent-onset, persistent asthma, and reduced the loss of lung function over time (1 & 3yrs).

O'donnell DE, et al. Effect of **Fluticasone Propionate/Salmeterol** on Lung Hyperinflation and Exercise Endurance in COPD. Chest. 2006 Sep;130(3):647-56.

Ostrom NK, Decotiis BA, et al. Comparative efficacy & safety of low-dose **fluticasone** propionate & **montelukast** in children with persistent asthma. J Pediatr.2005Aug;147(2):213-20.

Overbeek SE, et al. **Formoterol added** to low-dose budesonide has no additional antiinflammatory effect in asthmatic patients. Chest. 2005 Sep;128(3):1121-7. CONCLUSIONS: Our results demonstrate that BUD administered at a low dose has significant antiinflammatory effects in patients with mild asthma. No significant additional antiinflammatory effects could be demonstrated either by adding formoterol or by increasing the dose of BUD.

Papi A, et al. **Beclomethasone/formoterol vs budesonide/formoterol** combination therapy in asthma. Eur Respir J. 2006 Nov 15; [Epub ahead of print] The new fixed combination of beclomethasone and formoterol 200/12ug in HFA Modulite((R)) pMDI is equivalent to the marketed combination of budesonide and formoterol 400/12ug in terms of efficacy and tolerability profile.

Papi A, Canonica GW, Maestrelli P, et al. BEST Study Group. Rescue use of **beclomethasone and albuterol in a single inhaler** for mild asthma. N Engl J Med. 2007 May 17;356(20):2040-52. In patients with mild asthma, the symptom-driven use of inhaled beclomethasone (250 microg) and albuterol (100 microg) in a single inhaler is as effective as regular use of inhaled beclomethasone (250 microg twice daily) and is associated with a lower 6-month cumulative dose of the inhaled corticosteroid.

Paton J, et al. **Adrenal** responses to low dose synthetic ACTH (Synacthen) in kids receiving high dose inhaled fluticasone. Arch Dis Child. 2006Oct;91(10):808-13. Epub 2006Mar 23.

Pauwels RA, et al. **START** Investigators Group. Early intervention with **budesonide** in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003Mar 29;361(9363):1071-6.

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Pauwels RA, et al; **RELIEF** Study investigators. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J. 2003 Nov;22(5):787-94.

Pavord ID, Cox G, Thomson NC, et al Safety and Efficacy of **Bronchial Thermoplasty** in Symptomatic, Severe Asthma. Am J Respir Crit Care Med. 2007 Sep 27; [Epub ahead of print] Bronchial

thermoplasty is associated with a short-term increase in asthma-related morbidity. However, there is preliminary evidence of long-lasting improvement in asthma control.
Pearlman DS, et al. Once-daily **ciclesonide** improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. J Allergy Clin Immunol. 2005 Dec;116(6):1206-12.
Pedersen S, et al. A comparative study of inhaled **ciclesonide** 160 microg/day and fluticasone 176 microg/day in children with asthma. Pediatr Pulmonol. 2006 Oct;41(10):954-61.
Pinnock H, Shah R. **Asthma**. BMJ. 2007 Apr 21;334(7598):847-50.
Poels PJ, et al. **Spirometry** in chronic obstructive pulmonary disease. BMJ. 2006 Oct 28;333(7574):870-1.
Qaseem A, Snow V, Shekelle P, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2007 Nov 6;147(9):633-8.
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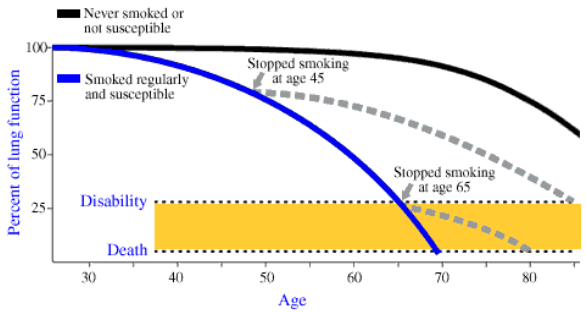

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Web sites:

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

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. [36]
12. Other references of interest: [37,38,39,40,41,42,43,44,45,46,47]; Tools to assess dependence. E.g. Fagerstrom Tolerance Scale [48]

