RxFiles - Drug Comparison Charts - 6th Edition

Objective, Comparative Drug Information
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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

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3. Individual Drug Product Monographs. 4. Micromedex 2006

{NOTE: for additional Canadian information on drugs in pregnancy & lactation see **http://www.motherisk.org/index.jsp** }

Common RxFiles ABREVIATIONS & 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
ς =indicates strength of tablet is scored ☺ = tastes good

DI =drug interaction **g**=generic avail. **M** =Monitoring Ⓟ =a concern if given **Pre-Op** **SE** =side effects **Sz** =seizure
= CDN (We are **Canadian**) ⊗ =Avoid → soybean & peanut allergy **LFT**=Liver Function tests

=↓ 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)

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RxFiles Academic Detailing Program

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

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BETA-BLOCKER (BB): Comparison Chart

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Perioperative Beta-Blockers. Pharmacist's Letter Aug,2006.

Peter K. Lindenauer, M.D., Penelope Pekow, Ph.D., Kaijun Wang et al. **Perioperative Beta-Blocker** Therapy and Mortality after Major Noncardiac Surgery. NEJM 2005; 353:349-361. *Conclusions:* Perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk, patients undergoing major noncardiac surgery. Patient safety may be enhanced by increasing the use of beta-blockers in high-risk patients (InfoPOEMs: Patients undergoing major surgery who are at high risk of complications -- those with heart disease, cerebrovascular disease, diabetes, or renal insufficiency -- benefit from perioperative beta-blockade. Low-risk patients (except perhaps those with hypertension and those undergoing high-risk surgery) do not. However, given the possible harms of suddenly discontinuing beta-blockers, those who are already taking them should continue doing so, even if they are at low-risk. (LOE = 2b))

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CALCIUM CHANNEL BLOCKER (CCB): Comparison Chart

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

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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))

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Thiazide Like Diuretics and Miscellaneous Antihypertensives

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Antihypertensives: Landmark & Recent Trials – Summary

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ORAL ANTIPLATELET & ANTITHROMBOTIC AGENTS

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136. Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction: The **OASIS-6** Randomized Trial. JAMA. 2006 Mar 14; [Epub ahead of print] CONCLUSION: In patients with STEMI, particularly those not undergoing primary percutaneous coronary intervention, **fondaparinux** significantly reduces mortality & reinfarction without increasing bleeding and strokes. (InfoPOEMs: Fondaparinux (Arixtra) reduces the risk of mortality and reinfarction without increasing the risk of severe bleeding events in patients with acute ST-segment elevation myocardial infarction. Patients undergoing primary percutaneous coronary intervention (PCI) received no additional benefit from fondaparinux compared with unfractionated heparin (UFH). (LOE = 1b-)) Mehta SR, et al.; ASPIRE Investigators. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation (ASPIRE) Pilot Trial. Circulation. 2005 Mar 22;111(11):1390-7.
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141 **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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myocardial infarction, treatment with enoxaparin throughout the index hospitalization is superior to treatment with unfractionated heparin for 48 hours but is associated with an increase in major bleeding episodes. (InfoPOEMs: For every 1000 patients treated with enoxaparin instead of unfractionated heparin there were 15 fewer nonfatal myocardial infarctions (MIs), 7 fewer urgent revascularizations, and 6 fewer deaths, but there were 4 additional episodes of nonfatal major bleeding. (LOE = 1b))
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warfarin to achieved INRs of 2 to 3 reduces stroke, disabling or fatal stroke, and death for patients with non-valvular AF. The benefits were not substantially offset by increased bleeding among these participants in randomized clinical trials. Limitations include relatively short follow up and imprecise estimates of bleeding risks from the selected participants enrolled in the trials. For primary prevention of stroke in AF patients, about 25 strokes and about 12 disabling or fatal strokes would be prevented yearly for every 1000 atrial fibrillation patients given OACs.

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

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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.

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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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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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Useful websites:
UK multicentre obesity management project www.counterweight.org
Lifestyle changes week by week plan for patients taking sibutramine www.changeforlifeonline.com
Rimonabant support site www.itswhatyougain.co.uk
Cochrane reviews www.cochrane.org
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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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1. [9] CADTH. Scientific Report: Evidence for PPIs use in Gastroesophageal Reflux Disease, Dyspepsia and Peptic Ulcer Disease (Draft-Dec 2006) www.cadth.ca { Extensive systematic review completed. Final Report of Expert Review Panel on PPIs in Process}

