Objective, Comparative, Drug Information

Editors: Brent Jensen & Loren D. Regier

Drug Comparison Charts www.RxFiles.ca

11th Edition March 2017

Objective, Comparative, Drug Information

Other Online EBM Resources/Links:

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

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

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

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

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

Dalhousie Katie Clinical Significance Calculator: http://ktcalc.cme.dal.ca/site/login.php Z-score: http://www.socscistatistics.com/pvalues/normaldistribution.aspx Teaching EBM Videos: McMaster Guyatt: http://ebm.mcmaster.ca/materials_videos.htm

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

Anemia: Trials Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Anemia-Key-Trials.pdf

Dementia: CATIE-AD: http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-CATIE-AD-trial-summary.pdf

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

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

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

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

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

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

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

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

ELIXA: Lixisenatide : http://www.rxfiles.ca/rxfiles/uploads/documents/Lixisenatide-ELIXA%20Trial%20Summary.pdf 2016

EMPA-REG: http://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf 2016

LEADER: Liraglutide: http://www.rxfiles.ca/rxfiles/uploads/documents/Leader-Liraglutide%20VICTOZA%20and%20Cardiovascular%20Outcomes%20in%20Type%202%20Diabetes.pdf 2016

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

SAVOR-TIMI 53: http://www.rxfiles.ca/rxfiles/uploads/documents/SAVOR-TIMI-53-Saxagliptin-CV-Outcomes-Trial-Summary.pdf

TECOS: Sitagliptin CV outcomes: http://www.rxfiles.ca/rxfiles/uploads/documents/TECOS-Trial-Summary.pdf 2016

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

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

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

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

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

SPRINT: http://www.rxfiles.ca/rxfiles/uploads/documents/SPRINT-BP-Trial-Overview.pdf 2015

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

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

PARADIGM-HF: http://www.rxfiles.ca/rxfiles/uploads/documents/PARADIGM-HF-Trial-Sacubitril.pdf 2015

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

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

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

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

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

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

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

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

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

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

FIELD Substudy: http://www.rxfiles.ca/rxfiles/uploads/documents/FIELD-Sub-Analysis-Women-Trial-Summary.pdf 2015

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

IMPROVE-IT: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-IMPROVE-IT-Trial-Summary-QandA.pdf 2014

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

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

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

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

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

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

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

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

CHARISMA: http://www.rxfiles.ca/rxfiles/uploads/documents/Charisma-QandA.pdf

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

DAPT: 12 vs 30months http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT-Trial-12vs30months.pdf

PCI-Clarity: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CLARITY%20Trial%20Summary.pdf 2016

PCI-CURE: http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CURE%20Trial%20Summary.pdf 2016

PEGASUS-TIMI 54: Ticagrelor vs Pl, prior-MI: http://www.rxfiles.ca/rxfiles/uploads/documents/PEGASUS%20Trial%20Summary.pdf 2016

PLATO: Ticagrelor vs clopidogrel ACS: http://www.rxfiles.ca/rxfiles/uploads/documents/PLATO%20Trial%20Summary.pdf 2016

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

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

TRITON-TIMI 38: Prasugrel vs clopidogrel, ACS: http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf 2016

MISC.:

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

FLAME*: Indacaterol+Glycopyrronium vs Salmeterol+Fluticasone for COPD:http://www.rxfiles.ca/rxfiles/uploads/documents/FLAME-Trial-Summary.pdf* 2016

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

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

SENIOR: http://www.rxfiles.ca/rxfiles/uploads/documents/Senior-Trial-Oxybutynin-Solifenacin-Elderly-Cognitive-Impairment.pdf

WARFASA: http://www.rxfiles.ca/rxfiles/uploads/documents/Aspirin-warfarin-trial-summary-WarfASA.pdf

RxFiles: Evidence Based Medicine (EBM) Overview - References

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RxFiles On-Line Extras:

Chart Abbreviations:

A1C =glycosolated hemoglobin A_{1C} **Apo**=apolipoprotein **BP**=blood pressure **BMI**=body mass index **CAC**=coronary artery calcification score **CAD**=coronary artery disease **CKD**=chronic kidney disease **CrCl**=creatinine clearance **CRP**=C-reactive protein **CVD**=cardiovascular disease **DBP**=diastolic blood pressure **DM**=diabetes mellitus **Dx**=disease **FBG**=fasting blood glucose **HD-CKD**=hemodialysis **HDL**=high density lipoprotein **hsCRP**=high sensitivity C-reactive protein **HTN**=hypertension **HF**=heart failure **hx**=history **ISH**=isolated systolic hypertension **LDL**=low density lipoprotein **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-significant **PAD**=peripheral arterial disease **PVD**=peripheral vascular disease **PPBG**=postprandial (2hr) blood glucose **pt**=patient **SAE**=serious adverse events **SBP**=systolic blood pressure **TG**=triglycerides **TIA**=transient ischemic attack **TOD**=target organ damage **tx**=treatment **yr**=year ♂=male ♀=female

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

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

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

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

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

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

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

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

Patients with **High risk→ ALL pts with CAD,CVD,PAD; most with DIABETES** age >40 or >30 with 15yr hx DM **& chronic renal dx** GFR <30ml/min regardless of risk score.

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

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

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

6) Cardiovascular Disease Risk Calculator: **http://bestsciencemedicine.com/chd/calc2.html**

7) AHA'13 CV Risk Calculator **http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp**

8) Risk Calculator: Joint British Societies' Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3). http://www.jbs3risk.com/

9) Systemic Cerebrovascular and Coronary Risk Evaluation (SCORE) risk calculator: http://www.score-canada.ca/

10) Patient friendly risk calculator: http://www.myhealthcheckup.com

For suggested lipid targets, see bottom of page 26 on the RxFiles Lipid chart.

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

Risk	TC /HDL
High	<4
Mod	>5
Low	>6

Previous TC/HDL ratio thresholds used in previous risk assessments.

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Additional Links:

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

Angina: Online Extras 💻

Other Agents - not available in Canada

GENERIC TRADE	THERAPEUTIC USE/COMMENTS	CONTRAINDICATIONS CI /ADVERSE EVENTS AE /DRUG INTERACTIONS DI	INITIAL, USUAL & MAXIMUM DOSE	$/30 DAY
LATE NA CHANNEL INHIBITOR:[37-47] Mechanism unknown; theory ↓ oxygen demand (via inhibition sodium channel which indirectly ↓ calcium overload [responsible for ↑ myocardial tension])				
Ranolazine **RANEXA** 500, 1000mg ER tab (available in EU & US)	**2nd line agent: in combo with BB** [AHA2012,] **and/or CCB** [, ESC 2013] **or monotx (if BB ineffective, CI or intolerable)** [AHA 2012] ✓ Long term management of stable angina [37 FDA, 38 EMA] -Ranolazine vs placebo (+/- background antianginal tx) ↓ angina frequency/wk (n=4 trials)[39 CARISA, 40 ERICA, 41TERISA,42]: -2.3 to -2.8 vs -0.9 to -2.4 & ↓ nitrate use/wk (n=4 trials): -0.7 to -2.4 vs -0.4 to -2.4; although n=3 trials significant, ? clinical importance as absolute change modest [43] -? Benefit diabetes pts, ↓ HbA1c vs placebo -0.28 to -0.7 (other important diabetes outcomes not assessed) [44]	**CI:** hepatic impairment, CrCl <30 mL/min, **strong CYP3A inhibitors or inducers** **AE:** dizziness, headache, nausea, constipation, QTc prolongation **DI:** ↑ ranolazine effect: CYP3A4 inhibiters (non-DHP CCB, erythromycin [max 500 mg BID]) & Pgp inhibitors: (cyclosporine); ↑ effect of: simvastatin (max 20 mg/day), digoxin, TCAs; QTc prolonging agents **M**: efficacy & AE- minimal impact on HR & BP	Initial: 500 mg BID Max: 1000mg BID Increase dose every two weeks until symptom relief.	$400 $650
SELECTIVE SINUS NODE I(f) INHIBITOR: [48-53] ✓Long term management of stable angina [48EMA]				
Ivabradine 5[c], 7.5 mg tabs ✗⊗ (available EU)	**2nd line agent: in combination with BB** [ESC'13] ?safety in stable angina; pre-specified subgroup CCS class II-IV ↑ death/nonfatal MI HR 1.18 (1.03-1.35) vs placebo.[49SIGNIFY]	**CI:** ↓HR, heart rhythm disorder, non-DHP CCB, strong CYP3A4i **AE**: headache, dizziness, visual disturbance, ↓HR	Initial: 2.5-5 mg BID Max: 7.5 mg BID	-
POTASSIUM CHANNEL ACTIVATOR & NITRATE-DERIVATIVE:[54-59] ✓Long term management of stable angina [ESC'13]				
Nicorandil 10, 20mg tabs (available EU)	**2nd line agent: in combination with BB or CCB** [ESC'13] (? tolerance with > 2 wk therapy[54]) ↓ composite (CV death, MI, admission for cardiac chest pain) vs placebo + standard anti-ischemic therapy, HR 0.83 (0.72-0.97, appears driven by admission for cardiac chest pain), no other angina outcomes reported & ↑ (>30%) withdrawal (mainly due to headaches with nicorandil);[55 IONA] other small (n<150 patients), RCTs with mixed anti-ischemic results [54,56-59]	**CI:** cardiogenic shock, HF **AE**: **headache**, dizziness, hypotension, ulcerations (oral, anal, GI)	initial 10 mg, max: 20 mg BID	-
3-KETOACYL-CoA THIOLATE INHIBITOR: ✓Long term management of stable angina [ESC'13]				
Trimetazidine 20 mg tab (available EU)	**2nd line agent: in combination with BB or CCB** [ESC'13] ↓ angina attacks/wk, nitrate use/wk but ↑heterogeneity (I^2 >90%)[60] minimal impact on HR & BP	**CI:** Parkinson's dx, motion disorders, renal impairment **AE**: movement disorders, headache, GI upset nausea, pain, constipation)	20mg TID or 60 mg daily	-

A note on stress testing - there are multiple strategies. The stress may refer to exercise, or phamacological stress (adenosine, dipyridamole, dobutamine). The test may refer to an ECG, nuclear myocardial perfusion imaging, or echocardiography.

Other Types of Angina - less common

	Vasospastic Angina (Prinzmetal's or variant angina) [ESC2013]	Microvascular Angina (Cardiac Syndrome X) [ESC2013, AHA2012]
Epidemiology	-??? (no widely utilized diagnostic criteria) [ESC2013, 29]. ~ 40% coronary angiograms normal/near normal coronary arteries[30]	-more common in ♀
Potential Cause(s) (myocardial O_2 demand > O_2 supply)	- coronary artery spasm	- dysfunction of small coronary arteries, ?abnormal cardiac pain sensitivity
Chest Pain Presentation (*similar: location & character; differing: duration & relationship to provoking or relieving factors*)	-**unprovoked: chest pain at rest** (typically during HS or early AM) & does not/rarely occurs with exertion -management: CCB (DHP or non-DHP) ± NTG; BB should be avoided[35]	-usually provoked by exercise in a stable pattern, but may also happen at rest (**relationship to exercise somewhat inconsistent**) - **duration: prolonged;** chest pain **lasts several mins after exertion has stopped** & has **slow/poor response to NTG**

Angina Online Appendix:

RISK ASSESSMENT: Stable Angina

Table 14. Noninvasive Risk Stratification

High risk (>3% annual death or MI)

1. Severe resting LV dysfunction (LVEF <35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities ≥10% of the myocardium in patients without prior history or evidence of MI
3. Stress ECG findings including ≥2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF <45% or drop in LVEF with stress ≥10%)
5. Stress-induced perfusion abnormalities encumbering ≥10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving >2 segments or 2 coronary beds)
8. Wall motion abnormality developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. CAC score >400 Agatston units
10. Multivessel obstructive CAD (≥70% stenosis) or left main stenosis (≥50% stenosis) on CCTA

Intermediate risk (1% to 3% annual death or MI)

1. Mild/moderate resting LV dysfunction (LVEF 35% to 49%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities in 5% to 9.9% of the myocardium in patients without a history or prior evidence of MI
3. ≥1 mm of ST-segment depression occurring with exertional symptoms
4. Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating 1 vascular territory with abnormalities but without LV dilation
5. Small wall motion abnormality involving 1 to 2 segments and only 1 coronary bed
6. CAC score 100 to 399 Agatston units
7. One vessel CAD with ≥70% stenosis or moderate CAD stenosis (50% to 69% stenosis) in ≥2 arteries on CCTA

Low risk (<1% annual death or MI)

1. Low-risk treadmill score (score ≥5) or no new ST segment changes or exercise-induced chest pain symptoms; when achieving maximal levels of exercise
2. Normal or small myocardial perfusion defect at rest or with stress encumbering <5% of the myocardium*
3. Normal stress or no change of limited resting wall motion abnormalities during stress
4. CAC score <100 Agaston units
5. No coronary stenosis >50% on CCTA

*Although the published data are limited; patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF <35%).

CAC indicates coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; LV, left ventricular; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

Adapted from Gibbons et al. (7).

Table 17 Definitions of risk for various test modalities[a]

Exercise stress ECG[b]	High risk	CV mortality >3%/year.
	Intermediate risk	CV mortality between 1 and 3%/year.
	Low risk	CV mortality <1%/year.
Ischaemia imaging	High risk	Area of ischaemia >10% (>10% for SPECT; limited quantitative data for CMR – probably ≥2/16 segments with new perfusion defects or ≥3 dobutamine-induced dysfunctional segments; ≥ 3 segments of LV by stress echo).
	Intermediate risk	Area of ischaemia between 1 to 10% or any ischaemia less than high risk by CMR or stress echo.
	Low risk	No ischaemia.
Coronary CTA[c]	High risk	Significant lesions of high risk category (three-vessel disease with proximal stenoses, LM, and proximal anterior descending CAD).
	Intermediate rick	Significant lesion(s) in large and proximal coronary artery(ies) but not high risk category.
	Low risk	Normal coronary artery or plaques only.

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; CV = cardiovascular; ECG = electrocardiogram; ICA = invasive coronary angiography; LM = left main; PTP = pre-test probability; SPECT = single photon emission computed tomography.

[a] For detailed explanation on rationale for risk stratification scheme see web addenda.

[b] From nomogram (see web addenda, Figure W1) or http://www.cardiology.org/tools/medcalc/duke/

[c] See Fig 2 consider possible overestimation of presence of significant multivessel disease by coronary CTA in patients with high intermediate PTP (≥50%) and/or severe diffuse or focal coronary calcifications and consider performing additional stress testing in patients without severe symptoms before ICA.

AN APPORACH TO DECISION MAKING:

(note: ischemia is based on % of total myocardium ischemia)

Table W3 Decision making according to severity of symptoms/ischaemia

Severe: Angina CCS III–IV or ischaemia >10%	➡ catheterization laboratory.
Moderate-to-severe: Angina CCS II or ischaemia 5–10%	➡ OMT[a] only or catheterization laboratory.
Mild-to-moderate: Angina CCS I or ischaemia <5%	➡ OMT[a] first and defer catheterization laboratory.

[a] If symptoms and/or ischaemia are markedly reduced/eliminated by OMT, then OMT may be continued; if not, catheterization should follow. CCS = Canadian Cardiovascular Society; OMT = optimal medical therapy.

RISK ASSESSMENT: Unstable Angina

GRACE (0–258)	Age (years)	
	<40	0
	40–49	18
	50–59	36
	60–69	55
	70–79	73
	≥80	91
	Heart rate (bpm)	
	<70	0
	70–89	7
	90–109	13
	110–149	23
	150–199	36
	>200	46
	Systolic BP (mmHg)	
	<80	63
	80–99	58
	100–119	47
	120–139	37
	140–159	26
	160–199	11
	>200	0
	Creatinine (mg/dL)	
	0–0.39	2
	0.4–0.79	5
	0.8–1.19	8
	1.2–1.59	11
	1.6–1.99	14
	2–3.99	23
	>4	31
	Killip class	
	Class I	0
	Class II	21
	Class III	43
	Class IV	64
	Cardiac arrest at admission	43
	Elevated cardiac markers	15
	ST-segment deviation	30

GRACE (Global Registry of Acute Coronary Events)Risk Score: derived from GRACE cohort and validated in subsequent GRACE & GUSTO IIb cohorts; used to predict in-hospital & post-discharge to 6-months mortality or mortality/MI.

- stratified to low, intermediate, and high risk categories based on GRACE score (http:// www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f)

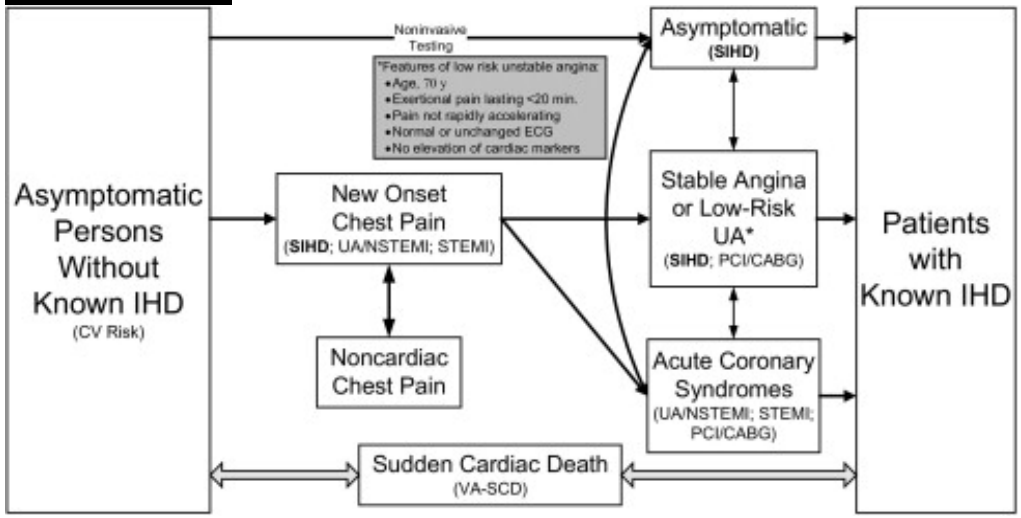
TIMI (Thrombolysis in Myocardial Infarction) Risk Score: derived from TIMI IIB trial and validated in TIMI IIb and ESSENCE trials; used to predict composite all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization within 14 days. (http://www.timi.org/index.php?page= calculators)

TIMI (0–7)	Age ≥65 years	1
	≥3 risk factors for CAD	1
	Use of ASA (last 7 days)	1
	Known CAD (stenosis ≥50%)	1
	>1 episode rest angina in <24 h	1
	ST-segment deviation	1
	Elevated cardiac markers	1

The TIMI score is simple to calculate; however, its accuracy is inferior to the GRACE risk score.

CRUSADE Bleeding Risk Score: developed from a registry which included NSTE-ACS patients.
(may be considered in patients undergoing coronary angiography to quantify bleeding risk) (http://www. crusadebleedingscore.org)

DISEASE PROGRESSION



Revascularization

Table W4 Indications to perform CABG or PCI in stable CAD

Clinical conditions	Type of preferred revascularization[a]
Single-vessel disease, non-proximal LAD, with or without diabetes mellitus.	PCI
Multi-vessel disease with SYNTAX score <22 and high surgical risk (e.g. EuroSCORE >6).	PCI
Revascularization in patient with contra-indication to surgery (severely impaired lung function, prior mediastinal irradiation, prior CABG or non-coronary cardiac surgery, bilateral carotid artery stenoses).	PCI
Elderly patient (>80 years) and co-morbidities or frailty [b]	PCI
Left main disease with SYNTAX score ≥33.	CABG
Multi-vessel disease (with or without diabetes) with LAD involvement and SYNTAX score >22.	CABG
Recurrent in-stent re-stenosis after DES implantation in proximal-mid LAD.	CABG
Revascularization in patients with concomitant significant structural heart disease also requiring surgery.	CABG
Multi-vessel disease or left main disease with SYNTAX score <22 and low surgical risk (e.g. EuroSCORE <6)	CABG or PCI
Left main disease with SYNTAX score <33.	CABG or PCI
Impaired LV function.	CABG or PCI
Renal insufficiency or dialysis.	CABG or PCI

[a]Decision to be taken in a Heart Team meeting.
[b]Frailty defined by means of validated scores (Charlson, Barthel, Frailty scores[10–12])
CABG = coronary artery bypass graft; CAD = coronary artery disease; DES = drug eluting stent; LAD = left anterior descending; LV = left ventricular; PCI = percutaneous coronary intervention.