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

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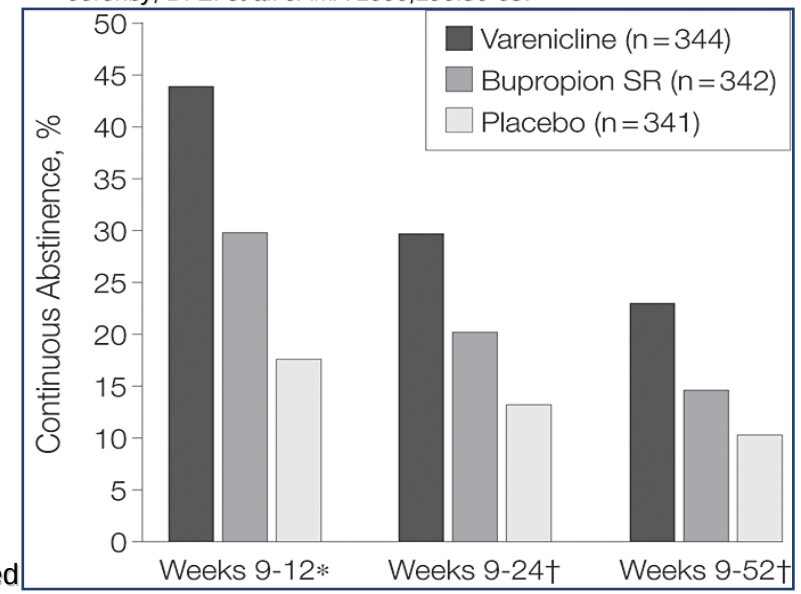

Summary: Compared to ZYBAN, 12 weeks of varenicline (Champix) offers:

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

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TOBACCO / SMOKING CESSATION PHARMACOTHERAPY Extra articles:

Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A,Robinson G, Beasley R. THE EFFECTS OF **CANNABIS** ON PULMONARY STRUCTURE, FUNCTION AND SYMPTOMS. Thorax. 2007 Jul 31; [Epub ahead of print] Smoking cannabis was associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. In contrast, cannabis smoking was seldom associated with macroscopic emphysema. The 1:**2.5 to 5 dose equivalence between cannabis joints and tobacco cigarettes** for adverse effects on lung function is of major public health significance.

Aubin HJ, Bobak A, Britton JR, et a. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial. Thorax. 2008 Feb 8; [Epub ahead of print] The Week 52 CAR (NRT,Weeks 8-52; varenicline,Weeks 9-52) was 26.1% for varenicline and 20.3% for NRT (OR 1.40, 95% CI, 0.99 to 1.99, p=0.056). Varenicline significantly reduced craving (p<0.001), withdrawal symptoms (p<0.001) and smoking satisfaction (p<0.001) versus NRT. The outcomes of this registered clinical trial (NCT00143325) established that abstinence from smoking was greater, and craving, withdrawal symptoms and smoking satisfaction less, at the end of treatment with varenicline than with transdermal nicotine.

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Aveyard P, Johnson C, Fillingham S, Parsons A, Murphy M. **Nortriptyline** plus nicotine replacement versus placebo plus **nicotine** replacement for smoking cessation: pragmatic randomised controlled trial. BMJ. 2008 Apr 27; [Epub ahead of print] Nortriptyline and nicotine replacement therapy are both effective for smoking cessation but the effect of the combination is less than either alone and evidence is lacking that combination treatment is more effective than either alone.

Bartecchi C, et al. Reduction in the incidence of acute myocardial infarction associated with a **citywide smoking ordinance**. Circulation. 2006 Oct 3;114(14):1490-6. Epub 2006 Sep 25. (InfoPOEMs: This observational study found that a citywide smoking ban was associated with a reduction in the incidence of acute myocardial infarction (AMI) by approximately 70 per 100,000 person-years (that is, approximately 1 fewer AMI for every 1400 persons per year). Share this information with local politicians and other community leaders who are resisting curbs on smoking. Another study by the Centers for Disease Control and Prevention found that a smoking ban in El Paso, Texas, had no negative economic consequences for bars and restaurants.* *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5307a2.htm (LOE = 4))

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Cahill K, Stead LF, Lancaster T. **Nicotine receptor partial agonists** for smoking cessation. **Cochrane** Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub2. Varenicline increased the odds of successful long-term smoking cessation approximately threefold compared with pharmacologically unassisted quit attempts.In trials reported so far, more participants quit successfully with varenicline than with bupropion. The effectiveness of varenicline as an aid to relapse prevention has not been clearly established. The main adverse effect of varenciline is nausea, but this is mostly at mild to moderate levels and tends to reduce with habituation.There is a need for independent trials of varenicline versus placebo, to test the early findings. There is also a need for direct comparisons with nicotine replacement therapy, and for further trials with bupropion, to establish the relative efficacy of the treatments.Cytisine may also increase the chances of quitting, but the evidence at present is inconclusive.