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[21] Leontiadis GI, Sharma VK, et al. Systematic review & meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. BMJ. 2005 Jan 31; [Epub ahead of print] (InfoPOEMs: Neither oral nor intravenous use of proton pump inhibitors decreases the risk of dying as the result of peptic ulcer bleeding. The likelihood of rebleeding or the need for surgery is reduced, with 1 episode of rebleeding avoided in every 10 pts treated & 1 surgery avoided for every 25 patients who received treatment. (LOE = 1a))

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

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Canani RB, et al. Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute **gastroenteritis and community-acquired pneumonia** in children. Pediatrics. 2006 May;117(5):e817-20. (InfoPOEMs: In this weak study, treatment of gastroesophageal reflux disease (GERD) with gastric acid suppressants increased the likelihood of pneumonia compared with the rate in healthy children. It's not known whether the treatment, the presence of GERD, or some other factor caused the pneumonia. Watch for confirmation in randomized research. (LOE = 4))

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

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Chan FK, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med. 2001 Mar 29;344(13):967-73. CONCLUSIONS: Among patients with H. pylori infection and a history of upper gastrointestinal bleeding who are taking low-dose aspirin, the eradication of H. pylori is equivalent to treatment with omeprazole in preventing recurrent bleeding. Omeprazole is superior to the eradication of H. pylori in preventing recurrent bleeding in patients who are taking other NSAIDs.

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

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

Cremonini F, Wise J, Moayyedi P, Talley N. Diagnostic and therapeutic use of proton pump inhibitors in non-cardiac chest pain. Am J Gastroenterol 205; 100:1226-32. (InfoPOEMs: The use of a proton pump inhibitor (PPI) is useful in the diagnosis of gastroesophageal reflux disease (GERD) and an effective treatment for patients with noncardiac chest pain. Because some smaller studies with negative results may not have been published, the estimate of the degree of benefit of PPIs in this study may be on the high side. (LOE = 1a))

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

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

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

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.

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.

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.

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.

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))

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

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.

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

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.

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-))

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))

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.

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.

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

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.

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.

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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.

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.

Wilkerson PM, et al. A poor response to proton pump inhibition is not a contraindication for laparoscopic **antireflux surgery** for gastro esophageal reflux disease. Surg Endosc. 2005 Sep;19(9):1272-7. Epub 2005 Jul 14.

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for relief of heartburn episodes. On-demand proton pump inhibitor therapy may work in a proportion of non-erosive gastro-oesophageal reflux disease patients excluded. The benefit did not persist through the next 5 months when patients could use medications as needed rather than in a scheduled manner. Ranitidine was more cost-effective than omeprazole. It still makes sense to try ranitidine first for these patients, then stepping up to omeprazole if their symptoms are not improved adequately, particularly since this is a benign, self-limited condition. (LOE = 1b))

The Rx Files - H. pylori Eradication
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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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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.
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Primaquine 26.3mg tab (= 15mg base) ✗▼ C

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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Hydroxychloroquine PLAQUENIL,g 200mg tab

{Not used very often!}

Second-line: chloroquine sensitive malaria C
- Only in chloroquine-sensitive P. *falciparum* malaria prevention

{Monitor: opthamological & neurological exam every 3 to 6 months if used >6months}.

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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URINARY TRACT INFECTIONS (UTI), ADULT – TREATMENT OPTIONS

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Saint S, et al. Condom versus indwelling urinary catheters: a randomized trial. J Am Geriatr Soc. 2006 Jul;54(7):1055-61. (InfoPOEMs: After adjusting for other factors, using condom catheters in men older than 40 is associated with fewer complications (bacteriuria, symptomatic urinary tract infection, death) than using indwelling catheters. Since more than 40% of men in each group had complications, I wonder if any kind of catheter is really necessary in most patients. (LOE = 2b))

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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)-

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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-)

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)

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NSAIDS, COXIBs & OTHER ANALGESICS: Comparison Chart

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[18] Bresalier RS, et al. Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial (**APPROVe**). *N Engl J Med 2005; 352:1092-102.* (InfoPOEMs: For every 62 patients who take rofecoxib instead of placebo for 3 years, 1 additional patient will experience a serious cardiovascular event. Remember, there is no greater symptomatic relief with COX-2 inhibitors than with older drugs; acetaminophen is a very safe alternative. The decrease in risk of serious gastrointestinal complications is marginal with COX-2 inhibitors and the cost is high. (LOE = 1b))