CABG: segments of arteries/veins to reroute blood around proximal coronary artery. Good outcomes & survival rates with some ↑ risk patients (i.e. left main coronary artery stenosis, three-vessel disease with abnormal LV function). **PCI ± Stent: catheter-borne mechanical/laser device to open short area of stenosis in coronary artery.** Although PCI ↓ angina sx, does **NOT** ↑ survival in stable pts may ↑ MI risk & does not ↓ long-term MI risk. These points should be considered when evaluating risks vs benefits for patients. **CABG vs PCI ± Stent:** In general, similar survival & MI rates at 1&5 yrs; ↑ stroke in CABG (1.2%) vs PCI (0.6%); ↑ angina relief in CABG vs PCI at 1& 5 yrs; ↑ repeat revascularization with PCI (46.1%) vs CABG (9.8%) after 5 yrs. AHA 2012

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FDA June/10 June 14, 2010 (Washington, DC) — The FDA is conducting a safety review of the angiotensin receptor blocker **olmesartan** (Benicar, Daiichi Sankyo) after determining that diabetic patients taking the drug in two completed phase 3 trials may have had an excess risk of **cardiovascular death**, the regulatory body has announced [1].The safety announcement says that the FDA's review is "ongoing, and the agency has not concluded that Benicar increases the risk of death. FDA currently believes that the benefits of Benicar in patients with high blood pressure continue to outweigh its potential risks." The agency also notes that "other controlled clinical trials evaluating Benicar and other ARBs have not suggested an increased risk of cardiovascular-related death."The primary end points of the two trials were dominated by measures of renal function.In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, conducted in Europe, 4447 patients with diabetes and at least one additional cardiovascular risk factor, but no evidence of renal dysfunction, were randomized to receive either olmesartan at 40 mg/day (n=2232) or placebo (n=2215). The trial, sponsored by Sankyo Pharma, ended in July 2009 [2]. In the Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT), conduced in Japan and Hong Kong, 566 patients with diabetes and renal dysfunction were randomized to receive olmesartan at 10 mg/day to 40 mg/day (n=282) or placebo (n=284).
FDA June/11 Food and Drug Administration drug safety: **No increase in risk of cancer** with certain blood pressure drugs—**angiotensin receptor blockers (ARBs).** June 2, 2011. http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm
FDA Apr/12 notified healthcare professionals of possible risks when using blood pressure medicines containing aliskiren with other drugs called angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with diabetes or kidney (renal) impairment. (Altitude study)
FDA July/13 is warning that the blood pressure drug **Olmesartan** Medoxomil (marketed as Benicar, Benicar HCTZ, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy. Symptoms of **sprue-like enteropathy** include severe, chronic diarrhea with substantial weight loss. FDA has approved changes to the labels of these drugs to include this concern. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.
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Health Canada Jan/12 **RASILEZ** (aliskiren) and RASILEZ HCT (aliskiren/hydrochlorothiazide) - Potential Risks of Cardiovascular and Renal Adverse Events in Patients with Type 2 Diabetes - Novartis Pharmaceuticals Canada Inc. The combination of **aliskiren with ACE inhibitors and ARBs is now contraindicated in patients with type 2 diabetes**. The Product Monograph will be updated accordingly.

Health Canada Feb/14 wishes to inform healthcare professionals and patients of the risks associated with **combining more than one of the following blood pressure medicines**: aliskiren (renin inhibitor), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).

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Antihypertensives: Landmark & Recent Trials – Summary

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What is bridging? What does it attempt to do?

"Bridging anticoagulation refers to giving a short-acting anticoagulant, typically low-molecular-weight heparin (LMWH), before and after surgery to minimize the time that patients are not anticoagulated, and thereby minimize the risk for thromboembolism."[2]

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ç=scored tab ☎=EDS in SK ✗ =Non formulary in SK ℘=prior approval for NIHB ⊗=not covered by NIHB ▼ =covered by NIHB **#**=facture **1º**=primary **2º**=secondary ♂=male ♀=female **ACEI**=angiotensin converting enzyme inhibitor **AF**=atrial fibrillation **ASA**=acetylsalicylic acid **ACS**=acute coronary syndrome **AVR**=atrial valve repair **ASx**=asymptomatic **BMS**=bare metal stent **BP**=blood pressure **CABG**=coronary artery bypass graft **CAD**=coronary artery dx **CBC**=complete blood count **CBZ**=carbamazepine **CVD**=cardiovascular dx **D/C**=discontinue **DES**=drug eluting stent **Dx**=disease **DVT**=deep vein thrombosis **EC**=enteric coated **EF**=ejection fraction **fx**=function **GI**=gastrointestinal **HA**=headache **HF**=heart failure **HIT**=heparin-induced thrombocytopenia **HR**=heart rate **HTN**=hypertension **hx**=history **ICH**=intracranial hemorrhage **LDUH**=low dose unfractionated heparin **LFT**=liver function test **LMWH**=low molecular weight heparin **LV**=left ventricular **LVH**=left ventricular hypertrophy **MHV**=mechanical heart valve **MI**=myocardial infarction **MOA**=mechanism of action **MVP**=mitral valve prolapse **MVR**=mital valve repair **MVS**=mitral valve strands **NNH/T**=number needed to harm/treat **NS**=non-significant **NSR**=normal sinus rhythm **OAC**=oral anticoagulant **OTC**=over the counter **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention **PE**=pulmonary embolism **PFO**=patent foramen ovale **P-gp**=P-glycoprotein **PK**=pharmacokinetics **Pts**=patients **RR**=relative risk **SX**=surgery **TIA**=transient ischaemic attack **THA**=total hip arthroplasty **TKA**=total knee arthroplasty **TTP**=Thrombotic thrombocytopenic purpura **tx**=treatment **VTE**=venous thromboembolism **WBC**=white blood cell **wt**=weight **wks**=weeks

RxFiles On-Line Extras: Oral Antiplatelet & Antithrombotic Agents

Landmark Trials	Intervention	Population	Contribution to Current Knowledge
AAASPS [18] ≤2 yrs, n=1,809	Ticlopidine TICLID 250mg po BID vs ASA 325mg po BID	African Americans with stroke hx	Recurrent MI, stroke or vascular death: TICLID 14.7% vs ASA 12.3%, p=0.12
CLASSICS [4] 28 days, n=1,020	Clopidogrel PLAVIX $_{(\pm 300mg)\ 75mg}$ + ASA $_{325mg\ po\ daily}$ vs Ticlopidine TICLID $_{250mg\ po\ BID}$ + ASA $_{325mg\ po\ daily}$	Post-stent	NS in safety/efficacy for PLAVIX (either regimen) or TICLID in 1st 28 day post-stenting.

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(InfoPOEMs: Aspirin reduces the risk of stroke and transient ischemic attack in women but does not reduce the risk of myocardial infarction or cardiovascular death. The reduction in strokes over 10 years (number needed to treat = 444) must be balanced against an increase in serious gastrointestinal bleeds (number needed to treat to harm = 553). No change was seen in this large, long study regarding all-cause mortality. (LOE = 1b)) {Low dose Aspirin in the Primary Prevention of Cancer WHS study JAMA. 2005;294:47-55. Conclusions: Results from this large scale, long-term trial suggest that alternate day use of 100mg every other day for an average of 10yrs does not lower the risk of total, breast, colorectal, or other site-specific cancers. A protective effect on lung cancer or a benefit of higher doses of aspirin cannot be ruled out}
Kurth T, Barr RG, Gaziano JM, Buring J. Randomised Aspirin Assignment And Risk Of Adult-Onset Asthma In The Women's Health Study. (**WHS**) Thorax. 2008 Mar 13; [Epub ahead of print] In this large, randomised clinical trial of apparently healthy adult women, assignment of 100 mg of aspirin on alternate days reduced the relative risk of newly reported diagnosis of **asthma**.
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Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. (OASIS-5) N Engl J Med. 2006 Mar 14; [Epub ahead of print] Conclusions Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long term mortality and morbidity. (InfoPOEMs: **Fondaparinux** is a safer alternative to enoxaparin in patients with acute coronary syndrome (ACS), and has slightly better long-term efficacy, as well. (LOE = 1b))
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Furie Karen L., Kasner Scott E., Adams Robert J., et al., and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the **Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack**. (Secondary Prevention) A Guideline for Healthcare Professionals From the American Heart Association (AHA)/American Stroke Association (ASA). Stroke published October 21, 2010, doi:10.1161/STR.0b013e3181f7d043. http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181f7d043v1
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http://www.cadth.ca/media/pdf/OP0508_warfarin_rec-report_e.pdf
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COMPLETE LIST OF ABBREVIATIONS

☎ = EDS in SK ⊗=not covered by NIHB 2˚=secondary **ABI**=ankle-brachial index **ACS**=acute coronary syndrome **AF**=atrial fibrillation **ARI**=absolute risk increase **ARR**=absolute risk reduction **ASA**=acetylsalicyclic acid **BG**=blood glucose **BMS**=bare-metal stent **BP**=blood pressure **CABG**=coronary artery bypass graft **CAD**=coronary artery disease **CI**=contraindication **CNS**=central nervous system **CV**=cardiovascular **DAPT**=dual antiplatelet therapy **d/c**=discontinue **DES**=drug-eluting stent **DM**=diabetes **g**=generic **G_1DES**=1st generation drug-eluting stent **GERD**=gastroesophageal reflux disease **GI**=gastrointestinal bleed **HF**=heart failure **hr**=hour **HTN**=hypertension **INR**=international normalization ratio **LD**=loading dose **LV**=left ventricular **MI**=myocardial infarction **new-DES**=newer drug-eluting stent **mos**=months **NA**=not applicable **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-statistically significant **NSAID**=non-steroidal anti-inflammatory drug **NSTEACS**=non-ST elevated ACS **OAC**=oral anticoagulant **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention **PPI**=proton-pump inhibitor **pt**=patient **RCT**=randomized controlled trial **SAPT**=single antiplatelet therapy **SK**=Saskatchewan **SSRI**=selective serotonin reuptake inhibitor **ST**=stent thrombosis **TIA**=transient ischemic attack **TT**=triple therapy **TTR**=time in therapeutic range **tx**=treatment **VKA**=vitamin K antagonist **VL-ST**=very late stent thrombosis **VTE**=venous thromboembolism **yr**=year **yo**=years old

RXFILES RELATED DOCUMENTS

- Perioperative Antithrombotic Management Chart (http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-Perioperative.pdf)
- Oral Antiplatelet & Antithrombotic Agents Chart (http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf)
- Atrial Fibrillation – Selection of Thromboembolic Therapy Chart (http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Atrial-Fibrillation.pdf)
- Oral Acid Suppression Chart (http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-AcidSuppression.pdf)
- Q&A Does Clopidogrel + ASA Impact Mortality (http://www.rxfiles.ca/rxfiles/uploads/documents/QandA_Clopidogrel_and_Mortality.pdf)
- ACTIVE-W (DAPT vs warfarin in AF) Trial Summary (http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf)
- DAPT (DAPT 12 vs 30 months) Trial Summary (http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT-Trial-12vs30months.pdf)
- PCI-CLARITY (ASA vs clopidogrel post STEMI + PCI) Trial Summary (http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CLARITY%20Trial%20Summary.pdf)
- PCI-CURE (ASA vs clopidogrel post NSTEACS + PCI) Trial Summary (http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CURE%20Trial%20Summary.pdf)
- PLATO (ticagrelor vs clopidogrel in ACS) Trial Summary (http://www.rxfiles.ca/rxfiles/uploads/documents/PLATO%20Trial%20Summary.pdf)
- TRITON (prasugrel vs clopidogrel ACS+PCI) Trial Summary (http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf)

RxFiles Duration of DAPT & TT Online Extras:

L Kosar MSc, K Koziol BSP, A Martens BSP, D Shmyr BSP © www.RxFiles.ca Apr 2016

DAPT SCORE CALCULATOR (www.daptstudy.org)

- The DAPT Score Calculator is a validated tool to help identify patients who may benefit from extended DAPT (i.e. beyond 1 year after a drug-eluting stent [**not** for those with a bare-metal stent]).
- The calculator should not be used at the time of coronary stent insertion. Instead, it may be used by a **cardiologist after the patient has been on DAPT for 12 months**.
- The score is based on the **DAPT** study – i.e. DAPT x 12 vs 30 months in patients with drug-eluting stent who were compliant & **event-free after 12 months of DAPT** (i.e. no MI, stent thrombosis, stroke, repeat revascularization, or major bleed).
- Balances risk of thrombosis (i.e. MI or stent thrombosis) vs bleeding.
- Risk of bleeding for the calculator was based solely on age.
- Variables that were risk factors for both thrombosis & bleeding were excluded from the calculator (e.g. HTN, CKD, & PAD).
- The score ranges from -2 to 10:
  - **Score <2:** bleed NNH=64 > ischemic risk NNT=153, DAPT x 12 months then stop.
  - **Score ≥2:** ischemic NNT=34 > bleeding risk NNH=272. May consider DAPT >12 months

VARIABLE	POINTS
Patient Characteristics	
Age: ≥75 years of age	-2
65-74 years of age	-1
<65 years of age	0
Diabetes Mellitus	1
Cigarette smoker within past 2 years	1
Prior PCI or Prior MI	1
History of HF or LVEF <30%	2
Index Procedure Characteristic	
MI at presentation	1
Vein graft PCI	2
Stent diameter <3mm	1
paclitaxel stent =1 point	

CKD=chronic kidney disease **DAPT**=dual antiplatelet therapy **HTN**=hypertension **HF**=heart failure **LVEF**=left ventricular ejection fraction **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention

SWITCHING $P2Y_{12}$ INHIBITORS (Clopidogrel vs Prasugrel vs Ticagrelor)

- The Canadian Cardiovascular Society 2012 Antiplatelet Guidelines suggest against switching the $P2Y_{12}$ inhibitor initially selected at discharge unless there is a compelling reason e.g. stent thrombosis, bleed, cardiovascular event. [CR/VLQ]
- The following information is based primarily on pharmacodynamics studies & registries. Unfortunately, the timeframe for "acute phase" and "chronic phase" was not defined in the publications. Of note, **the risk of stent thrombosis is greatest during the first month**.
- Clopidogrel & prasugrel bind to the $P2Y_{12}$ receptors at the same site where ADP binds – thus blocking ADP. Ticagrelor, on the other hand, binds to the P2Y12 receptor at a different site than ADP & induces a conformational change making the receptor inactive. As such, when switching between clopidogrel & prasugrel, it is a saturable process. Once all of the receptor sites are blocked, any additional drug is eliminated from the systemic circulation.
- **Loading Doses for Switching:** clopidogrel 300mg x1; ticagrelor 180mg x1; prasugrel 60mg x 1
- **Switching from clopidogrel → ticagrelor or prasugrel:** (e.g. clinical failure [e.g. stent thrombosis] despite adherence to therapy)
  - Acute Phase: administer loading dose (unless active bleeding) regardless of clopidogrel timing/dose
  - Chronic Phase: omit loading dose, start maintenance dose 24 hours after last clopidogrel dose.
  - In the **PLATO** trial (**ticagrelor** vs clopidogrel in ACS), 46% of the patients in the ticagrelor arm received a dose of clopidogrel prior to randomization. The loading dose of ticagrelor (180mg x 1) was administered to all of these patients.
  - In the **TRITON-TIMI** trial (**prasugrel** vs clopidogrel in ACS + PCI), all of the patients in the prasugrel arm were "$P2Y_{12}$ inhibitor naïve".
- **Switching from ticagrelor → clopidogrel or prasugrel:** (e.g. dyspnea or cost concerns)
  - Administer loading dose 24 hours after the last ticagrelor dose (pharmacodynamic study showed a residual effect 12 hours after the last dose).
  - If the patient presents with dyspnea, it is important to rule out heart failure before switching agents.
- **Switching from prasugrel → clopidogrel:** (e.g. history of stroke or TIA not known at time of stent insertion or cost concerns)
  - Acute Phase: administer loading dose (unless active bleeding) 24 hours after the last dose of prasugrel.
  - Chronic Phase: omit loading dose, start maintenance dose 24 hours after last prasugrel dose.
- **Switching from prasugrel → ticagrelor:** (e.g. history of stroke or TIA not known at time of stent insertion)
  - Administer loading dose unless active bleeding 24 hours after the last prasugrel dose.

$P2Y_{12}$ inhibitor=clopidogrel, prasugrel or ticagrelor **TIA**=transient ischemic stroke

STRENGTH OF RECOMMENDATIONS & LEVELS OF EVIDENCE

CARDIOVASCULAR INDICATIONS – DAPT

Stable CAD / Non-ACS / Stable Ischemic Heart Disease / Established CAD & Elective PCI

- Ideally, DAPT with ASA 81mg po daily + **clopidogrel** 75mg po daily 6 months [ESC/EACTS'14 (IB), ACA/AHA'16 (IB-R)] to 12 months [ACC/AHA'16 (IIb,A), CCS'12 (SR/HQ), ESC/EACTS'14 (IIb, C), ACCF/AHA/SCAI'11 (IB), CHEST'12 (2C)]
- Minimum Durations:
  - **BMS:** ↑ risk of bleeding, scheduled for non-cardiac surgery: minimum DAPT x 1 month [ACC/AHA'16 (IA), CCS'12 (SR/HQ), ESC/EACTS'14 (IA), ACCF/AHA/SCAI'11 (IB), CHEST'12 (IA)]
  - **BMS:** very high risk of bleeding – minimum DAPT x 2 weeks [CCS'12 (CR/LQ), ACCF/AHA/SCAI'11 (IB)]
  - **DES:** ↑ risk of bleeding, scheduled for non-cardiac surgery, OAC: minimum 3 [ACC/AHA'16 (IIb,C-LD), CCS'12 (CR/LQ)] to 6 months [ACC/AHA'16 (IB-R), ESC/EACTS'14 (IIb, A), CHEST'12 (IA)]
- ASA 81mg [ACC/AHA'16 (IB-NR), ACCF/AHA/SCAI'11 (IIa, B)] po daily indefinitely [ESC/EACTS'14 (IA), ACCF/AHA/SCAI'11 (IA)]

NSTEACS & PCI

- Ideally, DAPT x 12 months [ACC/AHA'16(IB-R), ESC'15 (IA), AHA/ACC'14 , CCS'12 (SR/HQ), CHEST'12(IB)] Options listed alphabetically:
  - Clopidogrel [ESC'15 (IB), AHA/ACC'14 (IB), CCS'12 (SR/HQ)] which is preferred for those requiring oral anticoagulation [ESC'15 (IB)]
  - Prasugrel preferred over clopidogrel if PCI planned [ACC/AHA'16(IIa, B-R), ESC'15 (IB), AHA/ACC'14 (IB), CCS'12 (SR/HQ)]. Not recommended if coronary anatomy is unknown, not treated with PCI, high bleed risk, or history of stroke/TIA. [ESC'15 (IIIB), AHA/ACC'14 (IB, IIIB), CCS'12 (SR/HQ)]
  - Ticagrelor, which is preferred over clopidogrel in those with moderate-to-high risk of ischemic events [ACC/AHA'16(IIa, B-R), ESC'15 (IB), AHA/ACC'14 (IB), CCS'12 (SR/HQ), CHEST'12 (2B)]
- Longer DAPT >12 months (balance ischemic & bleeding risks) [ACC/AHA'16 (IIb,A), ESC'15 (IIb,A), AHA/ACC'14 (IIb,C), CCS'12 (CR/LQ)]
- Shorter DAPT of 3 to 6 months after DES if high bleeding risk [ESC'15 (IIb,A), AHA/ACC'14 (IIa,C)]
- Minimum DAPT: BMS x 1 month, new-generation DES 3 to 6 months [ESC'15 (IIb,C)]
- ASA 81mg [ACC/AHA'16(I, B-NR), CCS'12 (SR/HQ), AHA/ACC'14 (IIa,B)] po daily indefinitely; [ESC'15 (IA), AHA/ACC'14 (IA)] ensure 81mg po daily if using ticagrelor. [AHA/ACC'14 (IA)] If ASA allergy or intolerance, use clopidogrel indefinitely. [CCS'12 (SR/HQ)]