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Harvard Study Confirms **Rise in Nicotine Delivery of Cigarettes** A reanalysis of data released last summer confirms that the nicotine yield from cigarettes increased about 11% from 1998 to 2005. A Harvard School of Public Health review of the data, which are annually reported to the Massachusetts Department of Public Health by cigarette manufacturers, was released online. It found the nicotine increase across brands from the four major manufacturers and in all categories of cigarettes, such as menthol and ultralight. The report said the nicotine boost was accomplished both by increasing the amount of nicotine in the cigarettes and by redesigning them to burn more slowly, so users take more puffs per cigarette. http://www.hsph.harvard.edu/nicotine/trends.pdf

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Health Canada July/07 Unauthorized Smoking Cessation Product **Resolve** May Pose Health Risk - Consumer Information. The product contains an unacceptable amount of an ingredient labelled as "CESTEMENOL-350." Consuming excessive amounts of this ingredient might result in damage to the kidney, liver or red blood cells.

Health Canada June/08 Pfizer Canada in collaboration with Health Canada would like to notify healthcare professionals of important safety information regarding **CHAMPIX**, and post-marketing reports of serious **neuropsychiatric adverse events**, including depressed mood, agitation, hostility, changes in behaviour, suicidal ideation and suicide, as well as worsening of pre-existing psychiatric illness (previously diagnosed or not). Since introduction of CHAMPIX in Canada, in April 2007 through April 30, 2008, a total of **226 Canadian cases** of neuropsychiatric adverse events have been reported. For the same time period, there have been **708 534 prescriptions filled** for CHAMPIX in Canada1. All patients attempting to quit smoking with CHAMPIX, their families & caregivers should be alerted about the need to monitor for symptoms of neuropsychiatric adverse events. Patients should be instructed to stop taking CHAMPIX and contact their healthcare provider immediately if they have or if their families or caregivers observe depressed mood, agitation, hostility or changes in behavior, that are not typical for the patient, or if the patient has suicidal ideation or suicidal behavior. Patients with concomitant psychiatric conditions, even if well controlled, or with a history of psychiatric symptoms, should be diligently monitored.

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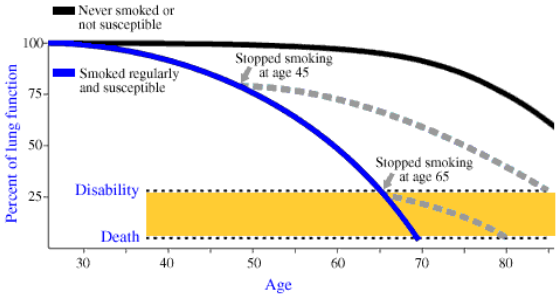

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References Cannabinoids:

Prepared by: Brent Jensen BSP, Loren Regier BSP BA for www.RxFiles.ca

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10. Marijuana Medical Access Division, Drug Strategy & Controlled Substances Program, AL: 3503B, Ottawa, On K1A 1B9 **1-866-337-7705**) or the **website** www.hc-sc.gc.ca/dhp-mps/marihuana/index_e.html -Forms **B1** & **B2** & **Daily** Amount Fact Sheet Info for Health care professionals: www.hc-sc.gc.ca/dhp-mps/marihuana/how-comment/medpract/infoprof/information_e.html
Marijuana Stakeholder statistics from Health Canada: http://www.hc-sc.gc.ca/dhp-mps/marihuana/stat/index-eng.php
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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 *
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 Information about **Pregnancy Exposure Registries** http://www.fda.gov/womens/registries/default.htm

1. Drugs in Pregnancy and Lactation, 8th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Baltimore, MD: 2008.
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{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)
✗ =non-formulary in Saskatchewan
$ Retail *Cost to Consumer* based on acquisition cost, markup & dispensing fee in Saskatchewan. Lowest generic price used where available

✆ =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**

BP =blood pressure **Bz** =benzodiazepine **CI** =contraindication **CV** =cardiovascular
HR =Heart rate **HSR** =Hypersensitivity reaction **LFT** =Liver Function tests
ς =indicates strength of tablet is scored ☺ = tastes good

DI =drug interaction **Dx** =diagnosis **g** =generic avail. **GI** =Gastrointestinal **HA** =headache **HF** =heart failure
M =Monitoring Ⓟ =a concern if given **Pre-Op** **SE** =side effect **Sx** =syndrome/symptom **Sz** =seizure **Tx** =treatment
= CDN (We are **Canadian**) ⊗ =Avoid → soybean & peanut allergy

=↓ 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)= most accurate, but need PDA with MedCalc to do the calculation.

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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