[19] Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention. (**APC** trial) N Engl J Med 2005; 352:1071-80. (InfoPOEMs: One additional cardiovascular event or cardiovascular death occurs for every 126 patients treated for 1 year with celecoxib. There appears to be a dose response relationship. It is difficult to justify continued use of this and other coxibs, except in the most exceptional circumstances. (LOE = 1b)) (Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. (APC study) N Engl J Med 2006; 355:873-884. Follow-up colonoscopies were completed at year 1 in 89.5 percent of randomized patients, and at year 3 in 75.7 percent. The estimated cumulative incidence of the detection of one or more adenomas by year 3 was 60.7 percent for patients receiving placebo, as compared with 43.2 percent for those receiving 200 mg of celecoxib twice a day (risk ratio, 0.67; 95 percent confidence interval, 0.59 to 0.77; P<0.001) and 37.5 percent for those receiving 400 mg of celecoxib twice a day (risk ratio, 0.55; 95 percent confidence interval, 0.48 to 0.64; P<0.001). Serious adverse events occurred in 18.8 percent of patients in the placebo group, as compared with 20.4 percent of those in the low-dose celecoxib group (risk ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3; P=0.5) and 23.0 percent of those in the high-dose group (risk ratio, 1.2; 95 percent confidence interval, 1.0 to 1.5; P=0.06). As compared with placebo, celecoxib was associated with an increased risk of cardiovascular events (risk ratio for the low dose, 2.6; 95 percent confidence interval, 1.1 to 6.1; and risk ratio for the high dose, 3.4; 95 percent confidence interval, 1.5 to 7.9).) (Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. (PreSAP trial) N Engl J Med 2006; 355:885-895. Colonoscopies were performed at year 1 on 88.7 percent of the subjects who had undergone randomization and at year 3 on 79.2 percent. Of the 557 subjects in the placebo group and the 840 subjects in the celecoxib 400mg od group who were included in the efficacy analysis, 264 and 270, respectively, were found to have at least one adenoma at year 1, at year 3, or both. The cumulative rate of adenomas detected through year 3 was 33.6 percent in the celecoxib group and 49.3 percent in the placebo group (relative risk, 0.64; 95 percent confidence interval, 0.56 to 0.75; P<0.001). The cumulative rate of advanced adenomas detected through year 3 was 5.3 percent in the celecoxib group and 10.4 percent in the placebo group (relative risk, 0.49; 95 percent confidence interval, 0.33 to 0.73; P<0.001). Adjudicated serious cardiovascular events occurred in 2.5 percent of subjects in the celecoxib group and 1.9 percent of those in the placebo group (relative risk, 1.30; 95 percent confidence interval, 0.65 to 2.62).

[20] Farkouh ME, Kirshner H., Harrington RA. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (**TARGET**), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364:675-84. At 1-year follow-up, incidence of the primary endpoint was low, both with lumiracoxib (59 events [0.65%]) and the non-steroidal anti-inflammatory drugs (50 events [0.55%]; hazard ratio 1.14 [95% CI 0.78-1.66], p=0.5074). Incidence of myocardial infarction (clinical and silent) in the overall population in the individual substudies was 0.38% with lumiracoxib (18 events) versus 0.21% with naproxen (ten) and 0.11% with lumiracoxib (five) versus 0.16% with ibuprofen (seven).

[21] Schnitzer TJ., Burmester GR., Mysler E., Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (**TARGET**), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665-74. (18325 patients age 50 years or older with osteoarthritis were randomised to lumiracoxib 400 mg once daily (n=9156), naproxen 500 mg twice daily (4754), or ibuprofen 800 mg three times daily (4415) in two substudies of identical design. Randomisation was stratified for low-dose aspirin use and age. In patients not taking aspirin, the cumulative 1-year incidence of ulcer complications was 1.09% (95% CI 0.82-1.36) with non-steroidal anti-inflammatory drugs (64 events) versus 0.25% (95% CI 0.12-0.39) with lumiracoxib (14 events; hazard ratio 0.21 [95% CI 0.12-0.37], p<0.0001). Reductions in ulcer complications were also significant in the overall population (0.34 [0.22-0.52], p<0.0001) but not in those taking aspirin (0.79 [0.40-1.55], p=0.4876). In the overall population, 0.55% (50/9127) of those on non-steroidal anti-inflammatory drugs and 0.65% (59/9117) of those on lumiracoxib reached the cardiovascular endpoint (1.14 [0.78-1.66], p=0.5074).) (see also Pharmacists Letter Dec/06)

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[23] **Treatment Guidelines**: Drugs for Rheumatoid Arthritis. **The Medical Letter**: January, **2003**; (5) pp. 25-32 & **Dec 2005**.

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[25] Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ. 2004 Aug 7;329(7461):324. (Towheed TE. **Pennsaid** therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2006 Mar;33(3):567-73.)

[26] Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. CMAJ. 2004 Aug 17;171(4):333-8.

[27] Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. Arch Intern Med. 2004 Oct 11;164(18):2017-23.