STRENGTH OF RECOMMENDATIONS & LEVELS OF EVIDENCE continued

CARDIOVASCULAR INDICATIONS – DAPT continued

STEMI & PCI

- Ideally, DAPT x 12 months [ACC/AHA'16(IB-R), ESC/EACTS'14 (IA), ACCF/AHA'13, CCS'12 (SR/HQ), CHEST'12(IB)] Options listed alphabetically:
  - Clopidogrel [ESC/EACTS'14 (IB), ACCF/AHA'13 (IB), CCS'12 (SR/MQ)]
  - Prasugrel [ESC/EACTS'14 (IB), ACCF/AHA'13 (IB), CCS'12 (SR/HQ)] avoid if a history of stroke/TIA, [ACC/AHA'16(III, B-R), ACCF/AHA'13 (IIIB)] high bleed risk [ACC/AHA'16(IIa, B-R)] & use 5mg daily if ≥75 years or weigh ≤60kg. [CCS'12 (SR/LQ)] Preferred over clopidogrel [ACC/AHA'16(IIa, B-R), CCS'12 (SR/HQ)] if not a high bleed risk. [ACC/AHA'16 (IIb,A)]
  - Ticagrelor [ESC/EACTS'14 (IB), ACCF/AHA'13 (IB), CCS'12 (SR/HQ)] is preferred over clopidogrel [ACC/AHA'16(IIa, B-R), CCS'12 (SR/HQ), CHEST'12(2B)]
- Longer DAPT beyond 12 months may be considered if DES [ACC/AHA'16 (IIb,A), ACCF/AHA'13 (IIb,C), CCS'12 (CR/LQ)]
- If high bleed risk & DES: may consider a minimum 6 months of DAPT.[ACC/AHA'16(IIb,C-LD)]
- ASA 81mg po [ACC/AHA'16(I, B-NR), ACCF/AHA'13 (IIa,B)] daily indefinitely.[ESC/EACTS'14 (IA), ACCF/AHA'13 (IA)] If ASA allergy or intolerance, use clopidogrel indefinitely. [CCS'12 (SR/HQ)]

MEDICALLY MANAGED ACS

- Ideally, DAPT with ASA 81mg po daily + clopidogrel 75mg po daily [CURE, CURRENT-OASIS] or ticagrelor 90mg po BID [PLATO, PLATO (non-invasive management subgroup analysis)] x 12 months. [ACC/AHA'16(IB-R), CCS'12(NSTEACS – SR/HQ, STEMI – CR/LQ), ESC'15 (IA), AHA/ACC'14 (IB), CHEST'12 (IB)]
- Preference for ticagrelor over clopidogrel, [ACC/AHA'16(IIa,B-R), CCS'12 (SR,HQ)] based on PLATO (~25% were medically managed), except in patients who receive fibrinolytics. Patients who received fibrinolytics were excluded from PLATO. If **fibrinolytics** are administered, clopidogrel is recommended. [CLARITY]
- Minimum Durations with clopidogrel: **STEMI:** 14 days [ACC/AHA'16(IA), CCS'10(IB), ACCF/AHA'13(IA)] to 1 month; [CCS'12(SR/HQ), COMMIT, CLARITY] **NSTEACS:** 1 month [CCS'10(IA), CURE]
- May be reasonable to continue DAPT longer than 12 months in ACS patients who were medically managed/STEMI with fibrinolytic. [ACC/AHA'16(IIb,A)]

PERIPHERAL ARTERY DISEASE

- **Symptomatic PAD:** CHEST 2012 & ESC 2011 recommend *against* the use of DAPT for symptomatic PAD. ACCF/AHA 2011 & CCS 2010 state the combination may be considered in patients at high vascular risk with a low risk of bleeding. [IIb,B for both] This is based on CHARISMA (clopidogrel + ASA vs ASA alone), in which 25% of the patients had PAD. The primary endpoint (MI, stroke, CV death) was non-statistically significant for the whole population. However, in a subgroup of symptomatic patients (i.e. established vascular disease): clopidogrel + ASA 6.9% vs ASA alone 7.9%, RR 0.88 (95% CI 0.77-0.998), p=0.046 (underpowered).
- **Below-knee bypass with a prosthetic graft:** may consider DAPT x 1 year. [CHEST 2012 (2C), ESC 2011 (IIb,B), CASPAR]

CARDIOVASCULAR INDICATIONS – TRIPLE THERAPY

GENERAL RECOMMENDATIONS

- Ensure there is a compelling indication for triple therapy: LV thrombus, [ACCF/AHA'13 (IIa,C)] anterior apical akinesis or dyskinesis; [ACCF/AHA'13 (IIb,C)] AF with CHA_2DS_2-VASc score ≥2, [recent or recurrent] VTE, mechanical valve prosthesis; [ESC'15 (IC), ESC/EACTS'14 (IC), ACCF/AHA'13 (IC)] or hypercoagulable disorder [ACCF/AHA'13 (IC)]
- In patients with AF, use the $CHADS_2$ or CHA_2DS_2-VASc score to estimate stroke risk & the HASBLED to estimate bleed risk. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IC), CCS'12 (CR/LQ)]
- New-generation DES are preferred over BMS, especially when HASBLED ≤2. [ESC'15 (IIa,B), ESC/EACTS'1 4 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)]
- Implement strategies to reduce bleeding: aim for a TTR>70%, [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IA)] target an INR 2-2.5, [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C), AHA/ACC'14 (IIb,C), ACCF/AHA'13 (IIb,C)] Avoid novel P2Y12 inhibitors (i.e. prasugrel or ticagrelor). [ESC'15 (III,C), ESC/EACTS'1 4 (III,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,C)] Use a PPI.[ESC'15 (IB), ESC/EACTS'1 4 (IA), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C), AHA/ACC'14 (IIa,C – IC)] Minimize duration.[AHA/ACC'14 (IC), ACCF/AHA'13 (IC)]

STABLE CAD + PCI & AF

- **CHA_2DS_2-VASc score ≤1:** consider using DAPT as an alternative to TT. [ESC/EACTS'1 4 (IIa,C)]
  - **HAS-BLED ≤2:** consider using DAPT or dual therapy (OAC + clopidogrel [or ASA]), as alternatives to TT. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)]
  - **HASBLED >3:** consider using DAPT, or dual therapy (OAC + clopidogrel [or ASA]) x 12 months, as alternatives to TT. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)]
- **CHA_2DS_2-VASc score ≥2:**
  - **HAS-BLED ≤2:** TT x 1 month, [ESC/EACTS'1 4 (IIb,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] (maximum 6 months) [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] regardless of stent type, followed by dual therapy (OAC + SAPT) up to 12 months.[ESC/EACTS'1 4 (IIb,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] May consider dual therapy x 1 year as an alternative. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C), AHA/ACC/HRS'14 (IIb,B)]
  - **HASBLED >3:** TT [ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] or dual therapy (OAC + clopidogrel [or ASA]) [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] x 1 month, followed by dual therapy x 11 months. [ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)]
- After 1 year post-PCI, long-term OAC. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IB)] May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal left anterior descending, proximal bifurcation, recurrent MIs, etc. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)]

STRENGTH OF RECOMMENDATIONS & LEVELS OF EVIDENCE continued

CARDIOVASCULAR INDICATIONS – TRIPLE THERAPY continued

NSTEACS + PCI & AF

- **CHA_2DS_2-VASc score of 1 (in males) or 2 (in females):** consider using DAPT as an alternative to TT. ESC'15 (IIa,C)
- **HASBLED 0-2:** TT x 6 months, then dual therapy (OAC + SAPT) x 6 months, ESC'15 (IIa,C), ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C) regardless of stent type. ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)
  - **CHA_2DS_2-VASc ≥2:** may continue TT or dual therapy (OAC + SAPT) between 6 and 12 months. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)
- **HASBLED ≥3:** TT x 1 month, then dual therapy (OAC + SAPT) x 11 months, regardless of stent type. ESC'15 (IIa,C), ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C) May consider dual therapy (OAC + SAPT) as an alternative to TT if low risk of stent thrombosis or high bleed risk. ESC'15 (IIb,B), ESC/EACTS'14 (IIb,B), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)
- After 1 year post-PCI, long-term OAC. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IB) May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal bifuraction, recurrent MIs, etc. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)
- **Medically Managed or CABG:** dual therapy (OAC + SAPT) preferred x 12 months. ESC'15 (IIa,C)
- Avoid TT with novel P2Y12 inhibitors, ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,B) however may consider one of these agents if the patient has a stent thrombosis while on TT with clopidogrel. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)

STEMI + PCI & AF

- **HASBLED 0-2:** TT x 6 months, regardless of stent type, then dual therapy (OAC + clopidogrel [or ASA]). ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)
  - **CHA_2DS_2-VASc score ≥2:** may continue TT or dual therapy (OAC + SAPT) between 6 and 12 months. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)
- **HASBLED ≥3:** TT x 1 month, regardless of stent type, followed by dual therapy (OAC + clopidogrel [or ASA]). ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C) May consider dual therapy (OAC + SAPT) as an alternative to TT if low risk of recurrent ischemic events & high bleed risk. ESC/EACTS'14 (IIb,B), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)
- After 1 year post-PCI, long-term OAC. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IB) May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal bifuraction, recurrent MIs, etc. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)
- Avoid TT with novel P2Y12 inhibitors, ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,B) however may consider one of these agents if the patient has a stent thrombosis while on TT with clopidogrel. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)

Triple Therapy for Secondary Prevention

- There are conflicting guideline considerations for the use of rivaroxaban for secondary prevention of ACS. Rivaroxaban 2.5mg BID x 1 year may be considered in select patients with a low risk of bleeding, but should not be used in preference to DAPT with a novel P2Y12 inhibitor. ESC'15 (IIb,B), ESC/EACTS'14(IIb,B), CCS'12 (CR/VLQ) Note: this is not an approved indication in Canada & rivaroxaban 2.5mg **is not** commercially available.
- Dabigatran & apixaban are NOT recommended for the sole indication of secondary ACS prevention. CCS'12 (SR/HQ), APPRAISE, REDEEM

CEREBROVASCULAR INDICATIONS

Non-cardoembolic Ischemic Stroke

- If antiplatelet therapy is initiated within 24 hours of minor ischemic stroke/TIA, may consider DAPT x 21 days CSBPR'14 (C), AHA/ASA'14 (IIb,B), CHANCE
- Long-term DAPT started days to years after a stroke/TIA is not recommended due to the increased risk of bleeding and mortality CSBPR'14 (A), AHA/ASA'14 (IIIA), SPS3, MATCH
- See following page for a summary of the trials that formed the basis of the guideline recommendations.

Intracranial Artery Stenosis

- **DAPT (ASA 325mg + clopidogrel 75mg po daily) x 90 days** for patients with recent stroke/TIA (within 30 days) due to severe stenosis (70-99%) of a major intracranial artery, CSBPR 2014 (B), AHA/ASA 2014 (IIb,B) with aggressive risk factor management (e.g. SBP<140mmHg or <130mmHg in DM, LDL-C < 1.81mmol/L, lifestyle modification) SAMMPRIS
- Aggressive medical management with percutaneous transluminal angioplasty and stenting (PTAS) had a NNH of 12/30 days, compared to aggressive medical management alone (rate of stroke 30 days to 1 year: NS); ARI at 30 days was 8.9% and at 3 years was 9% SAMMPRIS

SUMMARY OF ISCHEMIC STROKE DAPT TRIALS (NON-CARDIOEMBOLIC): SECONDARY PREVENTION					
Study	**Regimen ***	**Start of Treatment in Relation to Event**	**DAPT Duration**	**Benefit**	**Harm**
CHANCE (2013, in China)	- Days 1-22: DAPT vs ASA - Days 22-90: clopidogrel vs ASA 75mg daily	within 24 hours	21 days	- ↓ risk of stroke NNT=29/90 days	- NS for bleeding & all-cause mortality
SPS3 (2012)	DAPT vs ASA 325mg	within 2 weeks to 180 days (mean 62 days)	3.4 years	NS for primary endpoint (stroke/MI)	- ↑ risk of all-cause mortality NNH=44 (or 143/year) - ↑ risk of major bleeding NNH=32 (or 100/year) - discontinuation rates NNH=34
FASTER (2007)	DAPT vs ASA 81mg	within 24 hours	90 days	NS for primary endpoint (stroke)	- ↑ risk of symptomatic bleeding NNH=34 & bruising NNH=6
MATCH (2004)	DAPT vs clopidogrel	within 3 months (mean 26 days)	18 months	NS for primary endpoint (stroke, MI, vascular death or rehospitalization for acute ischemic event)	- ↑ risk of bleeding (life-threatening NNH=50, major NNH=100) - GI bleeds were the most common location for life-threatening (53%) & major (58%) bleeds. - Kaplan-Meier curve for intracranial hemorrhage suggests no difference in risk for the first 90 days; ↑ risk with DAPT beyond 90 days.

* All DAPT regimens with clopidogrel 75mg daily

ESTIMATING BLEEDING RISK for DAPT

- **DAPT** score calculator weighs the risk of thrombosis against the risk of bleeding... for patients who were compliant & event-free for 12 months on DAPT. As such, the DAPT score is unable to estimate the risk of bleeding in individuals whom may require less than 1 year of therapy due to bleeding risk.
- The **HASBLED** score was shown to have predictive value (score ≥3 indicated ↑ risk of bleeding) in Japanese patients who were on DAPT post-PCI. However, the HASBLED score has not been validated in this patient population (it has been validated in AF patients).
- The **REACH** registry bleeding risk score was developed & validated (CHARISMA patient population) in outpatients with/without atherothrombosis. Approximately 2/3 of the population had a history of CAD, but the authors did not report how many had undergone revascularization procedures.
- There are limitations to applying the HASBLED or REACH scores to patients who are on DAPT post-ACS; however, these tools may provide additional perspective into bleeding risk factors to consider for choice & duration of therapy.

HASBLED	
HASBLED RISK CRITERIA	**POINTS**
Hypertension (SBP>160mmHg)	1
Abnormal renal or liver function (1 point each)	1 to 2
Stroke (caused by a bleed)	1
Bleeding (hospitalization, ↓ Hgb >20g/L, transfusion)	1
Labile INRs (TTR<60%)	1
Elderly (age >65 years)	1
Drugs (ASA/NSAID) or alcohol (≥8 drinks/week) (1 point each)	1 to 2
TOTAL	
HASBLED score of ≥3 indicates ↑ risk of bleeding	

REACH	
REACH RISK FACTORS	**POINTS**
Age: 55-64 years	2
65-74 years	4
≥75 years	6
Peripheral Artery Disease	1
Congestive Heart Failure	2
Diabetes	1
Hypercholesterolemia	2
Hypertension	2
Smoking: Former	1
Current	2
Antiplatelet agents: ASA	1
Other	2
DAPT	4
Oral Anticoagulants	4
TOTAL	
REACH score >10 indicates ↑ risk of bleeding	

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

Risk Stratification Schemes Used to Predict Warfarin-Associated Hemorrhage

Risk Scheme (publication year)	Risk Factors	Risk Category	Points	Major Bleeding Rates in Validation Cohorts	Comment
ATRIA Risk Score [24] (2011) Adults with nonvalvular, nontransient atrial fibrillation on warfarin & enrolled in Kaiser Permanente of Northern California	Anemia (3 points) Severe renal disease=eGFR<30mL/min (3 points) Age ≥ 75 yrs (2 points) Any prior hemorrhage diagnosis (1 point) Diagnosed Hypertension (1 point)	Low Intermediate High	0-3 4 5-10	0.72%/yr 2.71%/yr 5.99%/yr	Clinical risk factors based on computerized databases Anemia not defined Simple to use Data on ethanol abuse, drug abuse, aspirin, OTCs, & genetic factors not available
RIETE risk scheme [25] (2008) Developed in patients with acute venous thromboembolism	Recent major bleeding (<15 days before thrombotic event) (1.5 points) Creatinine>106 mmol/L (1.5 points) Anemia (1.5 points) Malignancy (1 point) Clinically overt pulmonary embolism (1 point) Age > 75 yrs (1 point)	Low Intermediate High	0 1-4 >4	0.1% at 3 months 2.8% at 3 months 6.2% at 3 months	
HEMORR$_2$HAGES [26] (2006) Developed in hospitalized Medicare patients with atrial fibrillation discharged on warfarin	Hepatic or renal disease (1 point) Ethanol abuse (1 point) Malignancy (1 point) Older age > 75 yrs (1 point) Reduced platelet count or function (1 point) Rebleeding risk (2 points) Hypertension (1 point) Anemia (1 point) Genetic factors (1 point) Excessive fall risk or neuropsychiatric disease (1 point) Stroke (1 point)	Low Intermediate High	0-1 2-3 ≥4	1.9-2.5%/yr 5.3-8.4%/yr 10.4-12.3%/yr	
Shireman et al. [48] (2006) Developed in hospitalized Medicare patients with atrial fibrillation discharged on warfarin	Age ≥ 70 yrs Female Remote bleeding event Alcohol or drug abuse Diabetes mellitus Anemia (Hct<30% during index hospitalization) Antiplatelet drugs (aspirin, clopidogrel, or ticlopidine at discharge) Risk score = 0.49 (age ≥ 70) + 0.32 (female) + 0.58 (remote bleed) + 0.62 (recent bleed) + 0.71 (alcohol/drug abuse) + 0.25 (diabetes) + 0.86 (anemia) + 0.32 (antiplatelet use)	Low Intermediate High	≤ 1.07 1.07-2.18 ≥2.19	0.9% within 90 days 2.0% within 90 days 5.4% within 90 days	Complicated risk score formula
Kearon et al.[49] (2003) Developed in patients with acute venous thromboembolism enrolled in clinical trial. Risk score categories developed & validated by Gage et al.	Age ≥ 65 yrs (1 point) Prior stroke (1 point) Prior peptic ulcer disease (1 point) Prior GI bleeding (1 point) Creatinine > 141 mmol/L (1 point) Anemia or thrombocytopenia (1 point) Liver disease (1 point) Diabetes mellitus (1 point) Antiplatelet therapy (1 point)	Low Intermediate High	0-1 2 3 ≥4	2.5%/yr 6.5%/yr 9.3%/yr 15.3%/yr	
Kuijer et al.[50] (1999) Developed in patients with acute thromboembolism	Age>60 yrs (1.6 points) Female (1.3 points) Malignancy (2.2 points)	Low Intermediate High	0 1-2.9 ≥3	0.6% at 3 months 2% at 3 months 7% at 3 months	
Outpatient Bleeding Index[51] (1998) Developed in patients newly starting warfarin after hospital discharge	Age≥65 yrs (1 point) Prior stroke (1 point) Prior GI bleeding (1 point) Recent MI, diabetes mellitus, hematocrit < 30%, creatinine > 141 mmol/L (1 point if any of the above)	Low Intermediate High	0 1-2 3-4	3%/yr 8%/yr 30%/yr	

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

Bleeding risk ↑ as anti-thrombotic intensity ↑. Antithrombotics listed from lowest to highest bleeding risk: (note: based on extrapolated data from different studies & different populations)
1) ASA 75-325mg daily or clopidogrel 75mg daily alone, 2) ASA 75-325mg daily + clopidogrel, 3) apixaban 5mg BID (but ↑ bleed in ACS pts) or dabigatran 110mg BID, 4) dabigatran 150mg BID, rivaroxaban 20mg daily or warfarin.