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29. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet. 2005 Mar 12;365(9463):965-73.

30. Savage R. Cyclo-oxygenase-2 inhibitors : when should they be used in the elderly? Drugs Aging. 2005;22(3):185-200.

31. Hippisley-Cox J, Coupland C. Risk of MI in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ.2005 Jun 11;330(7504):1366.

32. Hudson M, et al. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. BMJ. 2005 Jun 11;330(7504):1370.

33. Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ. 2005 Apr 12;172(8):1039-43. (InfoPOEMs: The evidence that intra-articular hyaluronic acid helps patients with knee osteoarthritis is of poor quality. Improvements in pain at rest and pain during exercise is seen in a minority of studies, and those studies were of lower quality than those showing no benefit. There is no evidence of functional improvement. Injections like this have a potentially powerful placebo effect, so any benefit seen in unblinded studies without concealed allocation is likely represent the placebo effect rather than any effect of the drug. (LOE = 1a-)) Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol. 2006 May;33(5):951-6.

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Long-term use of NSAIDs is associated with a reduced incidence of oral cancer (including in active smokers), but also with an increased risk of death due to cardiovascular disease. These findings highlight the need for a careful risk-benefit analysis when the long-term use of NSAIDs. (Jan/06 The Norwegian daily newspaper Dagbladet reports that a number of **statistical improbabilities** were found in the data set of the cancer trial, published in the Lancet in October last year. Lancet editor Dr Richard Horton told the BBC he would be speaking to the coauthors of the study to seek their permission to retract the paper. One example of the improbabilities" is the fact that of the 908 people in the trial, 250 shared the same birthday.)

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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))

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

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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.

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Liccardi G, et al. Safety of celecoxib in patients with adverse **skin reactions** to acetaminophen (paracetamol) and other non-steroidal anti-inflammatory drugs. J Investig Allergol Clin Immunol. 2005;15(4):249-53.

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-))

Messier SP, et al. **Exercise and dietary** weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum. 2004 May;50(5):1501-10.

Ofori B, et al. Risk of **congenital anomalies** in pregnant users of non-steroidal anti-inflammatory drugs: a nested case-control study. Birth Defects Res B Dev Reprod Toxicol. 2006 Aug 23; [Epub ahead of print] Our study suggests that women prescribed NSAIDs during early pregnancy may be at a greater risk of having children with congenital anomalies, specifically cardiac septal defects.

Pharmacist's Letter Oct 2006. Alternative or **Off-label** Routes of Drug Administration. (Oral administration of: N-acetylcysteine Mucomyst)

Pharmacist's Letter Oct 2006. **Cardiovascular Risks** of NSAIDs and Cox-2 Inhibitors.

Psaty BM and Potter JD. Risks and benefits of celecoxib to prevent recurrent **adenomas**. N Engl J Med 2006; 355:950-952.

Psaty BM, Weiss NS. NSAID trials and the **choice of comparators**--questions of public health importance. N Engl J Med. 2007 Jan 25;356(4):328-30.

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 .

Scharf HP, et al. **Acupuncture** and knee osteoarthritis: a three-armed randomized trial. Ann Intern Med. 2006 Jul 4;145(1):12-20. Compared with physiotherapy and as-needed anti-inflammatory drugs, addition of either TCA or sham acupuncture led to greater improvement in WOMAC score at 26 weeks.

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.

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.

Solomon SD, et al.; APC and **PreSAP** Trial Investigators. Effect of **celecoxib** on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation. 2006 Sep 5;114(10):1028-35.

Sperber SJ, et al. Effects of **naproxen on experimental rhinovirus** colds. A randomized, double-blind, controlled trial. Ann Intern Med. 1992 Jul 1;117(1):37-41.

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

Towheed TE, et al. Acetaminophen for osteoarthritis (review). *The Cochrane Database of Systematic Reviews* 2006, Issue 1.

Treatment Guidelines from the Medical Letter. Pharmaceutical Drug Overdose. Sept 2006. (**Acetaminophen**: N-acetylcysteine treatment. **Aspirin**: sodium bicarbonate treatment)

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.

Witt CM, et al. **Acupuncture** in patients with osteoarthritis of the knee or hip: A randomized, controlled trial with an additional nonrandomized arm. Arthritis Rheum. 2006 Oct 30;54(11):3485-3493. These results indicate that acupuncture plus routine care is associated with marked clinical improvement in patients with chronic OA-associated pain of the knee or hip.

Yelland MJ, Nikles CJ, McNairn N, Del Mar CB, Schluter PJ, Brown RM. Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials. Rheumatology (Oxford). 2007 Jan;46(1):135-40. {InfoPOEMs – Feb07: In this short-term study emphasizing individual response, acetaminophen and celecoxib (Celebrex) are virtually indistinguishable in improving pain, stiffness, and function in patients with clinically diagnosed degenerative joint disease (DJD). Since acetaminophen is less expensive and has fewer safety concerns, it should be the drug of first choice. (LOE = 1b).}

Zapata-Colindres JC,et al. The association of Helicobacter pylori infection and nonsteroidal anti-inflammatory drugs in peptic ulcer disease. Can J Gastroenterol. 2006 Apr;20(4):277-80. The development of PUD was observed earlier in the combined H pylori and NSAID group than in patients with only NSAID use. This suggests a synergic effect between the two risks factors in the development of PUD.

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.

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.

[2] Micromedex 2006

[3] Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2005.

[4] Drugs in Pregnancy & Lactation 7th edition, 2005.

[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).

Additional references:

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

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

Ehret GB, et al. Drug-Induced Long QT Syndrome in Injection Drug Users Receiving **Methadone**: High Frequency in Hospitalized Patients and Risk Factors. Arch Intern Med. 2006 Jun 26;166(12):1280-7.

Fiellin DA, et al. Counseling plus **buprenorphine-naloxone maintenance** therapy for opioid dependence. N Engl J Med. 2006 Jul 27;355(4):365-74. (InfoPOEMs: More intensive counseling and more frequent medication dispensing does not improve outcomes for treatment of opioid dependence in the primary care setting. (LOE = 1b))

Foral PA, Malesker MA, Huerta G, Hilleman DE. **Nebulized opioids** use in COPD. Chest. 2004 Feb;125(2):691-4.

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Gana TJ, et al. The 023 Study Group. Extended-release **tramadol** in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. Curr Med Res Opin. 2006 Jul;22(7):1391-401.

Gowing L, et al. Opioid antagonists under heavy sedation or anaesthesia for **opioid withdrawal**. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD002022. Heavy sedation compared to light sedation does not confer additional benefits in terms of less severe withdrawal or increased rates of commencement on naltrexone maintenance treatment. Given that the adverse events are potentially life-threatening, the value of antagonist-induced withdrawal under heavy sedation or anaesthesia is not supported. The high cost of anaesthesia-based approaches, both in monetary terms and use of scarce intensive care resources, suggest that this form of treatment should not be pursued.

Green R, Bulloch B, Kabani A, Hancock BJ, Tenenbein M. Early analgesia for children with acute abdominal pain. Pediatrics. 2005 Oct;116(4):978-83. (InfoPOEMs: The immediate administration of morphine in children aged 5 years to 16 years with acute abdominal pain does not obscure the diagnosis of appendicitis and does not affect the surgeon's confidence in his or her diagnosis. It also causes a small decrease in pain. As with adults, pain relief should not be withheld in children until the cause of the pain is determined. (LOE = 2b))

Kokki H, Lintula H, Vanamo K, et al. Oxycodone vs placebo in children with undifferentiated abdominal pain: a randomized, double-blind clinical trial of the effect of analgesia on diagnostic accuracy. Arch Pediatr Adolesc Med 2005;159:320-25. (InfoPOEMs: Giving analgesics to children with abdominal pain does not obscure the surgical diagnosis. We don't need to make kids suffer while waiting for a surgeon to evaluate their abdominal pain. (LOE = 2b))

Lynch M. A review of the use of methadone for the treatment of noncancer pain. Pain Res Manage 2005;10(3):133-44.

Marsch LA, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. Arch Gen Psychiatry. 2005 Oct;62(10):1157-64.

Methadone: a focus on safety. Pharmacist's Letter Sept 2006. (FDA Nov/06 warning http://www.fda.gov/cder/drug/InfoSheets/HCP/methadoneHCP.htm)

Mora B, et al. **Transcutaneous electrical nerve stimulation**: an effective treatment for pain caused by renal colic in emergency care. J Urol. 2006 May;175(5):1737-41; discussion 1741. (InfoPOEMs: Local transcutaneous electrical nerve stimulation (TENS) is a rapid and effective nondrug treatment for pain caused by renal colic. TENS may be most useful in the difficult circumstance of out-of-hospital rescue. (LOE = 1b))

Pharmacist's Letter Oct 2006. Alternative or **Off-label** Routes of Drug Administration. (Rectal administration of: Ms Contin, OxyContin; Sublingual administration of: methadone, fentanyl & buprenorphine; Inhalational use of morphine, hydromorphone & fentanyl)

Ranji SR, Goldman LE, Simel DL, Shojania KG. Do opiates affect the clinical **evaluation** of patients with **acute abdominal pain**? JAMA. 2006 Oct 11;296(14):1764-74. (InfoPOEMs: Opiate analgesia for adults and children presenting with acute abdominal pain may alter the physical examination, but does not increase the risk of management errors. Since most patients prefer pain control, it makes sense to abandon the outdated and incorrect practice of withholding opiate analgesia from patients with acute abdominal pain. (LOE = 1a))

Reid CM, et al. **Oxycodone** for cancer-related pain: meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Apr 24;166(8):837-43.