ROCKET-AF, ARISTOTLE & RELY: Comparison Tables of Baseline Characteristics (Adapted with permission from M.Louie, PharmD)

Baseline	Age median	Male	HTN	DM	Prior TIA/S	Prior MI	$Time_{spent}$ INR 2-3	$CHADS_2$ (mean)	Trial design	n	Follow up
Dabigatran 110mg bid	71.5	63.3%	78.9%	23.2%	20%	16.5%	64% (mean)	2.1	RCT Open blinded assessment	18k	2 yr
Dabigatran 150mg bid								2.2			
Rivaroxaban 20mg od	73	60%	90.5%	39.5%	55%	17.5%	55% (mean)	3.4	RCT DB DD	14k	1.94 yr
Apixaban 5mg bid	70	65%	87.5%	25%	19.4%	14.2%	62% (mean)	2.1	RCT DB DD	18k	1.8 yr

ROCKET-AF, ARISTOTLE & RELY: Comparison Table of Results

Results	Stroke or systemic embolism	Ischemic stroke	Hemor-rhagic stroke	All cause death	MI/ACS	Major bleed	Intra-cranial bleed	GI bleed	Discontinue rate
Dabigatran 110 vs warf	NSS 3.0vs3.3%	NSS 2.6vs2.4%	0.2vs0.7% RR 0.31	NSS 7.4vs8.1%	NSS 1.4vs1.0%	5.4vs6.6% RR0.81	0.4vs1.4% RR 0.31	NSS 2.2vs2.0%	20.7vs16.6%
Dabigatran 150 vs warf	2.2vs3.3% RR 0.67	1.8vs2.4% RR 0.77	0.2vs0.7% RR 0.26	NSS 7.2vs8.1%	1.5vs1.0% RR 1.40?	NSS 6.2vs6.6%	0.6vs1.4% RR 0.41	3.0vs2.0% RR 1.5	21.2vs16.6%
Rivaroxaban vs warf	3.8vs4.3% RR 0.88_{pp}	NSS 2.1vs2.3%	0.4vs0.7% RR 0.58	NSS 2.9vs3.5&	NSS 1.4vs1.8%	NSS 5.6vs5.4%	0.8vs1.2%RR 0.66	NSS 3.2vs2.2%	23.9vs22.4%
Apixaban vs warf	2.3vs2.9% RR 0.80	NSS 1.8vs1.9%	0.4vs0.9% RR 0.51	6.6vs7.4 RR 0.90	NSS 1.0vs1.1%	3.6vs5.1% RR 0.70	0.6vs1.3% RR 0.42	NSS 1.2vs1.3%	25.3vs27.5%

ROCKET-AF, ARISTOTLE & RELY: Comparision Table of NNT & NNH

NNT NNH	Stroke or systemic embolism	Ischemic stroke	Hemor-rhagic stroke	All cause death	MI/ACS	Major bleed	Dyspesia	GI bleed
Dabigatran 110 vs warf			192			77	17 11.8vs5.8%	
Dabigatran 150 vs warf	88	132	182		239-284?		18 11.3vs5.8%	100
Rivaroxaban vs warf	135_{pp}		333					
Apixaban vs warf	167		238	132		67		

Recommendations 2012 for the prevention of stroke in patients with atrial fibrillation

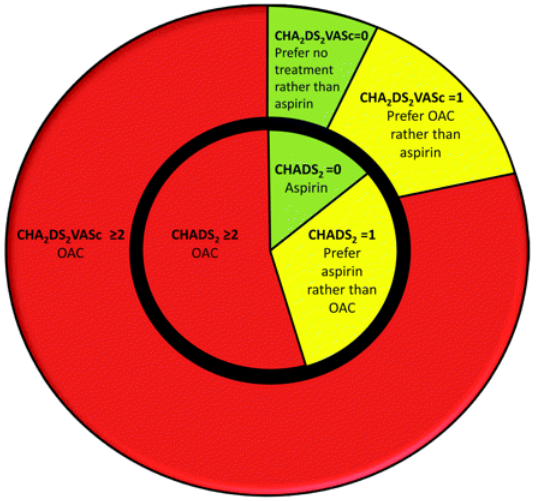

Figure. Recommendations for the prevention of stroke in patients with atrial fibrillation. The inner circle represents treatment recommendations based on the use of the $CHADS_2$ score, as in US guidelines. The outer circle represents recommendations based on the CHA_2DS_2–VASc model, as outlined in the European guidelines, which advise anticoagulant therapy in a larger proportion of patients with atrial fibrillation. Bleeding risk assessment is recommended for patients at intermediate stroke risk (yellow-shaded area), with particular caution and regular patient review for those on warfarin therapy when the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score is ≥3. For patients at very high risk of bleeding (eg, those with malignant hypertension or prior episodes of major bleeding), conservative monitoring without treatment should be considered. OAC indicates oral anticoagulation.

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http://thrombosiscanada.ca/wp-content/uploads/2015/06/DOAC_Monitoring-Checklist-Reference-Tables.pdf

Management of Recent-Onset AF & Flutter in the Emergency Department (ED):[52]

- Rate-control vs. Rhythm Control Treatment (Tx)
- Rate Control Tx = ventricular rate control, oral anticoagulation, no attempt to return the patient to sinus rhythm in the ED, & delayed cardioversion after 4 weeks, if indicated
- Rhythm Control Tx = cardiovert patients to sinus rhythm in ED (pharmacologically or electrically), then discharge home in sinus rhythm

PATIENT RESOURCES

- HealthLink BC: www.healthlinkbc.ca/kb
- Heart & Stroke: http://www.heartandstroke.com
- Medline Plus: www.nlm.nih.gov/medlineplus/
- National Heart Lung & Blood Institute: http://www.nhlbi.nih.gov/health/health-topics/topics/af/
- Thrombosis Interest Group of Canada: www.tigc.org

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FDA Dec/12: Pradaxa (**dabigatran** etexilate mesylate) should **not** be used to prevent stroke or blood clots (major thromboembolic events) in patients with **mechanical heart valves**, also known as mechanical prosthetic heart valves. A clinical trial in Europe (the RE-ALIGN trial) was recently stopped because Pradaxa was more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the Pradaxa users than in the warfarin users.

FDA Mar/15 is warning that serious slowing of the heart rate can occur when the antiarrhythmic drug **amiodarone** is taken together with either the hepatitis C drug Harvoni (ledipasvir/**sofosbuvir**) or with Sovaldi (**sofosbuvir**) taken in combination with another direct acting antiviral for the treatment of hepatitis C infection.

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Brain Natriuretic Peptide (BNP)/amioterminal fragment of propeptide BNP (NT-proBNP) has diagnostic value for both types of HF and is recommended where available, when diagnosis in unclear; may also be used in patients with established HF for prognostic stratification. The use of BNP or NT-BNP in ambulatory HF patients with systolic dysfunction may be considered to decrease HF-related hospitalizations & potentially reduce mortality (benefit uncertain in those >75 years of age).[2, 3]

Table: Brain natriuretic peptide (BNP mainly secreted by ventricular myocardium**) & prohormone of BNP (NT-proBNP** longer half life, affected by renal fx**) assay cut-off points for the diagnosis of HF** [3]

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

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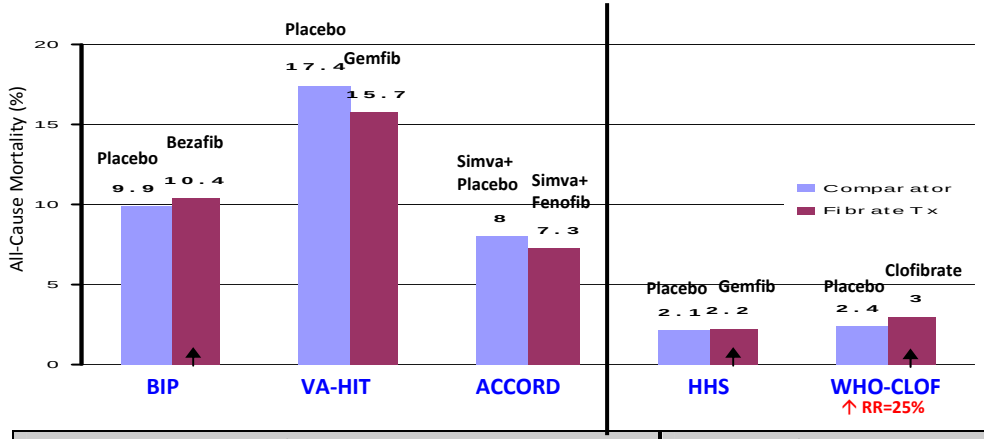
MAJOR LIPID TRIALS: All-Cause Mortality Outcomes (Fibrates and Meta-Analyses)

L Regier, B Jensen, K Krahn © www.RxFiles.ca Nov 2013



	SECONDARY (2°) PREVENTION (hx of CHD)			PRIMARY (1°) PREVENTION (no hx of CHD)	
Study Name	**BIP**	**VA-HIT**	**ACCORD** (1° & 2°)	**HHS**	**WHO-CLOF**
Drug and Dose	**Bezafibrate** 400mg daily [26]	**Gemfibrozil** 600mg BID [27]	**Simvastatin** ≤40mg daily + **Fenofibrate** ≤160mg daily[28] vs simva + placebo	**Gemfibrozil** 600mg BID [29]	**Clofibrate** 1.6g per day [25]
ARR all death	NS	NS	NS	NS	-0.6% (p<0.05)
NNT mortality	NS	NS	NS	NS	NNH=**167**
Duration	6.2 years	5.1 years	4.7 years	5 years	5.3 years
All-Cause Mortality in *English*	No statistical difference (Sub-group: ? better if ↑ HDL)	No statistical difference	No statistical difference	No statistical difference	Treating **167** pts for 5.3 years **caused 1 extra death**
n (♀ + ♂) *Publication yr*	265 + 2825 *2000*	2531 ♂ *1998*	1694 + 3824 *2010*	4081 ♂ *1987*	15745 ♂ *1978*
Patients Studied	Recent history of MI or stable angina; age 45-74	♂ with CHD, low HDL & normal LDL; age <74	Pts with T2DM, A1C ≥7.5%; age 40-79 if CVD, age 55-79 if subclinical CVD with ≥2 risk factors	♂ with high levels of non-HDL cholesterol; age 40-55	♂ with normal or high TC; age 30-59
LDL (avg) initial→end	3.9 → 3.6	2.9; ↔ LDL	Both groups: 2.6→2.1↓19%	4.9→4.5	not available
1° Endpoint Placebo/ Drug	MI or sudden death **NS** 15/ 13.6%	↓ MI / death CHD 21.7/17.3% NNT=23	↓ CV events & death **NS** 11.3/10.5%	↓ MI / death CHD 4.14/2.73% NNT=70	↓ heart disease
Comment	Benefit only in pts with TG >2.3	some benefit in ↑HDL & ↓TGs	? Bad in ♀, ? Good if ↑ TG & ↓ HDL	↑ in non-CHD mortality?	**↑ death**; ↑ liver/GI risk

MORTALITY FIBRATE OUTCOMES (see RCT Graph at left):

No benefit; sometimes harm as with WHO-CLOF.

Other CV outcomes: some benefit with Gemfibrozil, however this drug is not commonly used as it interacts with statins, increasing risk of adverse events.

META-ANALYSES:

SECONDARY PREVENTION - STATINS:

CTT 2010

- Intensive vs standard dose statin
- High CV risk: Death 2.1 vs 2.3% NNT=500/year

ACS Meta 2011

- Intensive statin decreased mortality > moderate statin
  - NNT=77/2 years (CI: 46-225)
- **A-Z:** simvastatin 40-80mg; **Prove-It:** atorvastatin 80mg

PRIMARY PREVENTION - STATINS:

- Tx in low risk 1° not studied
- Tx with high-doses over long term for low risk 1° also not studied

HIGH-RISK 1° META 2013 [30]

- n=56 934 with 1 to 5.3 years of follow-up
- Decreased all cause mortality (RRR=12%) n=48,060
  - NNT=138/ 5yrs
- Decreased CHD (RRR=27%) NNT=56/ 5yrs
- Decreased CVD (RRR=25%) NNT=49/ 5yrs
- Decreased stroke (RRR=22%) NNT=155/ 5yrs
- ↑ Type 2 diabetes (RRI=18%) NNH=198/5yrs

BMJ META 2009 [31]

- n=70 388 for 4.1 years (on average) on statins
- Decreased all cause death (OR=0.88, CI: 0.81-0.96)
  - NNT=173 / 4.1yrs
- Decreased CHD (OR=0.70)
  - NNT=81 / 4.1yrs
- Decreased cerebrovasular outcomes (OR=0.81)

PRIMARY AND SECONDARY PREVENTION - FIBRATES:

FIBRATE META 2010 [32]

- n=45 058 with at least 100 patient years of follow-up
- ns all cause death (RR=1.0; CI: 0.93-1.08)
- ns stroke (RR=1.03; CI 0.91-1.16)

1°=primary **2°**=secondary ♀=women ♂=men **A1C**=glycated hemoglobin **ARR**=% absolute risk reduction **avg**=average **BID**=twice daily **CHD**=coronary heart disease **CI**=confidence interval **CV**=cardiovascular **CVD**=cardiovascular disease **GI**=gastrointestinal **hx**=history **Lipid Values in mmol/L** (**HDL**=high density lipoprotein **LDL**=low density lipoprotein **TC**=total cholesterol **TG**=triglycerides) **MI**=myocardial infarction **n**=number **NNH**= # needed to harm one additional pt **NNT**= # needed to treat to benefit one (e.g. in 4S trial, treating 30patients for 5.4yr would prevent 1 death) **NS**=not statistically significant **OR**=odds ratio **pts**=patients **RR**=relative risk **simva**=simvastatin **T2DM**=type 2 diabetes mellitus **tx**=treatment **yr**=year **NOTE**: This collection of data is from different studies of varying patient groups and with varying methodology; it presents data and demonstrates overall trends but can not be used for direct quantitative comparison.

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

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Shepherd J, Kastelein JJ, et al.; TNT (Treating to New Targets) Investigators. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. J Am Coll Cardiol. 2008 Apr 15;51(15):1448-54. [PubMed - in process] Aggressive lipid lowering with atorvastatin 80 mg was both safe and effective in reducing the excess of cardiovascular events in a high-risk population with CKD and CHD.

Shepherd J, Kastelein JP, Bittner VA, Carmena R, Deedwania PC, Breazna A, Dobson S, Wilson DJ, Zuckerman AL, Wenger NK; Treating to New Targets Steering Committee and Investigators. Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. Mayo Clin Proc. 2008 Aug;83(8):870-9. The absolute risk reduction in patients with diabetes and CKD was substantial, yielding a number needed to treat of 14 to prevent 1 major cardiovascular event over 4.8 years.

Patients with diabetes, stable coronary artery disease, and mild to moderate CKD experience marked reduction in cardiovascular events with intensive lipid lowering, in contrast to previous observations in patients with diabetes and end-stage renal disease.

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(InfoPOEMs: The intensive reduction of low-density lipoprotein (LDL) levels to well below 100 mg/dL (2.5 mmol/L) did not result in a significant reduction in the recurrence of major coronary events or all-cause mortality among patients with stable coronary artery disease. Intensive lowering is associated with an increased risk of discontinuing medication because of adverse events and significant drug costs. Aiming for an LDL of approximately 100 mg/dL (2.5 mmol/L) seems optimal for the majority of patients with stable disease. (LOE = 1b-))

Tikkanen MJ, Holme I, Cater NB, et al.; Incremental DEcrease through Aggressive Lipid Lowering Investigators. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 versus >or=65 years with coronary heart disease (from the Incremental DEcrease through Aggressive Lipid Lowering [IDEAL] study). Am J Cardiol. 2009 Mar 1;103(5):577-82. Epub 2009 Jan 17. Rates of any reported serious adverse event were higher in older patients, but did not differ between the 2 statin groups. In conclusion, except for any CV events in the older group, significant reductions in primary and secondary end points were observed only in patients <65 years of age. The safety of atorvastatin (80 mg) and simvastatin (20 to 40 mg) was similar in patients aged <65 and >65 years with stable coronary disease.

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

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

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

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

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

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

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

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

Patients with **High risk→ ALL pts with CAD,CVD,PAD; most with DIABETES** if age >40, or >30 with >15yr hx of DM **& chronic renal dx** GFR <30ml/min regardless of risk score.

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

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

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

6) Cardiovascular Disease Risk Calculator: **http://bestsciencemedicine.com/chd/calc2.html**

7) AHA'13 CV Risk Calculator **http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp**

8) Risk Calculator: Joint British Societies' Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3). http://www.jbs3risk.com/

9) Systemic Cerebrovascular and Coronary Risk Evaluation (SCORE) risk calculator: http://www.score-canada.ca/

10) Patient friendly risk calculator: http://www.myhealthcheckup.com

For suggested lipid targets, see bottom of page 26.

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

Alternate CVD 5yr Risk Assessment Tables (Adapted From New Zealand Guideline 2009 Group with permission - http://www.nzgg.org.nz/guidelines/0154/090311_CVD_poster_Final.pdf [25]; **also BMJ** [26] **& CMAJ** [27])

See: Updated current FULL version on the **WEB** at

http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-CVD-risk-table.pdf

or

see page 2 in the RxFiles Drug Comparison Chart **BOOK**.

Table: TARGETS Canadian

BLOOD PRESSURE [28]

LIPID [23]

BLOOD GLUCOSE [29, 30]

"Individualize"

Let the target serve the patient, not the patient the target!

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

LIPID LOWERING THERAPY: DYSLIPIDEMIA Comparison Chart

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46. InfoPOEMs July, 2005. More adverse events with rosuvastatin than other statins. Bottom line: The United States Federal Drug Administration (FDA), Health Canada, and European regulators have recently issued advisories to physicians regarding higher doses of rosuvastatin. These data -- though inherently limited by their voluntary nature and the possibility of reporting bias- lend credence to concerns that rosuvastatin is less safe than other statins. It is also the only statin for which we do not have patient-oriented outcome data. (LOE = 2c). *Circulation 2005;111:3051-57.*
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Adams SP, Tsang M,Wright JM. **Lipid-lowering efficacy of atorvastatin**. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD008226. DOI: 10.1002/14651858.CD008226.pub3. This update resulted in no change to the main conclusions of the review but significantly increases the strength of the evidence. Studies show that atorvastatin decreases blood total cholesterol and LDL-cholesterol in a linear dose-related manner over the commonly prescribed dose range.New findings include that atorvastatin is more than three-fold less potent than rosuvastatin, and that the cholesterollowering effects of atorvastatin are greater in females than in males and greater in non-familial than in familial hypercholesterolaemia. This review update does not provide a good estimate of the incidence of harms associated with atorvastatin because included trials were of short duration and adverse effects were not reported in 37% of placebo-controlled trials.

Afilalo J, Duque G, Steele R, et al. **Statins for secondary prevention in elderly patients**. J Am Coll Cardiol. 2008;51:37-45. The posterior median estimate of the number needed to treat to save 1 life was 28 (95% CI 15 to 56). CONCLUSIONS: Statins reduce all-cause mortality in elderly patients and the magnitude of this effect is substantially larger than had been previously estimated. (InfoPOEMs: Treating 28 elderly patients with coronary heart disease (CHD) for 5 years will prevent 1 of them from dying during that period. For every 38 people treated for 5 years, 1 nonfatal myocardial infarction will be prevented; for every 58 patients treated for 5 years, 1 stroke will be prevented. (LOE = 1a))

Afilalo J, Majdan AA, Eisenberg MJ. **Intensive statin** therapy in **acute coronary syndromes** and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart 2007;93(8):914-921. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1727734 9&dopt=Abstract> Intensive statin therapy will decrease overall mortality rates compared with lower doses in patients with a recent history of acute coronary syndrome (ACS) but not in patients with stable coronary heart disease. However, **80 patients must be treated to prevent 1 additional death over 2 years**. Intensive treatment decreases overall hospital admissions for heart failure in both groups and decreases major cardiac events in pts with stable coronary heart disease, but, again, the results are not striking. (LOE = 1a)

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

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found that muscle injury, including rhabdomyolysis, was more common among patients on the 80-mg dose of simvastatin versus a 20-mg dose (0.9% vs. 0.02%). In addition, 11 (0.02%) of the patients in the simvastatin-80-mg group developed rhabdomyolysis compared with no patients in the simvastatin-20-mg group.

FDA June/11: Food and Drug Administration drug safety communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. June 8, 2011. Limit using the 80-mg dose unless the patient has already been taking the drug for 12 months and there is no evidence of myopathy.

FDA Nov/11 notified healthcare professionals the cholesterol-lowering medicine Trilipix (**fenofibric** acid) **may not lower a patient's risk of having a heart attack or stroke**.

FDA Feb/12 has approved important safety label changes for the class of cholesterol-lowering drugs known as statins. The changes include **removal of routine monitoring of liver enzymes** from drug labels. Information about the potential for generally **non-serious and reversible cognitive side effects** and reports of **increased blood sugar** and glycosylated hemoglobin (HbA1c) levels has been added to the statin labels. The **lovastatin** label has been extensively updated with new contraindications and dose limitations when it is taken with certain medicines that can increase the risk for **muscle injury**.

FDA Mar/12 notified healthcare professionals of updates to the prescribing information concerning interactions between **protease inhibitors (HIV & HCV)** and certain statin drugs. Protease inhibitors and statins taken together may raise the blood levels of statins and increase the risk for muscle injury (myopathy/ rhabdomyolysis).