Safdar B, et al. Intravenous **morphine plus ketorolac** is superior to either drug alone for treatment of acute renal colic. Ann Emerg Med. 2006 Aug;48(2):173-81, 181.e1. (InfoPOEMs: Intravenous morphine 5 mg combined with ketorolac (Toradol) 15 mg provided greater pain relief than either drug alone. The combination did not increase the likelihood of nausea or vomiting. (LOE = 1b))

Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim **methadone** maintenance. Arch Gen Psychiatry. 2006 Jan;63(1):102-9.

See also RxFiles Newsletter – Fall, 2005 - Opioids in Chronic Non-Malignant Pain Troubleshooting Drug Therapy Issues www.RxFiles.ca

Shirk MB, Donahue KR, Shirvani J. Unlabeled uses of **nebulized** medications. Am J Health Syst Pharm. 2006 Sep 15;63(18):1704-16.

Sinha M, et al. Evaluation of **nonpharmacologic** methods of pain and anxiety management for laceration repair in the pediatric emergency department. Pediatrics. 2006 Apr;117(4):1162-8.
Smith J, Owen E, Earis J, Woodcock A. Effect of codeine on objective measurement of **cough** in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006 Apr;117(4):831-5. Epub 2006 Feb 7.
Taddio A, et al. Intravenous morphine and topical tetracaine for treatment of pain in preterm neonates undergoing central line placement.JAMA. 2006 Feb 15;295(7):793-800.
Treatment Guidelines from the Medical Letter. Pharmaceutical **Drug Overdose**. Sept 2006. (Opiates: naloxone treatment)
Van den Brink W, Haasen C. Evidenced-based treatment of **opioid-dependent** patients. Can J Psychiatry. 2006 Sep;51(10):635-46.

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

RHEUMATOID ARTHRITIS: DMARD Comparison Chart

1. **Guidelines** for the management of rheumatoid arthritis: **2002 Update**. Arthritis Rheum. 2002 Feb;46(2):328-46. http://www.rheumatology.org/publications/guidelines/raguidelines02.asp?aud=mem
2. **Treatment Guidelines**: Drugs for Rheumatoid Arthritis. **The Medical Letter**: January, **2003**; (5) pp. 25-32. Updated Vol 3 (Issue 40) **Dec 2005**
3. Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. **1996** May;39(5):713-22.
4. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. **1996** May;39(5):723-31.
5. Drugs for Rheumatoid Arthritis. The Medical Letter July 10, 2000; (1082) pp. 57-64.
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8. Anakinra (Kineret) for Rheumatoid Arthritis. The Medical Letter: February 18, 2002; (1124) pp. 18-19.
9. Aletaha D, Kapral T, Smolen JS. Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. Ann Rheum Dis. 2003 May;62(5):482-6.
10. Adalimumab (Humira) for Rheumatoid Arthritis. The Medical Letter: March 31, 2003; (1153) pp. 25-27.
11. Micromedex 2005
12. Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2005.
13. Drug Information Handbook 10th edition, 2002-2003
14. Drugs in Pregnancy & Lactation 7th edition, 2005
15. Geriatric Dosage Handbook 7th Edition, 2002
16. Handbook of Clinical Drug Data 10th edition, 2002
17. Therapeutic Choices 4rd edition, 2003
18. Moreland LW, O'Dell JR. Glucocorticoids and rheumatoid arthritis: back to the future? Arthritis Rheum. 2002 Oct;46(10):2553-63.
19. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.
20. Olsen NJ, Stein CM. **New drugs** for rheumatoid arthritis. N Engl J Med. **2004** May 20;350(21):2167-79.
21 . USA Food & Drug Administration: Safety update meeting on TNF blocking agents Mar 4 & 5, 2003 http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t1.htm , http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t2.htm
22. O'Dell, James R., Therapeutic Strategies for Rheumatoid Arthritis. N Engl J Med **2004** 350: 2591-2602.
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25. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2005 Sep 15;72(6):1037-47.
26. Health Canada Jan/06 Hepatitis B Reactivation assoc. with the anti-TNFα products ENBREL (etanercept), HUMIRA (adalimumab), and REMICADE (infliximab) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/anti-tnf_therap_hpc-cps_e.pdf
27. New drug: Orencia (abatacept). Pharmacist's Letter/Prescriber's Letter 2006;22(2):220207. (& also Medical Letter Feb 27,2006.)
28. Emery P. Treatment of rheumatoid arthritis. BMJ. 2006 Jan 21;332(7534):152-5.