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Triple Therapy (warfarin + DAPT) AHA STEMI'13

- STEMI & AF $CHADS_2$ ≥2, mechanical heart valves, VTE or hypercoagulable disorder;(IC) STEMI & asymptomatic LV mural thrombi (IIa,C) or STEMI & anterior apical akinesis or dyskinesis (IIb, C)
- Minimize duration to limit bleed risk (IC) - VKA x 3 months if LV thrombosis, PCI – DAPT duration based on stent type (see page 16)
- Consider targeting INR 2-2.5 (IIb,C)

g=generic **♥=cardioselective** **A1C**=glycosylated hemoglobin **AA**=aldosterone antagonist **ACEI=**angiotensin converting enzyme inhibitor **ACS**=acute coronary syndrome **AE**=adverse events **AF**=atrial fibrillation **ARB**=angiotensin receptor blocker **ASA**=acetylsalicylic acid **BG**=blood glucose **BID**=twice daily **BMS**=bare metal stent **BP**=blood pressure **CI**=contraindication **CNS**=central nervous system **COX-2**=cyclooxygenase 2 inhibitor **CV**=cardiovascular **CVD**=cardiovascular death **DAPT**=dual antiplatelet therapy **DES**=drug-eluting stent **DI**=drug interaction **DM**=diabetes mellitus **dysfx**=dysfunction **EF**=ejection fraction **FBG**=fasting blood glucose **GI**=gastrointestinal **HDL**=high density lipoprotein **HF**=heart failure **HR**=hazard ratio/heart rate **HRT**=hormone replacement therapy **HS**=bedtime **hx**=history **ISA**=intrinsic sympathetic activity **ICH**=intracranial hemorrhage **IV**=intravenous **K^+**=potassium **LD**=loading dose **LDL**=low density lipoprotein **LFT**=liver function tests **LVD**=left ventricular dysfunction **LVEF**=left ventricular ejection fraction **LVF**=left ventricular function **M**=monitor **MA**=meta-analysis **MACE**=major adverse coronary event **MI**=myocardial infarction **mos**=month **n**=number **NNT/H**=number needed to treat/harm **NS**=non-statistically significant **NSAID**=non-steriodal anti-inflammatory drug **OD**=daily **PAD**=peripheral arterial disease **PCI**=percutaneous coronary intervention **PPBG**=postprandial blood glucose **PPI**=proton pump inihibitor **pts**=patients **RRR**=relative risk reduction **SBP**=systolic blood pressure **SCr**=serum creatinine **STEMI**=ST elevation MI **TIA**=transient ischemic attack **TC**=total cholesterol **TG**=triglycerides **TID**=three times daily **wk**=week(s) **yr**=year(s)

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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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QT Prolongation: Online Extras

What can the pharmacist do to prevent Torsades de Pointes?

1. Watch for initiation of QT-prolonging drugs in patients at high risk of QT-prolongation (e.g. elderly, on other QT-prolongers, on loop diuretics, diagnosis of heart failure, female). Contact physician for ECG monitoring when risk appears high. Risk can be calculated using the Tisdale Risk Score, which does not require a baseline ECG (useful for community pharmacists).
2. Watch for drug interactions - which can cause drugs normally at low-risk of causing QT-prolongation to become high risk.
3. Be extra cautious in patients with chronic kidney disease - these patients are more likely to have electrolyte disturbances, and may be unable to properly excrete some drugs.

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FDA Nov/10 is requesting that manufacturers of the painkiller **propoxyphene** pull the drug from the market because of concerns over cardiotoxicity. (Propoxyphene is marketed alone as Darvon & combined with acetaminophen as Darvocet.) The agency's request is based on data showing that, even when taken at therapeutic doses, the drug can lead to potentially dangerous changes in the heart's electrical activity, including prolonged PR & QT intervals & widened QRS complex. FDA advises clinicians to stop prescribing propoxyphene and to ask current users to discontinue the drug. FDA's MedWatch alert
FDA Dec/10 The injectable form of dolasetron mesylate (Anzemet) should not be used to prevent nausea or vomiting related to chemotherapy because the drug increases the risk for torsade de pointes, the FDA announced on Friday. The FDA recommends against using Anzemet injections in patients with congenital long-QT syndrome. The warning does not apply to Anzemet tablets because the risks for developing an abnormal heart rhythm are not as high as with the injections. FDA MedWatch alert (Free)
FDA July/11 FDA has added a warning to the label of the atypical antipsychotic quetiapine (Seroquel) cautioning about potential increases in the QT interval. Postmarketing cases of QT prolongation have been reported in some 17 patients, according to the *New York Times.* These patients had overdosed on quetiapine, had other illnesses, or were taking other medications that can cause electrolyte imbalance or QT prolongation.
FDA Aug/11 The antidepressant citalopram (marketed as Celexa) should not be prescribed at doses above 40 mg/day because higher dosages can cause arrhythmias, the FDA has warned.
FDA Sep/11 The U.S. Food and Drug Administration (FDA) is informing the public of an ongoing safety review of the anti-nausea drug Zofran (ondansetron, ondansetron hydrochloride and their generics). Ondansetron may increase the risk of developing abnormal changes(QT prolongation & torsades) in the electrical activity of the heart.
FDA July/12 Alerting clinicians that a single 32-mg intravenous dose of ondansetron (Zofran and generics) may lead to QT interval prolongation, which in turn may put patients at risk for torsades de pointes.
FDA Dec/12 is working with the manufacturers of all **32 mg dose Ondansetron** Injectable Products (brand and generic) to voluntarily recall them from the market due to QT serious cardiac toxicity.
FDA Mar/13 is warning the public that **azithromycin (Zithromax or Zmax)** can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing **QT interval prolongation**, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias.
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Health Canada Aug/10 **Droperidol** Injection USP is associated with severe arrhythmia (eg. QT) and the Canadian Monograph of this product has been updated to reflect this risk.
Health Canada Nov/10 **Darvon-N (dextropropoxyphene) - Recall and Withdrawal in Canada** - Paladin Labs Inc. Paladin Labs Inc. in collaboration with Health Canada would like to inform healthcare professionals of the voluntary recall and withdrawal of the opioid analgesic Darvon-N (dextropropoxyphene) in Canada. (widen the QRS complex, prolong the QT interval and therefore increase the risk of serious abnormal heart rhythms.)
Health Canada Feb/12 has recently approved vandetanib (CAPRELSA) to treat medullary thyroid cancer in adult patients where either the tumour cannot be removed by surgery or it has spread from the thyroid gland to other parts of the body. CAPRELSA can cause serious QT heart rhythm changes which may result in sudden death, if left untreated.
Health Canada Mar/12: **Domperidone** should be used at the lowest possible dose. The risk of serious ventricular arrhythmias and sudden cardiac death may be higher in patients taking daily doses greater than 30 mg, and in patients over 60 years old.
Health Canada Oct/12: Ondansetron can cause a dose-dependent prolongation of the electrocardiographic-corrected QT interval (QTc), which can lead to Torsade de Pointes, a potentially life-threatening heart rhythm abnormality. The new maximum recommended single intravenous (IV) dose of ZOFRAN ® is 16 mg infused over 15 minutes.
Health Canada Oct/13 has completed a safety review of the drug Sensipar (**cinacalcet**) that identified a possible link between the drug and abnormal heart rhythm (QT) associated with low blood calcium.
Health Canada Feb/14: **TELZIR** (fosamprenavir) should not be used with the antiarrhythmic drugs amiodarone, lidocaine (systemic), or quinidine, as this may cause serious and/or life-threatening reactions such as abnormal heart rhythm (arrhythmias). In addition, Telzir should not be used with delavirdine, another antiviral drug to treat HIV, because it may reduce the effectiveness of delavirdine.
Health Canada Mar/14: REMERON / REMERON RD (**mirtazapine**) – Abnormal Heart Rhythm - Merck Canada Inc. Cases of abnormal heart rhythm (eg. QT prolongation) have been reported with the antidepressant REMERON / REMERON RD (mirtazapine) mainly with drug overdose or when taking other drugs known to cause heart rhythm problems. The product information has been updated.
Health Canada Jun/14 Zofran (ondansetron) – Dosage and Administration of Intravenous Ondansetron in Geriatrics (>65 years of age) – GlaxoSmithKline Inc. Zofran (ondansetron) is associated with a risk of QT interval prolongation, which is expected to be greater with faster rate of infusion and larger doses for the intravenous administration. New dosing restrictions are recommended to mitigate this risk in elderly patients. The dosing restrictions for geriatrics are summarized below: In patients ≥75 years of age, the initial IV dose must not exceed 8 mg. In patients <75 years of age, the initial IV dose must not exceed 16 mg. Subsequent IV doses must not exceed 8 mg and may be given 4 and 8 hour after the initial dose. All IV doses must be diluted in 50–100 mL of saline or other compatible fluid. All IV doses must be infused over no less than 15 minutes.
Health Canada Jan/15 **Domperidone** Maleate - Association with Serious Abnormal Heart Rhythms and Sudden Death (Cardiac Arrest). Domperidone may be associated with a small increased risk of serious abnormal heart rhythms and sudden death. Prescribing information changes include a new recommended maximum daily dose, new restrictions of use and stronger warnings.
Health Canada June/16: **ATARAX (hydroxyzine)** is an antihistamine that can increase the risk of QT prolongation (QTP) and torsade de pointes (TdP) which may lead to dizziness, palpitations, syncope, seizures, and sudden cardiac death.
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Krantz MJ, Martin J, et al. QTc Interval Screening in **Methadone** Treatment. Ann Intern Med. 2009 Jan 19. [Epub ahead print] Recommendation 1 (Disclosure): Clinicians should inform patients of arrhythmia risk when they prescribe methadone. Recommendation 2 (Clinical History): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope. Recommendation 3 (Screening): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures. Recommendation 4 (Risk Stratification): If the QTc interval is greater than 450 ms but less than 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy. Recommendation 5 (Drug Interactions): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone.
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MHRA Apr/16 **Apomorphine with domperidone**: minimising risk of cardiac side effects. Patients receiving apomorphine and domperidone require an assessment of cardiac risk factors and ECG monitoring to reduce the risk of serious arrhythmia related to QT-prolongation. https://www.gov.uk/drug-safety-update/apomorphine-with-domperidone-minimising-risk-of-cardiac-side-effects
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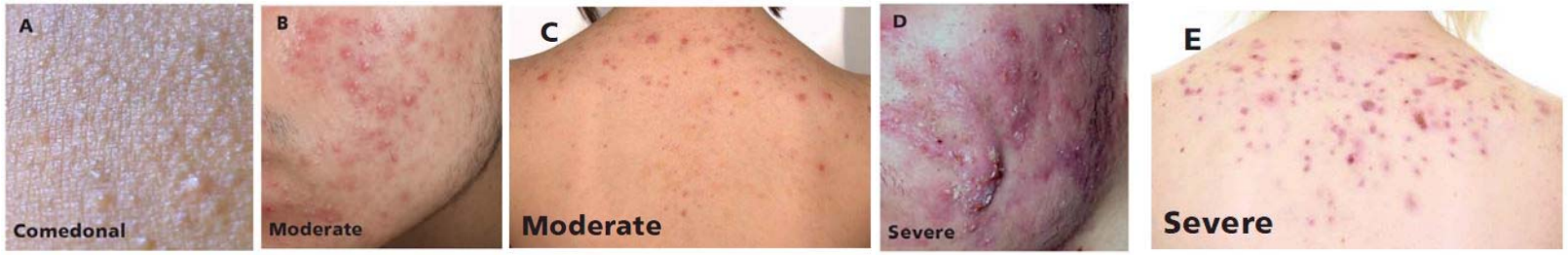
ACNE: Online Extras 💻

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% PL	**Common:** less irritating than BPO, 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 BPO). DI: ↑ **skin irritation or drying effect**: Abrasive or medicated soaps or cleansers; Acne preps (e.g., BPO, Resorcinol, Sulfur, Tretinoin); alcohol-containing topicals (After-shave lotions, perfumed toiletries, cosmetics/soaps with a strong drying effect); Isotretinoin DAILY or BID, 3-6% is keratolytic , OTC: $**10-15**

Tetracycline Lactation Ratings: a more conservative approach was used for acne (i.e. safe/likely safe changed to caution) as lactation data is only available for short-term courses versus the 8-12 weeks of therapy for acne.

Determining severity of acne (examples):



Reference: Canadian 2015 Acne Guidelines (Asai et al)

Benzoyl Peroxide Products:

Adasept B.P 5% acne gel; Clean & Clear Continuous Control = BPO 5% lotion = WATER based; CLEAN & CLEAR PERSA-GEL = BPO 5% gel = WATER BASED; OVERNIGHT ACNE CONTROL LOTION = BPO 3% lotion = WATER based; CLEAR ACNE TREATMENT CREAM = BPO 5% cream = WATER based; CLEAR PORE ON-THE SPOT ACNE TREATMENT, VANISHING = BPO 2.5% lotion; CLEAR SKIN TREATMENT REPAIRING LOTION = BPO 3.7% lotion; CLEAR ZONE ACNE SYSTEM SKIN PURIFYING MOISTURIZER = BPO 3.5% lotion; CLEARASIL STAYCLEAR ACNE TREATMENT CREAM BPO PLUS - VANISHING = BPO 5% cream; CLEARZ - IT = BPO 5% lotion; CLINIQUE ACNE SOLUTIONS CLEARING MOISTURIZER = BPO 2.5% lotion; CLINIQUE ACNE SOLUTIONS EMERGENCY LOTION = BPO 5% lotion; DERMACNE LOTION TRAITMENT 5% = BPO 5% lotion; DERMALOGICA SPECIAL CLEARING BOOSTER = BPO 5% lotion; LIFE ACNE MEDICATION = BPO 5% gel; MEDICATED ACNE GEL 5% = BPO 5% gel; NATURE'S CURE ACNE TREATMENT = BPO 5% cream; OBAGI CLENZIDERM ACNE GEL = BPO 5% gel; OXY 5 COVER UP FORMULA = BPO 5% cream; OXY 5 SENSITIVE SKIN VANISHING LOTION = BPO 2.5% lotion; OXY 5 VANISHING FORMULA = BPO 5% lotion; OXYDERM LOT 20% = BPO 20% lotion - Schedule F; OXYDERM LOTION 10% = BPO 10% lotion - Schedule F; OXYDERM LOTION 5% = BPO 5% lotion; PURE PEFECTION CLASSIC REPLENISHING CLEANSER = BPO 2.5% cream; PURE PERFECTION CLASSIC RENEWING CREME = BPO 2.5% cream; RODAN & FIELDS/PROACTIV SOLUTION:RENEWING CLEANSER = BPO 2.5% lotion; RODAN & FIELDS/PROACTIV SOLUTION:REPAIRING LOTION = BPO 2.5% lotion; SPECTRO ACNECARE DEEP PORE VANISHING LOTION = BPO 5% lotion; SPECTRO ACNECARE VANISHING LOTION FOR SENSITIVE SKIN = BPO 2.5% lotion; CLEAR ZONE ACNE SYSTEM SKIN PURIFYING WASH = BPO 3.5% liquid (WASH); PANOXYL CREAMY WASH 4% = BPO 4% (WASH)

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Additional info:

AADA Nov/10 American Academy of Dermatology Association (AADA) updated its position statement on the use of isotretinoin. http://www.aad.org/forms/policies/Uploads/PS/PS-Isotretinoin.pdf
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Health Canada Sept/07 is advising consumers not to use BuXie PaiDu XiaoDou Su is used as an acne treatment and was found to contain the prescription drug rifampicin (rifampin).
Health Canada Feb/10 Accutane has been associated with cases of severe skin reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme).
Health Canada Dec/15 is advising Canadians that the use of over-the-counter acne products applied to the skin containing benzoyl peroxide or salicylic acid may cause rare but serious allergic reactions.
Health Canada Sep/16 reinforces the importance of preventing pregnancy while taking the acne drug isotretinoin to avoid birth defects.
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November 8, 2006 -- QLT Inc. announced positive results of a Phase IV clinical trial of Aczone(TM) dapsone in more than 50 patients with G6PD deficiency that was performed to meet a post-approval commitment requested by the FDA. Mar/08 FDA removes G6PD screening & labeling requirements from the label. June 6/08 /CNW/ - QLT Inc. (NASDAQ: QLTI; TSX: QLT) announced today that Health Canada has completed its review of QLT USA, Inc.'s labeling supplement (SNDS) for Aczone(R) and has removed the glucose-6-phosphate dehydrogenase (G6PD) screening and blood monitoring requirements.
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Web sites:
American Academy of Dermatology www.skincarephysicians.com/acnenet/FAQ.html www.aad.org/public/publications/pamphlets/common_acne.html?media=print
Medline Plus www.nlm.nih.gov/medlineplus/tutorials/acne/htm/index.htm
National Institute of Arthritis and Musculoskeletal and Skin Diseases www.niams.nih.gov/Health_Info/Acne/default.asp

Online Extras for TOPICAL CORTICOSTEROIDS Comparison Chart:

Eczema in Children – NICE guideline approach http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11636

Tx Escalator ⇧			
			Systemic treatment
			Phototherapy
		Bandages	Bandages
		Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Mild potency corticosteroids	Mild potency corticosteroids	Mild potency corticosteroids
	emolliants	emolliants	emolliants
	Mild	**Moderate**	**Severe**
	Atopic ezema severity		

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Relative Absorption	
Forearm	***1.0***
Sole	***0.14***
Back	***1.7***
Scalp	***3.5***
Forehead	***6.0***
Cheek	***13.0***
Scrotum	***42.0***

Cushing Syndrome (pituitary-adrenal axis suppression)**:**
- 50g of 0.05% clobetasol/wk or
- 500g of 1% hydrocortisone/wk
- in infants: a little as 1g/day x several days may ↓ HPA

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Useful tables from Canadian Glaucoma Guidelines 2009:

Table 19—Staging each eye for glaucoma damage

Suspect	One or two of the following: IOP >21 mm Hg; suspicious disc or cup to disc (C/D) asymmetry of >0.2; suspicious 24-2 (or similar) VF defect
Early	Early glaucomatous disc features (e.g. C/D* <0.65) and (or) mild VF defect not within 10° of fixation (e.g. MD better than –6 dB on HVF 24-2)
Moderate	Moderate glaucomatous disc features (e.g. vertical C/D* 0.7–0.85) and (or) moderate VF defect not within 10° of fixation (e.g. MD from –6 to –12 dB on HVF 24-2)
Advanced	Advanced glaucomatous disc features (e.g. C/D* >0.9) and (or) VF defect within 10° of fixation† (e.g. MD worse than –12 dB on HVF 24-2)

Adapted from Damji et al.[160]

Please refer to text in order to decide whether a nerve exhibits characteristics of glaucomatous damage.
*Refers to vertical C/D ratio in an average size nerve. If the nerve is small, then a smaller C/D ratio may still be significant; conversely, a large
nerve may have a large vertical C/D ratio and still be within normal limits.
†Also consider baseline 10-2 VF (or similar)
Note: MD, mean deviation; HVF, Humphrey Visual Field Analyzer.

Table 20—Suggested upper limit of initial target IOP for each eye

Stage	Suggested upper limit of target IOP. Modify based on longevity, QOL and risk factors for progression	Evidence
Suspect in whom a clinical decision is made to treat	24 mm Hg with at least 20% reduction from baseline	OHTS,[47] EGPS[325]
Early	20 mm Hg with at least 25% reduction from baseline	EMGTS,[48] CIGTS[326]
Moderate	17 mm Hg with at least 30% reduction from baseline	CNTGS,[12] AGIS[11]
Advanced	14 mm Hg with at least 30% reduction from baseline	AGIS,[11] Odberg[327]

Adapted from Damji et al.[160]

Note: Target IOP may need to be adjusted during the course of follow-up. Extremes of CCT may be helpful in the setting of target IOP. For example, if the cornea is very thin, this may encourage a more aggressive approach with more frequent follow-up.[161]

Table 21—Advantages and disadvantages of single and combined cataract and glaucoma procedures

Procedure	Advantages	Disadvantages
Phacoemulsification alone	Quick procedure with more rapid visual recovery	Postoperative IOP spike is a potential risk, particularly in patients with advanced VF loss
	Improved vision, which benefits QOL	Not regarded as a consistent or powerful means of lowering IOP
	May lower IOP a small amount in some patients	IOP should be watched closely in both the early postoperative period and later
Trabeculectomy alone	Quicker than combined procedure	Will not improve vision
	May achieve superior long-term IOP lowering than combined procedure or cataract alone	May cause or worsen cataract
Combined procedure	Minimizes anesthetic risk by combining 2 procedures in 1	May not be as effective at long-term IOP control as trabeculectomy alone
	Convenience to patient with 1 trip to operating room rather than 2	Increased risk of complications with 2 procedures rather than 1
	Cost savings	Slower visual recovery than doing cataract alone
	May blunt potentially damaging postoperative IOP spikes in patients with advanced VF loss	
	Opportunity to improve IOP control and improve vision at the same time with enhanced QOL	

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NICE April 2009 -- The National Institute for Health and Clinical Excellence (NICE) and the National Clinical Guideline Centre will issue a guideline to improve the diagnosis and management of chronic open angle glaucoma (COAG) and ocular hypertension (OHT). People who have COAG, who are suspected of having COAG or who have OHT should be offered a suite of tests including assessments of the eye pressure, the thickness of the cornea, the drainage area in the eye and field of vision, and an assessment and image of the appearance of the optic nerve heads. People at risk of developing glaucoma should be monitored regularly using tests similar to those used to diagnose glaucoma. The frequency of these tests will depend on how high the risk is of developing glaucoma. Clarity on monitoring intervals for testing people who have glaucoma or are at risk of developing it, and recommendations on follow-up of patients who turn out not to have glaucoma after a period of careful monitoring. Treatment with prostaglandins or beta-blockers to reduce high eye pressure in people with glaucoma or those at risk of the condition. After previous treatment switches, earlier consideration of alternative treatments for worsening glaucoma, such as surgery or laser treatment to avoid disease progression. The guidance will be available at http://www.nice.org.uk/CG85

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    Peña-Rosas JP, De-Regil LM, Dowswell T,Viteri FE. **Daily oral iron supplementation during pregnancy**. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD004736.DOI: 10.1002/14651858.CD004736.pub4. Prenatal supplementation with daily iron are effective to reduce the risk of low birthweight, and to prevent maternal anaemia and iron deficiency in pregnancy. Associated maternal side effects and particularly high Hb concentrations during pregnancy at currently used doses suggest the need to update recommendations on doses and regimens for routine iron supplementation.
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(dos Santos RV, Magerl M, Mlynek A, Lima HC. Suppression of histamine- and allergen-induced skin reactions: comparison of first- and second-generation antihistamines. Ann Allergy Asthma Immunol. 2009 Jun;102(6):495-9. These results indicate that hydroxyzine is more effective than nsAHs when given as recommended in suppressing histamine-induced or allergic skin reactions. Our results suggest that higher doses of nsAHs than those currently recommended are required for the treatment of skin responses to obtain antihistaminic and antiallergic effects that are equivalent to those of fgAHs.)