Clinical trials:

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Bathon JM, Martin RW, et al A comparison of **etanercept** and **methotrexate** in patients with **early** rheumatoid arthritis. (**ERA trial**) N Engl J Med. 2000 Nov 30;343(22):1586-93.

Bisset L, et al. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for **tennis elbow**: randomised trial. BMJ. 2006 Nov 4;333(7575):939. Epub 2006 Sep 29.

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Bongartz T, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of **serious infections & malignancies**: systematic review & meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. (see also Pharmacist's Letter July 2006) Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI, 39-125) within a treatment period of 3 to 12 months. (Health Canada July/06 Possible Association of REMICADE® with hepatosplenic T-cell lymphoma in pediatric and young adult patients with Crohn's disease http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/remicade_3_hpc-cps_e.html) (Setoguchi S, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Aug 31;54(9):2757-2764 [Epub ahead of print] Our results indicate that users of biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with MTX users. Despite the use of large combined data sets, studying the effect of an infrequent exposure (biologic DMARDs) on rare diseases (hematologic malignancies) remains a challenge.)

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Behavioral & Psychological Symptoms of DEMENTIA (BPSD) Treatment Chart

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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)))
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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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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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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

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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))

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HERBAL DRUG INTERACTION CHART

Additonal references:

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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-)

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Chuchalin AG, Berman B, Lehmacher W. Treatment of acute bronchitis in adults with a pelargonium sidoides preparation (EPS 7630): a randomized, double-blind, placebo-controlled trial. Explore 2005;1:437-45. (InfoPOEMs: The pelargonium sidoides extract (Umckaloabo in Germany) produced a significantly greater reduction in symptoms of acute bronchitis than placebo, & more patients were satisfied with treatment. As with all herbal products, results may be different with pelargonium products other than this extract. (LOE = 1b))

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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

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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-))

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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 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.

Henley DV, Lipson N, Korach KS, Bloch CA. Prepubertal gynecomastia linked to lavender and tea tree oils. N Engl J Med. 2007 Feb 1;356(5):479-85.

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Kobak KA, Taylor LV, Warner G, Futterer R. **St. John's Wort** Versus Placebo in Social Phobia: Results From a Placebo-Controlled Pilot Study. J Clin Psychopharmacol. 2005 Feb;25(1):51-8.

Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for **menopausal symptoms**: a review of randomized, controlled trials. Ann Intern Med. 2002 Nov 19;137(10):805-13.

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Laing C, et al. **Chinese herbal** (**Longdan Xierganwan**) uropathy and nephropathy. Lancet. 2006 Jul 22;368(9532):338.

Larsson SC, Wolk A. **Tea Consumption and Ovarian Cancer** Risk in a Population-Based Cohort. Arch Intern Med. 2005 Dec 12;165(22):2683-2686.

Lim WS, Gammack JK, Van Niekerk J, Dangour AD. **Omega 3 fatty acid** for the prevention of dementia. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005379.

Liu J, Manheimer E, Yang M. Herbal medicines for treating **HIV infection** and AIDS. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003937.

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Pittler MH, Ernst E. **Kava** extract for treating anxiety. Cochrane Database Syst Rev. 2003;(1):CD003383. CONCLUSIONS: Compared with placebo, kava extract appears to be an effective symptomatic treatment option for anxiety. The data available from the reviewed studies suggest that kava is relatively safe for short-term treatment (1 to 24 weeks), although more information is required. Further rigorous investigations, particularly into the long-term safety profile of kava are warranted.
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Red yeast: Most clinical studies have used a specific brand product (Cholestin). However, most other red yeast brands contain similar amount of red yeast, 600 mg. For hypercholesterolemia, a typical dose of red yeast is 1200 mg two times daily with food (2624). A total daily dose of 2400 mg red yeast contains approximately 9.6 mg total statins, of which 7.2 mg is lovastatin (2624). For dyslipidemia related to HIV infection, 1200 mg twice daily has been used (9475). www.naturaldatabase.com
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level, and we can't be sure that he or she has anemia if the hemoglobin level is low. Screening for iron deficiency in toddlers by checking serum hemoglobin misses most children with a deficiency, and most of the children with anemia do not have an iron deficiency. As the author of this study suggests, it might make more sense to continue low-dose supplementation of iron in all children rather than use a policy of screen and treat. (LOE = 1c)) (Rimon E, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med. 2005 Oct;118(10):1142-7. CONCLUSIONS: Low-dose iron treatment is effective in elderly patients with iron-deficiency anemia. It can replace the commonly used higher doses and can significantly reduce adverse effects.) Iron deficiency anemia USPSTF 2006 http://www.ahrq.gov/clinic/uspstf06/ironsc/ironrs.htm (Drueke TB, et al. Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia. N Engl J Med. 2006 Nov 16;355(20):2071-2084. In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events. & Singh AK, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. N Engl J Med. 2006 Nov 16;355(20):2085-2098. The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life. If epoetin alfa (Epogen) is used in patients with chronic kidney disease, the target hemoglobin should be 11.3 g/dL rather than 13.5 g/dL. A higher hemoglobin target was more likely to lead to death or adverse cardiac events (number needed to treat to harm [NNTH] = 25 for 16 months). (InfoPoems LOE =1b)) (Ceriani Cernadas JM, et al. The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. Pediatrics. 2006 Apr;117(4):e779-86. Epub 2006 Mar 27. & van Rheenen PF, Brabin BJ. A practical approach to timing cord clamping in resource poor settings. BMJ. 2006 Nov 4;333(7575):954-8. & Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy & low socioeconomic status: longitudinal analysis of cognitive test scores to age 19yrs. Arch Pediatr Adolesc Med. 2006 Nov;160(11):1108-13.)

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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 2003-2004 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
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 ÷ q12h x8 weeks
Ranitidine – Maintenance		2.5-5mg/kg/day given OD
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.

ANXIETY DISORDER MEDICATION Comparison Chart

[1] Therapeutic Choices 4th Edition, 2003
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[12] Stein DJ. Obsessive-compulsive disorder. Lancet. 2002 Aug 3;360(9330):397-405.
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Additional articles:

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Gao K, Muzina D, Gajwani P, Calabrese JR. Efficacy of **typical and atypical antipsychotics** for primary and comorbid **anxiety** symptoms or disorders: a review. J Clin Psychiatry. 2006 Sep;67(9):1327-40. Except for trifluoperazine, there is no large, well-designed study of antipsychotics in the treatment of primary or comorbid anxiety symptoms or disorders. The efficacy of these agents in various anxiety conditions needs to be further investigated with large, well-designed comparison studies.

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NICE Mar 2005 Anxiety: Management of **post-traumatic stress disorder** in adults in primary, secondary and community care http://www.nice.org.uk/page.aspx?o=CG026

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BENZODIAZEPINE (BZ) COMPARISON CHART

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

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MOOD STABILIZERS & ADJUNCT AGENTS

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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. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/lamictal_2_hpc-cps_e.html

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infants unaffected by PPHN, so the potential benefits and harms of continuing SSRIs in these patients should be carefully weighed. (LOE = 3b)) Health Canada Mar/06 warning http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_11_e.html
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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))
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Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. **Early Onset** of Selective **Serotonin Reuptake Inhibitor** Antidepressant Action: Systematic Review and Meta-analysis. Arch Gen Psychiatry. 2006 Nov;63(11):1217-23.

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ANTIPSYCHOTIC COMPARISON CHART

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TOBACCO / SMOKING CESSATION PHARMACOTHERAPY

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]

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TOBACCO / SMOKING CESSATION PHARMACOTHERAPY Extra articles:

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Etter JF. **Cytisine** for smoking cessation: a literature review and a meta-analysis. Arch Intern Med. 2006 Aug 14-28;166(15):1553-9.

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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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Canadian Medical Association (CMA): Statement: http://www.cma.ca/index.cfm/ci_id/3396/la_id/1.htm accessed 19Jun06.

Tetranabinex/nabidiolex SATIVEX

- Buccal spray solution (Narcotic)
- Indicated for adjunctive symptomatic relief of neuropathic pain in MS pts >18yrs
- Canada: 1st country to approve use
- Limited evidence (66 person trial)
- Cost $537/4 bottles (40 days)

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Cannabis -contains ~70 cannabinoids

- Delta 9 THC is most psychoactive form
- Delta-8 THC & cannabinol less psychoactive
- Cannabidiol may have analgesic activity
- Dronabinol MARINOL & Nabilone CESAMET for N&V with chemo & anorexia in AIDS pts
- Marijuana-Medical Access Regualtions
- 9-THC 2.7mg & cannabidiol 2.5mg SATIVEX
  - buccal spray; often 4-5 sprays/day
  - conditional approval for neuropathic pain in MS

4 bottles=$500 (about 200sprays= 40 days tx)

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