117. FDA Warns Against Abuse of **Dextromethorphan** May/05 http://origin.www.fda.gov/bbs/topics/ANSWERS/2005/ANS01360.html (Detromethorphan abuse, Pharmacist's Letter Feb 2007.)
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121. Drugs for **acne**, rosacea and psoriasis. Treat Guidel Med Lett. 2005 Jul;3(35):49-56.
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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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184. May/10 Novartis Consumer Health Canada Inc., in consultation with Health Canada, would like to bring to your attention important safety information concerning the differences between our product Maalox Multi Action liquid and other Maalox liquid products. Maalox Multi Action contains bismuth subsalicylate, which is chemically related to acetylsalicylic acid (ASA) and can lead to similar adverse effects, such as bleeding. Other Maalox liquid products are mineral based, contain different ingredients, and are indicated for different symptoms. However, due to the similarity in the name, label and package between **Maalox Multi Action** and other Maalox liquid products, they have the potential to be confused and result in medication incidents.
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191. FDA Oct/12 is warning healthcare professionals & the public that accidental ingestion by children of **over-the-counter eye drops** used to relieve redness and nasal decongestant sprays can result in serious and life-threatening adverse events. The eye drops and nasal sprays that have been involved in the cases of accidental ingestion contain the active ingredients **tetrahydrozoline, oxymetazoline, or naphazoline**.
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195. Health Canada is releasing an updated Labelling Standard for **acetylsalicylic acid (ASA) products for use in adults and children aged 12 years and older**.
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Additional Pediatric Dosing Information for Physicians & Pharmacists (from 2008-2009 Formulary – The Hospital for Sick Children (Toronto, Canada)

Aluminum & Magnesium Hydroxide	infant	2.5-5ml po q1-2h
	child	5-15ml po after meals & qhs
Bisacodyl		0.3mg/kg/dose po 6-12h before desired effect
Dextromethorphan		1mg/kg/day (÷ q6-8h)
Dimenhydrinate		5mg/kg/day po/IV/IM/pr (÷ q6h)
Diphenhydramine		5mg/kg/day po/IV/IM (÷ q6h)
Docusate Sodium		5mg/kg/day po (÷ q6-8h or single daily dose)
Iron – Treatment		6mg Fe++/kg/day po OD (or ÷ TID)
Iron – Prophylaxis		0.5-2mg Fe++/kg/day given OD (or ÷BID-TID)
Lactulose - for Constipation		5-10ml/day po OD (double daily dose till stool produced)
Mineral Oil (Heavy)		1ml/kg/dose po HS (Avoid in <1 yr old)
Magnesium Hydroxide (MgOH) 80mg/ml (33mg elemental Magnesium/ml)		20-40 mg elemental Magnesium/kg/day po (÷ TID) –for treatment of hypomagnesemia
Polyethylene Glycol 3350 (Lax-A-Day)		Initial up to 1-1.5 g/kg/day x ≤3 days, then 0.4-1g/kg/day po (Max 17g/day)
Pseudoephedrine:	<2yrs	4mg/kg/day (÷ q6h prn)
Ranitidine – Treatment		5-8mg/kg/day po (÷ q8-12h) x8 weeks
Ranitidine – Maintenance		2.5-5mg/kg/day (given OD or divided bid)
Senna Syrup	2-5yrs	3-5ml/dose qhs
	6-12yrs	5-10ml/dose qhs
Senna Tablet	6-12yrs	1-2 tablets/dose po qhs
Sorbitol Syrup 70%		1.5-2ml/kg/dose po (Max 150ml/dose)

Taste of some medications – MgOH, docusate, lactulose - may be masked by giving with milk (chocolate mix), juice or infant formula.

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Bodybuilding.com and FDA Nov/09 notified healthcare professionals and patients of a nationwide and international recall of all lots and expiration dates of 65 dietary supplement products that were sold through the Company's website, www.bodybuilding.com. FDA believes that the recalled products contain the following ingredients that are currently classified, or the FDA believes should be classified, as steroids: **"Superdrol," "Madol," "Tren," "Androstenedione," and/or "Turinabol."** Acute liver injury is known to be a possible harmful effect of using steroid-containing products. In addition, steroids may cause other serious long-term adverse health consequences in men, women, and children. These include shrinkage of the testes and male infertility, masculinization of women, breast enlargement in males, short stature in children, a higher predilection to misuse other drugs and alcohol, adverse effects on blood lipid levels, and increased risk of heart attack, stroke, and death.
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FDA May/09 notified healthcare professionals that it will require two prescription topical testosterone gel products, AndroGel 1% and Testim 1%, to include a boxed warning on the products' labels after receiving reports of adverse effects in **children** who were **inadvertently exposed** to testosterone through contact with another person being treated with these products. Of the fully reviewed cases, adverse events reported in these **children** included inappropriate enlargement of the genitalia (penis or clitoris), premature development of pubic hair, advanced bone age, increased libido and aggressive behavior.
FDA Aug/09 not to use body-building products marketed as containing **steroids or steroid-like substances** such as TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, and TT-40-Xtreme..
FDA Nov/09 & IDS Sports notified consumers that five of the IDS's dietary supplement products (**Bromodrol, Dual Action Grow Tabs, Grow Tabs, Mass Tabs, and Ripped Tabs TR**) contain the following undeclared substances, which FDA considers to be steroids: "Madol," "Turinabol," "Superdrol," &/or "Androstenedione."
FDA Dec/09 for **S-DROL**: a voluntary recall by the manufacturer of one lot (lot# 810481, expiry date 01/2012) of S-DROL after FDA testing found it to contain undeclared desoxymethyltestosterone.
FDA Dec/09 warned consumers to stop using bodybuilding products manufactured by American Cellular Labs after they were found to contain unauthorized synthetic steroids in **TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, TT-40-Xtreme.**
FDA Jan/10 & **MuscleMaster(dot)com**, Inc. notified consumers and healthcare professionals of the voluntary nationwide recall of all lots and expiration dates of the seventeen dietary supplements listed in the firm press release, sold between June 1, 2009 and November 17, 2009. FDA informed MuscleMaster(dot)com that it believes that the recalled products contain ingredients that are **steroids**.
FDA Oct/11 notified the manufacturer that lab analyses found that the product; **Uprizing 2.0** , sold as a testosterone booster, contains **superdrol**, a synthetic steroid, making it an unapproved new drug.
FDA Aug/13 Purity First Health Products is recalling two lots of **Healthy Life Chemistry B-50** (100 capsules), one lot of **Healthy Life Chemistry Multi-Mineral** (200 capsules) and all lot numbers for **Healthy Life Chemistry Vitamin C** (200 capsules). The B-50 capsules were found on testing by FDA to contain Methasterone (a schedule III controlled substance) and Dimethazine. Testing of the Multi-Mineral and Vitamin C capsules appear to indicate the presence of Dimethyltestosterone.
FDA Dec/13 is advising consumers to immediately stop using a product called **Mass Destruction**, marketed as a dietary supplement for muscle growth. The product is labeled to contain at least one synthetic anabolic steroid and has been linked to at least one reported serious illness.
FDA Feb/14 is investigating the **risk of stroke, heart attack, and death in men taking FDA-approved testosterone products**. We have been monitoring this risk and decided to reassess this safety issue based on the recent publication of two separate studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy.
FDA Jun/14 is requiring manufacturers of testosterone products to include a general warning in the drug **labeling of all approved testosterone products about the risk of blood clots in the veins**.
FDA Mar/15 is requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. FDA is also requiring these manufacturers to add information to the labeling about a **possible increased risk of heart attacks and strokes** in patients taking testosterone. FDA cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone.
FDA Oct/16 approved class-wide labeling changes for all prescription testosterone products, adding a new Warning and updating the **Abuse and Dependence** section to include new safety information from published literature and case reports regarding the risks associated with abuse and dependence of **testosterone and other AAS (Anabolic Androgenic Steroids).** Abuse of testosterone, usually at doses higher than those typically prescribed and usually in conjunction with other AAS, is associated with serious safety risks affecting the heart, brain, liver, mental health, and endocrine system. Reported serious adverse outcomes include **heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, and male infertility. Individuals abusing high doses of testosterone have also reported withdrawal symptoms, such as depression, fatigue, irritability, loss of appetite, decreased libido, and insomnia.** The new Warning will alert prescribers to the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health that have been reported in association with testosterone/AAS abuse.
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Health Canada July/07 is warning Canadians not to use the dietary supplement **MdMt**, or any other supplements containing the synthetic steroids methyl-1-testosterone or methyldienolone that are obtained without a prescription, due to potentially serious health risks including reduced fertility and liver disorders.
Health Canada Jul/14 is advising patients and healthcare professionals of new safety information regarding testosterone hormone replacement products and a risk of serious and **possibly life-threatening cardiovascular** (heart and blood vessel) problems.
Health Canada Jul/16 is informing Canadians that two unauthorized health products were seized from Next Level Fitness in Richmond and in Surrey,BC. The products **TRT** (**Testosterone Booster**) and **Freak'n Test** (**Testosterone Enhancer**) were labelled to contain a prescription drug substance (L-dopa) that may pose serious health risks to Canadians.
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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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Death/MACE

1. Drug manufacturers must establish CV safety (one-sided upper boundary of 95% CI ≤ 1.3) vs comparator (typically placebo) in a RCT for all new agents in ↑ CV risk patients.[1] FDA
2. Metformin vs conventional diet; obese >120% IBW & small sample n=753; **↓ all-cause mortality NNT 14/10.7 yr**, and **↓ MI NNT=14/10.7 yr**.[2] UKPDS-34 10 yr observational follow-up **↓ all-cause mortality NNT=14/~20 yr**, and **↓ MI NNT=16/~20 yr**.[3] UKPDS-80
3. Intensive HbA1c target (included gliclazide) vs standard HbA1c target; MACE 10% vs 10.6% p=NS, all-cause mortality 8.9% vs 9.6% p=NS.[4] ADVANCE
4. Intensive therapy (chlorpropamide, glipizide[USA], glibenclamide or insulin) vs conventional diet; all-cause mortality 17.9% vs 18.9% p=NS, MI 14.7% vs 17.4% p=NS, and stroke 5.6% vs 5% p=NS.[5] UKPDS-33 10 yr observational follow-up **↓ all-cause mortality NNT=29/~20 yr**, and **↓ MI NNT=36/~20 yr**.[3] UKPDS-80
5. SU (2nd or 3rd generation) vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, I^2=0%), CV mortality OR 1.12 (0.87-1.42, I^2=12%), MI OR 0.92 (0.76-1.12, I^2=NR), stroke OR 1.16 (0.81-1.66, I^2=NR).[6]
6. Metformin vs glipizide; Chinese, small sample n=304, & medically undertreated 100% CAD, but ≤10% taking ACEi; Metformin **↓ MACE NNT=10/5 yr**.[7] SPREAD-DIMCAD
7. Pioglitazone vs placebo; T2DM & high CV risk; **↓ MACE NNT=50/2.9 yr**,[8] PROACTIVE insulin resistance & recent TIA/stroke; **↓MACE NNT=36/4.8 yr**.[9] IRIS
8. Rosiglitazone vs placebo; **↑ MACE** 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mons early,[10] DREAM ↑ MI NNH=167 & CV death 0.87% vs 0.39% p=0.06.[10] Rosiglitazone vs glyburide **↑ MACE NNH 63/4 yr**.[12] ADOPT
9. Acarbose vs placebo; impaired glucose tolerance; **↓ MACE NNT 40/3.3 yr**.[13] STOP-NIDDM
10. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, **non-inferior** (p<0.001), but not superior (p=0.99).[14] SAVOR-TIMI 53 Alogliptin vs placebo; MACE 11.3% vs 11.8%, **non-inferior** (p<0.001), but not superior (p=0.32).[15] EXAMINE Sitaglipin MACE vs placebo; MACE 9.6% vs 9.6%, **non-inferior** (p<0.001), but not superior (p=0.65).[16] TECOS Meta-analysis(SAVOR-TIMI 53, EXAMINE, TECOS) MACE RR 0.99 (95% CI, 0.93-1.06, I^2=0%).[17]
11. Linagliptin CV trial ongoing, estimated completed 2018.[18] CARMELINA
12. Liraglutide vs placebo; **MACE** 13.0% vs 14.9%, **non-inferior** (p<0.001), **AND superior** (p=0.01, **NNT=53/3.8 yr**), but results neutral in North America subgroup; **↓ CV death NNT=77/3.8 yr** and **↓ all-cause mortality NNT 72/3.8 yr**.[19] LEADER Semaglutide vs placebo; MACE **non-inferior AND superior**; nephropathy was better; however, retinopathy complications were worse).[20] SUSTAIN6
13. Lixisenatide vs placebo; MACE 13.4% vs 13.2%, **non-inferior** (p<0.001), but not superior (p=0.81).[21] ELIXA
14. Exenatide CV trial ongoing, estimated completed 2018.[22] EXSCEL Dulaglutide[USA] CV trial ongoing, estimated completed 2018.[23] REWIND Aliglutide CV trial ongoing, estimated completed 2019.[24] HARMONY
15. Empagliflozin vs placebo; **MACE** 10.5% vs 12.1%, **non-inferior** (p<0.001), **AND superior** (p=0.04, **NNT=63/3.1 yr**); **↓ CV death NNT=46/3.1 yr** and **↓ all-cause mortality NNT 39/3.1 yr**.[25] EMPA-REG
16. Canagliflozin CV trial ongoing, estimated completed 2017; ↑ MACE in 1st 30 days (n=13 vs n=1, p=NS, non-dose related); ↓ MACE (NS) after 30 days (HR 0.89, 95% CI 0.64, 1.25); numeric imbalance not present in non-CANVAS trials.[26,27] CANVAS Dapagliflozin CV trial ongoing, estimated completed 2019.[28] DECLARE Ertugliflozin CV trial ongoing, estimated completed 2019.[29] VERTIS CV
17. Basal insulin (glargine) vs standard care; all-cause mortality 15.2% vs 15.4% p=NS, MI 5.4% vs 5.2% p=NS, and stroke 5.3 vs 5.1% p=NS.[30] ORIGIN
18. Basal insulin vs basal/bolus insulin; small sample n=152; CV mortality 3.8% vs 6.7% p=NS, MACE 20% vs 32% p=NS.[31]
19. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up **↓ MACE NNT=23/ ~17 yr**.[32] DCCT, 33 EDIC
20. Insulin basal/bolus vs conventional diet; all-cause mortality 18.6% vs 19.9% p=NS, MI 15.8% vs 17.9% p=NS, and stroke 5.4% vs 5.0% p=NS.[5] UKPDS-33 10 yr observational follow-up **↓ all-cause mortality NNT=29/~20 yr**, and **↓ MI NNT=36/~20 yr**.[3] UKPDS-80
21. Greater insulin use (any & bolus) with intensive therapy vs standard therapy; **↑ MACE NNT=33/3.5 yr** and **↑CV death NNT=125/3.5 yr**.[34] ACCORD

Weight (weight gain/loss variable, diabetic agents used in conjunction with diet and lifestyle interventions as well as other concomitant medications)

A1. Metformin: ↓ 2.9 kg/4 yr [1] ADOPT
A2. Sulfonylureas: ↑ 1.6 kg/4 yr [1] ADOPT
A3. Pioglitazone: ↑ 3.6 kg/3 yr [2] PROACTIVE
A4. Rosiglitazone: ↑ 4.8 kg/4 yr; rosiglitazone statistically significant ↑ weight vs. both metformin & glyburide [1] ADOPT
A5. Acarbose: ↓1.15 kg/3 yr [3] STOP-NIDDM
A6. Repaglinide: ↑ ~1.7 kg/12-24 wks;[4,5] nateglinide: ↑ 0.7-1 kg/16-24 wks[4,6]
A7. DDP4-inhibitors (generally considered neutral)[7]
- saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo) [8] SAVOR-TIMI 53
- alogliptin ↑ 1 kg/18 months (similar to placebo) [9] EXAMINE
- sitagliptin ↑ ≤ 0.5 kg/12 weeks[10]

A8. GLP-1 agonists
- exenatide ↓ 2.8 kg/24-52 weeks[11]
- liraglutide ↓ 2.3 kg/3.8 yr [12] LEADER
- dulaglutide ↓1.3-3 kg/5-52 weeks[13]

A9. SGLT2 inhibitors[14]
- canagliflozin ↓ 2.8-4 kg/4-52 weeks[15,16] CANTATA-M
- dapagliflozin ↓ 2 kg/12-52 weeks[17]
- empagliflozin ↓ ~1.5-2 kg/3.1 y[18] EMPA-REG

A10. Insulin
- intensive therapy vs standard therapy; avg weight ↑ 3.5 kg vs 0.4 kg/3.5 y; weight ↑ >10 kg 28% vs 14% p<0.00[19] ACCORD
- Note: detemir -1.27 to -0.8 kg vs NPH (glargine no difference vs NPH)[20]

HF/Edema

22. MF should still be considered 1st line in HF patients with eGFR > 30 mL/min [Grade D, Consensus].[1] CDA'13
23. Retrospective cohort (n=10,920 patients hospitalized with HF); MF vs SU **↓ all-cause mortality aHR 0.85 (95% CI 0.75-0.98)**, MF + SU vs MF **↓ all-cause mortality aHR 0.89 (95% 0.82-0.96),** MF + insulin vs SU neutral aHR0.96 (95% CI 0.82-1.13), MF+SU+insulin neutral aHR 0.94 (0.77-1.15).[2]
24. Intensive A1C target (included gliclazide) vs standard A1C target; HF (HF death, HF hospitalization, worsening NYHA class) 3.9% vs 4.1% p=NS.[3] ADVANCE
25. Glyburide vs rosiglitazone; **↓HF (serious events) NNT 167/3.5 yr, ↓HF (total events) NNT=67/3.5 yr.**[4] ADOPT
26. Pioglitazone vs placebo; **↑ hospitalization for HF NNH=50/2.9 yr** (not adjudicated), **↑ edema (without HF) NNH=8/2.9 yr**.[5] PROACTIVE
27. Rosiglitazone +meformin or SU vs control; **↑ hospitalization for HF or HF death NNH=69/5.5 yr**.[6] RECORD Rosiglitazone vs placebo; **↑ HF NNT=250/3 yr**.[7] DREAM
28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A.[8] STOP-NIDDM
29. Repaglinide vs rosiglitazone: peripheral edema 0% vs 3.2%, p=N/A.[9]
30. Saxagliptin vs placebo; **↑ hospitalization for HF NNH=143/2.1 yr**; however, subgroup without a history of HF at baseline **↑ hospitalization for HF NNH=147/2.1 yr**, subgroup eGFR <60 mL/min **↑ hospitalization for HF NNH=68/2.1 yr** & no difference from 12 months on HR 1.05, 95% CI 0.81-1.35.[10, 11] SAVOR-TIMI 53 Alogliptin vs placebo; hospitalization for HF 3.9% vs 3.3% p=0.22; subgroup without a history of HF at baseline **↑ hospitalization for HF NNH=111/1.5 yr**.[12,13] EXAMINE Sitaglipin vs placebo; hospitalization for HF 3.1% vs 3.1% p=0.98; and neutral results when adjusted for baseline HF (aHR 1.00, 95% CI 0.83-1.20 [unpublished data]).[14,15] TECOS Meta-analysis(SAVOR-TIMI 53, EXAMINE, TECOS) HF admission RR 1.12 (95% CI, 1.00-1.25, I^2=42%).[16] FDA warnings for both saxagliptin & alogliptin.[17]
31. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14.[18] LEADER Lixisenatide vs placebo; hospitalization for HF: 4.0% vs 4.2% p=0.75.[19] ELIXA
32. Empagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002.[20] EMPA-REG
33. Basal insulin (glargine) vs standard care; hospitalization for HF 4.9% vs 5.5% p=NS.[21] ORIGIN

Other

35. Pioglitazone & Rosiglitazone FDA +/- Health Canada warnings/label changes:
    - ?↑ HF (see above) [1] PROACTIVE, [2] RECORD, [3] DREAM,[4, 5]
    - ?↑ fractures ♀; pioglitazone vs placebo 5.1 vs 2.5%, calculated p=0.005 ?↑ fractures ♀ **NNH=38/2.9 yr** (unpublished PROACTIVE data).[6] Rosiglitazone vs MF ↑ fractures ♀ **NNH=24/4 yr**, rosiglitazone vs glyburide ↑ fractures ♀ **NNH=17/4 yr**.[8] ADOPT Post marketing data: pioglitazone exposure in women associated **0.8 excess fractures (distal upper and lower limbs)/100 patient-years** vs comparator treated group.[8] No ↑ risk in males.[8,9]
    - ?↑ diabetic macular edema: retrospective cohort, TZD users vs nonusers ↑ macular edema 1 yr follow up aOR 2.3 (1.5-3.6) & 10 yr follow up HR 2.3 (1.7-3.0).[10] Cross-section of **ACCORD** ↑macular edema aOR, 0.97 (0.67-1.40).[11] Note- only rosiglitazone has a warning.[12]
36. Piog: ?↑ bladder cancer; France, retrospective observational cohort pioglitazone exposure vs other diabetic agent HR 1.22 (1.03-1.43), pioglitazone exposure **cumulative dose > 28 000** mg vs other diabetic agent HR 1.75 (1.22-2.5), pioglitazone **exposure >12 months** vs other diabetic agent HR 1.28 (1.09-1.51).[13] US, prospective observational cohort (5 yr interim analysis) pioglitazone exposure vs never exposed HR 1.2 (0.9-1.5), pioglitazone exposure >12 months vs never exposed HR 1.4 (0.9-2.1), & piogltazone exposure >24 months vs never exposed HR 1.4 (1.03-2.0).[14] FDA calculated pioglitazone >12 months associated **27.5 excess cases of bladder cancer /100,000 person-yrs** vs never exposed.[15,16]
37. Rosigltazone FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ?↑ CV events- see MACE/mortality.[17-21]
38. DPP-4 inhibitors FDA +/- Health Canada warnings/label changes:
    - ?↑ HF risk with saxagliptin and alogliptin (see above).[10, 11] SAVOR-TIMI 53, [12,13] EXAMINE,[16, 22]
    - ?↑ arthralgia risk; n=33 cases of severe arthralgia, of which n=10 cases were hospitalized due to disabling joint pain; n=8 cases reported a positive rechallenge (2006-2013).[23]
39. Incretin agents (DDP-4 inhibitors and GLP-1 agonists) ?↑ pancreatitis:[24] US case control study; incretin agent (exenatide or sitagliptin) within 30 days **aOR 2.24 (95% CI, 1.36-3.68)**.[25] FDA: n=30 cases of pancreatitis with exenatide of which n=21 cases hospitalized, n=3 cases reported positive rechallenge.[26] FDA: n=88 cases of pancreatitis with sitagliptin or sitagliptin/metformin of which n=58 cases were hospitalized (n=4 cases admitted to the ICU), n=2 cases of hemorrhagic or necrotizing pancreatitis.[27] Listed adverse event for other agents (e.g., liraglutide) in product monograph.
40. Incretin agents (DDP-4 inhibitors and GLP-1 agonists) ?↑ pancreatic cancer: n=13 pancreatic cancer cases suspected of being associated with all incretin-based therapies (July 31, 2014).[24,28]
41. Liraglutide: ?↑ thyroid C-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent).[29]
42. ?↑/↓ GI (nausea, diarrhea, vomiting) AE with long acting agents[30,31]: **↑ GI AE**: taspoglutide once weekly 59% vs exenatide BID 35% (clinical development of taspoglutide has been stopped).[32] **↓ GI AE:** Exenatide once weekly 28% vs exenatide BID 48%, albiglutide once weekly 29.8% vs liraglutide daily 52%, exenatide once weekly 19.1% vs liraglutide daily 44.5%.[33] DURATION-5,[34] HARMONY-7,[35] DURATION-6 Neutral GI: dulaglutide once weekly 39.4% vs liraglutide daily 38.3%.[36] AWARD-6
43. SGLT-2 inhibitors FDA +/- Health Canada warnings/label changes:
    - ?↑ diabetic ketoacidosis; n=5 Canadian cases, some requiring hospitalization (May 2016); n= 73 US cases (n=44 T2DM cases, n=15T1DM cases, n=13 NR) (Mar 2013-2015) all requiring hospitalization or emergency department care.[37,38]
    - ?↑ urosepsis & pyelonephritis; n=19 cases requiring hospitalizations (canagliflozin [n=10 cases] and dapagliflozin [n=9 cases]), of which n=4 cases required ICU admission and n=2 cases required hemodialysis (Mar 2013-Oct 2014).[38]
    - ?↑ AKI; n=2 Canadian cases (Canagliflozin) (Oct 2015); n=101 US cases (Mar 2013-Oct 2015), of which n=96 cases required hospitalization (n=22 cases required ICU admission), n=15 cases required hemodialysis, and n=4 cases resulted in death. ~50% of cases occurred within 1 month of drug initiation; empagliflozin not included in review due to recent approval.[39,40]
    - ?↑ fracture; canagliflozin 100 mg-300 mg vs placebo 1.4-1.5 fractures vs 1.1 adjudicated bone fractures/100 patient yrs. ?↓BMD (total hips, lumbar spine, femoral neck, & distal forearm).[41]
34. Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=NS.[22] ArchInternMed1997

Other- continued

- ?↑ lower limb amputation; canagliflozin 100-300 mg vs placebo; ↑ lower limb amputation 5-7/1000 patient years vs 3/1000 patients years.[CANVAS] Other trials neutral.[e.g.,CANVAS-R 42,43]

44. ?↑UTI; SGLT2 inhibitor vs placebo: **OR 1.34 (1.03-1.74, I^2=0%)**, vs active agent: OR 1.42 (1.06-1.9, I^2=25%). ↑ genital tract infection; SGLT2 inhibitor vs placebo **OR 3.50 (2.46-4.99, I^2=0%)**, vs active agent: OR 5.06 (3.44-7.45, I^2=0%).[44]
45. Dapagliflozin: ? ↑ bladder/breast cancer; approved by FDA 2014 (rejected in 2012 due to breast & bladder cancer concerns). Dapagliflozin vs control; bladder cancer: n=10 cases vs n=1 case & breast cancer: n=12 cases vs n= 3 cases (up to 2013).45
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References: Death/MACE

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Hypoglycemics & Sulfa Allergy

Articles: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1783707/?tool=pubmed
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Summary & Overview:

⇨Warnings don't always correspond with available evidence; there is little information to suggest cross-sensitivity among the different sulfa chemical classes, however, those who have experienced a previous allergic reaction (to any drug) are more likely to experience a subsequent allergic reaction (to a related or unrelated drug)

⇨ Specific drugs

- *Chlorpropamide (Diabinese) (Apo-Chlorpropamide - Canada) - no warning*
- *Gliclazide (Diamicron) – Warning- (Contraindicated-Health Canada)*
- *Glimepiride (Amaryl)- Warning- (Contraindicated-Health Canada)*
- *Glipizide (Glucotrol)- no warning*
- *Glyburide (DiaBeta, others) - Warning (Contraindicated-Health Canada)*
- *Tolbutamide (Orinase) (Apo-Tolbutamide - Canada) - Warning*

⇨One case report of contact dermatitis with tolbutamide in a patient with sensitivity to sulfanilamide vaginal cream. After discontinuation of tolbutamide, therapy was changed to chlorpropamide, which was tolerated without difficulty.

⇨Another case report describes an allergic reaction to glyburide in a patient with a known allergy to sulfamethoxazole.

New Agents – CV Outcomes awaiting trials

Canagliflozin: ?CV risk: awaiting results of **CANVAS** (RCT, n~4500, T2DM at high risk of CVD; canagliflozin 100mg vs. 300mg vs. placebo; completion 2018)

Dapagliflozin: ?CV risk: awaiting results of **DECLARE** (RCT, n~17,000 T2DM; CV events with dapagliflozin added to existing tx; completion 2019)

Rosiglitazone: link to Health Canada's warning: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2010/14591a-eng.php

(This also contains the link to GSK's consent form to be completed RE patient approval.)

DC'd

Glimepiride/rosiglitazone AVANDARYL ✗ ⊗

(1,2,4/4mg tabs) daily with a meal ($325) D/C 2011

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FDA Aug/09 Patients with diabetes who take therapeutic products containing nonglucose sugars (e.g., **peritoneal dialysis solution and some immunoglobulins**) can have falsely elevated readings from blood glucose test strips that use glucose dehydrogenase pyrroloquinoline quinone (**GDH-PQQ**) technology, according to an FDA public health notification. The strips are in wide use, and we have provided a link to a listing of the affected products. The FDA cites 13 deaths associated with hypoglycemia not detected by the test strips, which cannot distinguish between lucose and other sugars such as maltose and xylose. Ten patients were receiving icodextrin peritoneal dialysis solution. The FDA advises physicians to avoid using GDH-PQQ test strips in health care facilities and to rely, instead, on laboratory assays of glucose — especially in patients taking the therapeutic products listed in the alert. Interfering products containing nonglucose sugars include icodextrin peritoneal dialysis solution, certain immunoglobulins, abatacept (Orencia, Bristol-Myers Squibb), tositumomab (Bexxar, GlaxoSmithKline), and any product containing or metabolized into maltose, galactose, or xylose. Several test strips and associated monitors use GDH-PQQ methodology: ACCU-CHEK (Roche), FreeStyle (Abbott Diabetes Care), TRUEtest (Home Diagnostics), CoZmonitor blood glucose module (for use with the Deltec Cozmo insulin pump, Smiths Medical MD), and OmniPod insulin management system (Insulet).

FDA Sep/10 & Takeda, conducted a planned analysis of the study data at the five-year mark, and submitted their results to FDA. Overall, there was no statistically significant association between **Actos exposure and bladder cancer risk**. However, further analyses were also performed looking at how long patients were on Actos and the total amount of the drug they received during that time. An increased risk of bladder cancer was observed among patients with the longest exposure to Actos, as well as in those exposed to the highest cumulative dose of Actos. FDA notified healthcare professionals and patients that the Agency is reviewing data from an ongoing, ten-year epidemiological study designed to evaluate whether Actos (pioglitazone) is associated with an increased risk of bladder cancer.

FDA May/11 Updated risk evaluation and mitigation strategy **(REMS) to restrict access to rosiglitazone**-containing medicines including Avandia, Avandamet, and Avandaryl. May 18, 2011. http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm

FDA June/11 **Victoza** (liraglutide [rDNA origin]) Injection: REMS - Risk of **Thyroid C-cell Tumors, Acute Pancreatitis**. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm

FDA June/11 drug safety communication: Update to ongoing safety review of **Actos (pioglitazone) and increased risk of bladder cancer**- use for more than 12 months linked to an increased risk of bladder cancer. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm

FDA Mar/13 is evaluating unpublished new findings by a group of academic researchers that suggest an increased risk of **pancreatitis and pre-cancerous cellular** changes called pancreatic duct metaplasia in patients with type 2 diabetes treated with a class of drugs called incretin mimetics **(glucagonlike peptide-1 (GLP-1) agonists and the DPP-4 inhibitors, or "gliptins**). These findings were based on examination of a small number of pancreatic tissue specimens taken from patients after they died from unspecified causes.

FDA Aug/13 Nova Diabetes Care initiated a **voluntary recall of 21 lots of the Nova Max Glucose Test Strips** distributed both in the USA and outside the continental USA.

FDA May/15 is warning that the type 2 diabetes medicines **canagliflozin**, **dapagliflozin**, and **empagliflozin** may lead to **ketoacidosis**, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. FDA is continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

FDA Aug/15 The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines **sitagliptin, saxagliptin, linagliptin, and alogliptin** may cause joint pain that can be severe and disabling **joint pain**.

FDA Sep/15 The U.S. Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine **canagliflozin (Invokana, Invokamet)** related to the increased risk of bone fractures and added new information about **decreased bone mineral density**.

FDA Dec/15 safety review has resulted in adding warnings to the labels of a specific class of type 2 diabetes medicines called **sodium-glucose cotransporter-2 (SGLT2) inhibitors** about the risks of too much **acid in the blood and of serious urinary tract infections**.

FDA Dec/15 is **eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone**-containing type 2 diabetes medicines, which are approved as Avandia, Avandamet, Avandaryl, and generics. The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

FDA Apr/16 safety review has found that type 2 diabetes medicines containing **saxagliptin and alogliptin** may increase the risk of **heart failure**, particularly in patients who already have heart or kidney disease.

FDA Apr/16 is also requiring manufacturers to revise the labeling to recommend that the measure of **kidney function** used to determine whether a patient can receive **metformin** be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of renal function (i.e., glomerular filtration rate estimating equation (eGFR)). Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m2.

FDA Apr/16 **Dexcom** Inc. is recalling the **Continuous Glucose Monitoring Systems** because the audible alarm may not activate in the receiver piece when low or high glucose levels (hypoglycemia or hyperglycemia) are detected. Relying on this product for notification of low or high blood sugar could result in serious adverse consequences, including death as the auditory alarm may not sound and users might not be notified of low or high blood sugar.

FDA June/16 has strengthened the existing warning about the risk of **acute kidney injury** for the type 2 diabetes medicines **canagliflozin** (Invokana, Invokamet) and **dapagliflozin** (Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

FDA Dec/16: As a result of an updated review, the FDA has concluded that use of the type 2 diabetes medicine **pioglitazone** (Actos, Actoplus Met, Actoplus Met XR, Duetact, Oseni) may be linked to an **increased risk of bladder cancer**.

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Health Canada Apr/07 is warning consumers from The Hong Kong Department of Health found **Lanmei Keili Ji to be adulterated with gliclazide**, a hypoglycaemic agent (lowers blood sugar).
Health Canada May/07 is advising consumers not to use **Xiaokeshuping Jiangtangning Jiaonang** capsules in Hong Kong to contain the undeclared pharmaceutical drugs phenformin, rosiglitazone, and glibenclamide, which may be used in diabetes to lower blood sugar.
Health Canada May& June/07 is advising consumers & health professionals about heart risks with **Avandia** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2007/avandia_pc-cp_3_e.html
Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang, J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.
Health Canada Nov/07 Rosiglitazone (**AVANDIA®**) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated. Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated. Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV).
Health Canada April/08 warns that Singapore's Health Sciences Authority (HSA) advised the public not to use the product **Power 1 Walnut**, because it was found to contain the prescription drugs sildenafil and glibenclamide.
Health Canada April/08 is advising consumers not to use The Hong Kong Department of Health advised the public not to use the product **Tian Sheng Yi Bao** because it was found to contain two pharmaceutical products, glibenclamide and phenformin.
Health Canada June/08 **Nangen Zengzhangsu** (may also be known as Nangen or Nangeng), Sanbianwan, Jiu Bian Wang, Tian Huang Gu Shen Dan, Zui Xian Dan Gong Shi Zi, and Power Up. The Hong Kong Department of Health has warned consumers not to use these herbal/proprietary Chinese medicine products promoted for erectile dysfunction because they have been found to contain sildenafil and/or glibenclamide.
Health Canada June/08 **Zhong Hua Niu Bian**. Zhong Hua Niu Bian is an herbal/proprietary Chinese medicine product promoted for erectile dysfunction. Singapore's Health Sciences Authority has warned against the use of this product because it has been found to contain sildenafil, glibenclamide, tadalafil and sibutramine
Health Canada Nov/08 is advising consumers not to use foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lu Quan** because it contains undeclared glibenclamide and sildenafil.
Health Canada Nov/10 AVANDIA®/AVANDAMET®/AVANDARYL® is now indicated only in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance. Prior to starting or renewing a prescription for **AVANDIA®/AVANDAMET®/ AVANDARYL®,** physicians should consider whether a rosiglitazone-containing product is an appropriate therapeutic choice, and if so: Document the eligibility of patients to meet the above criteria; Counsel each patient on the risks and benefits of AVANDIA®/AVANDAMET®/ AVANDARYL®, including the cardiovascular risks; and Obtain the patient's written informed consent to take the drug.
Health Canada Nov/11 **Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a prescription drug (glyburide). **Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al, and Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine).
Health Canada Apr/12 has recently completed a safety assessment of the available data for **rosiglitazone-ACTOS**, an oral anti-diabetic drug, and the label was updated to reflect the potential risk of **bladder cancer** in treated patients.
Health Canada May/12 1. **Jin Yu Tang Tai Han Kang Pai Pu Ling Jiao Nang; TangBaoKouFuYiDaoSuJiaoNang; Tangren 365 Kangxunpai sangge huoyisu jiaonang; Tong Ren Xiu Fu Kou Fu Yi Dao Su.** The Hong Kong Department of Health warned that these products contain a combination of prescription drugs (metformin, glibenclamide [also known as glyburide], rosiglitazone, glimepiride, hydrochlorothiazide) and unauthorized drugs (phenolphthalein, phenformin).
Health Canada Jan/13: informing Canadians of a labelling update for all cholesterol-lowering drugs (also known as **statins**) regarding the risk of increased blood sugar levels and a small increased **risk of diabetes** among patients already at risk for the disease.
Health Canada Apr/14: **San Xiao Ping Tang Jin Qi Jiao Nang**: The Hong Kong Department of Health warned consumers not to use this product after it was found to contain phenformin, pioglitazoneand glibenclamide**.**
Health Canada June/15 **Forxiga, Invokana**: Health Canada begins safety review of diabetes drugs known as SGLT2 inhibitors and risk of **ketoacidosis**.
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Health Canada May/16 **SGLT2 Inhibitors** [INVOKANA (canagliflozin), FORXIGA (dapagliflozin), XIGDUO (dapagliflozin/metformin), JARDIANCE (empagliflozin)] - Risk of **Diabetic Ketoacidosis** - Janssen Inc., Boehringer Ingelheim (Canada) Ltd. Serious, sometimes life-threatening and fatal cases of diabetic ketoacidosis (DKA) have been reported in patients on sodium glucose co-transporter 2 (SGLT2) inhibitors for type 1 and type 2 diabetes. In a number of these cases, the presentation of the condition was atypical with only moderately increased blood glucose levels observed. SGLT2 inhibitors are NOT indicated for treatment of type 1 diabetes mellitus and should not be used in type 1 diabetes.
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MHRA Dec/15: Storing home use **GlucoMen LX Sensor test strips incorrectly**, especially in high humidity, can lead to falsely high readings.

MHRA Apr/16 **SGLT2 inhibitors**: updated advice on the risk of **diabetic ketoacidosis**. Test for raised ketones in patients with ketoacidosis symptoms, even if plasma glucose levels are near-normal. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis

MHRA June/16 **Canagliflozin** (Invokana▼ , Vokanamet▼): signal of increased risk of **lower extremity amputations** observed in trial in high cardiovascular risk patients.

MHRA June/16 **TRUEyou blood glucose test strips** - certain lots of test strips may give incorrect low blood glucose results that could lead to undetected hyperglycaemia.

MHRA Aug/16: The manufacturer, Nipro Diagnostics, found an issue with the packaging meaning that test strips in specific lots are not sealed properly. This can affect how the strips measure blood glucose levels and could lead to undetected high blood glucose (hyperglycaemia) which can have serious health implications. People using these test strips, which are used in **TRUEresult, TRUEresult twist, and TRUEtrack blood glucose meters**, are asked to check if they use affected blood glucose test strips with the lot numbers below.

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Mayo Clinic – **Shared Decision Making** – diabetes tools: http://dev.shareddecisions.mayoclinic.org/decision-aids-for-diabetes/diabetes-medication-management/

Health Canada – Advisory on rosiglitazone (Avandia) (June 01, 2007) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/avandia_hpc-cps_4_e.html
Important Advice for Managing Your Patients

In Canada, Avandia® is NOT approved for use:
- with insulin therapy
- with the combination of metformin AND a sulfonylurea
- in patients with pre-diabetes.

Avandia® is contraindicated in patients with NYHA Class III and IV cardiac status.
Avandia® should be used with caution in any patient with NYHA Class I and II cardiac status.
All patients should be monitored for signs and symptoms of fluid retention, edema, and rapid weight gain.

The dose of Avandia® used in combination with a sulfonylurea should not exceed 4mg daily.

More links, information and a RxFiles Q&A Summary available at: http://www.rxfiles.ca/Rosiglitazone-CV-Controversy.htm

Background considerations:

- Weighing the benefits & risks of intensive therapy: [See also Diabetes - Landmark Outcome Trials Chart[24]]
  - The results of clinical trials evaluating outcomes of intensive glycemic control have been somewhat disappointing. Achieving an A1C of less than 6.5% may ↓ microvascular endpoints, but over 100,000 patient years of RCT data have failed to show a benefit on CV endpoints.[25] {The 10 year observational follow-up to the UKPDS suggests CV benefit of intensive glycemic control (FBG <6; mean baseline A1Cs 7.9% vs 8.5%) especially with metformin.[26]}
  - Individualization of antihyperglycemic therapy has become a common theme[27,28] as some evidence & experience suggests that some patients may do worse with more intensive regimens (e.g. ↑ mortality (NNH=95/3.5yrs) in the ACCORD RCT n=10,251 in patients randomized to achieve an intensive A1c of 6% vs 7 - 8%; actual A1c achieved was 6.4% vs 7.5%)[29].
  - Although an A1C of <7% is suggested for most, individual patient & treatment regimen factors may result in acceptance of less aggressive targets. For example the American Geriatric Society[30] noted that an A1C of 8% may be more suitable in frail elderly & those with a life expectancy <5yrs.
  - A recent observational cohort trial found a "U" shaped curve for mortality related to A1C. An A1C of 7.5% was associated with the lowest mortality, with higher mortality seen at higher and lower A1C values.[31]

- CADTH Exec Summary: Within the limitations of available evidence, this report concludes:
  - Use of SMBG appears to be associated with improvements in glycemic control among patients with insulin-treated type 2 diabetes. Evidence was limited and of low quality.
  - Few studies compared different frequencies of SMBG for patients with either type 1 or insulin-treated type 2 diabetes, and the evidence from these studies was of low quality. Well-designed studies may prove beneficial in optimizing SMBG frequency for these individuals.
  - Use of SMBG in patients with type 2 diabetes who are not using insulin is associated with a statistically significant, albeit clinically modest, improvement in glycemic control. Performing SMBG may reduce the number of symptomatic hypoglycemic events in patients using sulfonylureas. There was little or no evidence that SMBG provides other benefits, such as improved quality of life, or greater patient satisfaction. Longer-term studies are needed to determine whether or not SMBG reduces diabetes related clinical endpoints (e.g., blindness, reduction in myocardial infarctions, end-stage renal disease) or mortality. Studies of specific subgroups within this population who may be more likely to benefit from SMBG are also warranted.
  - The effect of using SMBG in women with gestational diabetes requires further investigation.
- Estimated 40 year NNTs for SMBG in non-insulin T2DM: 266 for MI; 500 for stroke; 1,389 for end stage renal disease[15]

Comparison: CADTH & Canadian Diabetes Association (CDA).

- CADTH review includes detailed systematic review of the clinical evidence as well as cost evaluation. Significant effort goes into limiting, minimizing the possible effects of, and acknowledging conflicts of interest.
- CDA guidelines include clinical evidence only. Conflicts of interest are more extensive; however they are acknowledged.

Other Major Meta-analysis Reviews

- Poolsup et al SMBG Meta-analysis: suggests that SMBG in non-insulin T2DM may benefit those with a baseline A1C of >8%, but not < 8%.[32]
- St John meta-analysis: suggests similar ↓ in A1C of -0.22 (95% CI: -0.34—0.11). St John A, Davis WA, Price CP, Davis TM. The value of self-monitoring of blood glucose: a review of recent evidence. J Diabetes Complications. 2009 Feb 19.
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  Outlines strip costs for elderly in ON; found potential for reduce costs by $26 million - $302 million if less testing in low-risk.

Health Canada Related Alerts

- Possible interference of icodextrin, intravenous immunoglobulins, galactose and d-xylose with certain blood glucose meters - Notice to Hospitals http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/gluc_met_nth-aah-eng.php

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

Why consideration of reagants in test strips is important -e.g., peritoneal dialysis - use meters that are not affected by GDH-PQQ
Rationale: drug products or therapies that contain certain non-glucose sugars, such as maltose, galactose, and xylose will produce falsely elevated glucose result if measuring your glucose using a GDH-PQQ test strip. This could result in insulin dosing errors or not detecting low (hypoglycemic) readings. Avoid use of these test strips in patients using interfering drug products or therapies. Glucose oxidase – may be important at certain altitudes, although very rare.

[A] Strips with glucose dehydrogenase (GDH) pyrroloquinolinequinone (PQQ) will have cross-reactivity with maltose, galactose or xylose but are unaffected by pO2.
[B] Strips with glucose oxidase are affected by pO2 in the blood but not by maltose, galactose and xylose
[C] Strips with glucose dehydrogenase (GDH) Flavin adenine dinucleotide (FAD) can be affected by xylose but unaffected by pO2, maltose and galactose.

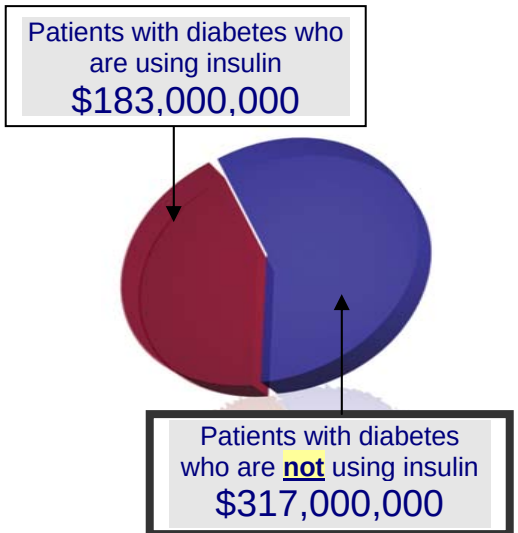
Maltose: found in IV solutions (i.e. immunoglobulin) and other solutions containing dialysate icodextrin

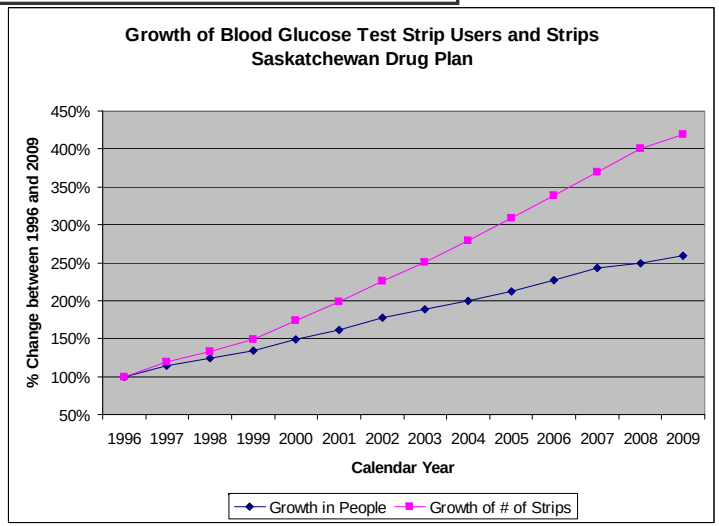
Alternate site testing: not recommended if hypoglycemia suspected, especially if prone to hypoglycemic confusion. In these cases, the finger tip method is the best way to get an accurate result.

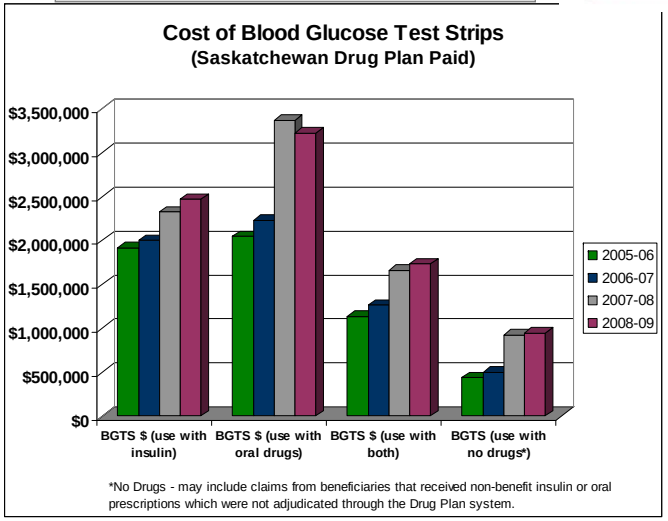
If practice changes to reflect the evidence, $450 million to $1.2 billion* could be freed up between 2012 and 2015 for spending on antidiabetes interventions that are proven effective.
Patient health would not be affected negatively.
http://www.cadth.ca/media/compus/pdf/C1109-Prescribing-Aid-Web-e.pdf?&utm_source=c1109&utm_medium=vo2-issue-8&utm_campaign=communique-03-13-12 Revised March 2012
[These results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public and Private Drug Plans Databases, 2000-2011]

- Cost to drug plans public+private = $330 million 2006 Canadian data
- Cost per QALY (quality adjusted life year) is estimated at $113,643 for routine use of SMBG (at least 1 strip each day on average).
- Annual cost per patient: $165 - $2,400 (see Table below).

Thanks to CADTH-COMPUS for assistance the development of this document.







Data provided from Saskatchewan Health; used by permission.

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FDA Aug/10 and CDC have noted a progressive increase in the reports of bloodborne infection transmission over the past 10 to 15 years (primarily hepatitis B virus), resulting from shared use of fingerstick and point-of-care [POC] blood testing devices.

FDA Aug/13 Nova Diabetes Care initiated a voluntary recall of 21 lots of the Nova Max Glucose Test Strips distributed both in the USA and outside the continental USA.

FDA Jan/14 Nipro Diagnostics initiated a voluntary recall and replacement of a limited number of TRUEbalance and TRUEtrack Blood Glucose Meters distributed both in the United States and outside the United States. The company determined that certain isolated TRUEbalance and TRUEtrack Blood Glucose Meters have an incorrect factory-set unit of measure that displays the glucose result in mmoi/L rather than mg/dl. If a consumer were not to notice the incorrect unit of measure, it is possible that the meter result could be read as a lower than expected blood glucose result. BACKGROUND: There are 501 affected TRUEbalance meters and 105 affected TRUEtrack meters that were distributed in the United States from September 2008 to May 2013. The company is sending notifications to pharmacies, durable medical equipment providers, mail order companies and distributors where the TRUEbalance and TRUEtrack meters are recommended or sold in the United States.

FDA Mar/14 Abbott is conducting a recall for the FreeStyle Blood Glucose Meter and the FreeStyle Flash Blood Glucose Meter. When used with the Abbott FreeStyle test strips, the FreeStyle Blood Glucose Meter and the FreeStyle Flash Blood Glucose Meter may produce mistakenly low blood glucose results.

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FDA Jun/14 Diabetic Supply of Suncoast, Inc. initiated a nationwide voluntary recall of all BMB-BA006A Advocate Redi-Code+ blood glucose test strip lots manufactured by BroadMaster Bio-Tech Corp due to a labeling error which could result in confusion about which meter models the Redi-Code+ BMB-BA006A blood glucose test strips are designed to be used with. In the incorrect labeling, the test strips model (BMB-BA006A) was omitted.

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Ontario Aug 2013: introducing limitations in funding for diabetes test strips. And these new r estrictions are okay with the Canadian Diabetes Association, which worked with the government to ensure that new self-management of diabetes reflects the best evidence and clinical experience available. According to a notice posted on the Ontario Public Drug Programs (OPDP) website, research indicates that Blood Glucose Test Strips (BGTS) have a limited clinical benefit for many patients who don't take insulin. Based on this evidence, Ontario will restrict the number of BGTS allowed in a 365-day period, while ensuring continued access to those who need test strips to manage their blood sugar. The province's Health Network System (HNS) will track and determine the reimbursement level based on each patient's diabetes treatment. Under the new rules, patients managing diabetes with insulin will be allowed 3,000 BGTS a year, while patients managing diabetes with anti-diabetes medication with high risk of causing hypoglycemia will get 400 BGTS. Patients managing diabetes using anti-diabetes medication with low risk of causing hypoglycemia and those who are managing diabetes through diet/lifestyle therapy only will be allowed 200 BGTS.

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Extras for Insulin Pen Delivery Devices:

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

AutoPen 24 (3ml penfill) A) green – up to 21 units 1-21 units in 1 unit increments B) blue – up to 42 units 2-42 units in 2 unit increments		**LANTUS** (glargine) ◆ free with Lantus insulin	◆ has side-mounted injection button ◆ small white numbers on a dark background; does not have number window (e.g. number not magnified.) ◆ does NOT have dial back capabilities, dose must be wasted if overdialed ◆ if insufficient insulin in cartridge, number remaining on dial will show remaining dose to be given
Novolin-Pen Junior (3ml penfill) 1-35 units in ½ unit increments {Blue with green or yellow with green}		As per NovoPen 4 [Novo-Pen Junior being replaced by NovoPen Echo]	◆ small increments useful: children & insulin sensitive pts ◆ does NOT have dial back capability; barrel and cartridge holder should be pulled apart & button reset to correct dose ◆ small white numbers on a black background ◆ if insufficient insulin in cartridge, number remaining on dial will show remaining dose to be given
HumaPen Luxura (3ml cartridge) 1-60 units in 1 unit increments {Champagne or Burgundy with hard case}		**HUMULIN** (R, N, 30/70) **HUMALOG** (lispro) **HUMALOG** Mix25 (lispro+lispro protamine) **HUMALOG** Mix50 (lispro+lispro protamine) [HumanPen Luxura being replaced by HumaPen Savvio]	◆ has dial back capability, decreases wastage ◆ audible click on dialing doses ◆ dark numbers on a white background ◆ if insufficient insulin in cartridge, number remaining on dial will show remaining dose to be given ◆ Luxura last up to 6 years

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Temporary Extras:

◆{Pen devices: ↑'d portability, convenience & ease of use; but ↑ potential for contamination, needle sticks, malfunction & cost}

◆T1DM: A1C difference between SAIA and HI is less than 1/10th of the difference between intensive and conventional tx groups in the DCCT; based on this, expected NNT for 1 less retinopathy = 650 / year

◆Epidural Corticosteroids: expect ↑BG levels for a few days Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. Spine 2012;37(1):E46-50.

◆Insulin Pump (CSII): may allow for ↓A1C by 0.3-0.6%; ↓ insulin dose by 10-20%; potentially useful if ↑ A1C despite best attempt with MDI &/or who have continued disabling hypoglycemia. Also of use in 1st trimester of pregnancy, or before, if A1C <6.1% not achieved.

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there is no evidence that SMBG affects patient satisfaction, general well-being or general health-related quality of life. More research is needed to explore the psychological impact of SMBG and its impact on diabetes specific quality of life and well-being, as well as the impact of SMBG on hypoglycaemia and diabetic complications.

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peritoneal dialysis solution, certain immunoglobulins, abatacept (Orencia, Bristol-Myers Squibb), tositumomab (Bexxar, GlaxoSmithKline), and any product containing or metabolized into maltose, galactose, or xylose. Several test strips and associated monitors use GDH-PQQ methodology: *ACCU-CHEK* (Roche), *FreeStyle* (Abbott Diabetes Care), *TRUEtest* (Home Diagnostics), *CoZmonitor* blood glucose module (for use with the *Deltec Cozmo* insulin pump, Smiths Medical MD), and *OmniPod* insulin management system (Insulet).

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EXTRAS Page for Diabetes Landmark Outcome Trials: Glycemic Control & Prevention Summary

Other Trials of Interest

◆ EXAMINE: aloglyptin after ACS in T2DM – aloglyptin not inferior to placebo for major CV in high-CV risk patients. White WB, Cannon CP, Heller SR, Nissen SE, et al; the EXAMINE Investigators. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. N Engl J Med. 2013 Sep 2.

Upcoming Trials in Diabetes/CV Risk Prevention:

◆ **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)- NEJM Mar/10; ◆ **TRANSCEND** (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease); **RAPSODI** (rimonabant in diabetes prevention); **CANOE** (rosiglitazone 2mg bid & metformin 500mg bid in diabetes prevention);

Prediabetes [ADA]:

- Includes: 1) Impaired Fasting Glucose {8hr fasting BG between 5.6-6.9mmol/L) & 2) Impaired glucose tolerance {Postprandial BG of 7.8-11.0mmol/L 2hrs post 75g oral glucose challenge}
- Risk factors: family hx, obesity – especially around waist, age >45, hypertension, gestational diabetes hx, sedentary lifestyle. Screening recommendations vary; USPSTF recommends screening particularly if BP >135/80. Oral Glucose Challenge most recommended, but A1c screen also advocated by some.
- QDScore diabetes risk calculator: (UK Prediction Calculator for T2DM): http://www.qdscore.org/

Insulin Analogues Systematic Review/Reports, 2008: http://www.cadth.ca/index.php/en/compus/insulin-analogs/reports

Tight glucose control in critically ill hospitalized pts may ↑mortality & ↑↑risk of hypoglycemia. JAMA'08; 31 Nice-Sugar NNH=38/90day

Q&A: Limitations & Unanswered Questions Regarding A1C Control and Clinical Outcome - Benefits or Risks

There are some important qualifiers on the commonly quoted observational data that "with every 1 % drop in A1C the risk of developing long-term diabetes complications decreases". (Concept originally based on observational data driven by an eye related microvascular endpoint in the UKPDS). **RCT evidence does not support this assumption**!

- Most recently the **ACCORD** trial (established, higher risk T2DM) was halted after looking at whether a A1C target of <6% would result in beneficial clinical outcomes compared to 7-7.9%. According to the preliminary results still awaiting publication, it would appear from this RCT, in this population group, the extra 1.1% drop in A1C seen in the intensive group was actually associated with increased all cause death compared to the standard group. Explanations for this are still pending; some possibilities noted with 5yr follow-up discussion below.
  (See also; http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf).
  ◆ 5 year ACCORD[7b] follow-up results published [Mar 2011 NEJM]: A1C lowering intensiveness relaxed for balance of study period; participants continued in BP or lipid lowering arms; A1C at 5 yrs ~ 7.2% vs 7.6%.
  1) ↑ death sustained in intensive glucose lowering group 5.5% vs 4.5% [NNH=100/5yr];
  2) ↓ non-fatal MI, but fatal CV ↑;
  3) severe hypoglycaemia equivalent in follow-up period;
  4) those most at risk of ↑ death were those with baseline A1C > 8%;
  5) possible explanations for harm with intensive glucose lowering:
  A) different outcomes associated with different drugs or drug combinations?: **B)** impact of ↑ wt gain?; **C)** impact of intense BG lowering.
- With the current RCT evidence with rosiglitazone, there is some concern that lowering A1C does not necessarily result in CV event reductions? With the limited evidence, it appears to at best be neutral, and at worst, harmful in RCTs/durations studied so far (e.g. up to 5.5 year RCTs.) Patients studied, agents used & study limitations [e.g. dropouts] may affect the benefit/risk balance.
- The UKPDS-33, ~ 10 year trial saw reductions predominantly in the microvascular events (predominantly photocoagulation), with stroke and heart related endpoints not significant, but trending favorably and contributing to the composite endpoint benefit. (Exception: metformin had all-cause death reduction in obese T2DM in UKPDS-34)
- In UKPDS 34,[p860] which noted a mortality benefit for metformin in obese T2DM, there is inconsistency in the association of A1C & outcomes (less A1C difference but more benefit [UKPDS34 VS 33])
- In UKPDS 34 Metformin + Sulfonylurea combination led to a lower A1C than Sulf alone (7.7 vs 8.2) but had higher incidence of DM death and all cause death (perhaps due to design issues and a several year delay in moving to combination therapy) .
- The UKPDS epidemiologic evidence for the 1% drop in A1C did not control for obesity/BMI/waist circumference. [UKPDS 35]
- In ADOPT, rosiglitazone decreased A1C more that metformin or glyburide, but glyburide had the lowest rate of CV outcomes.
- In VADT, a 1.5% reduction (6.9% [intensive] vs 8.4% [standard]) in A1C for an average follow-up of 5.6 years resulted in no benefit (microvascular or macrovascular) but increased serious adverse events (predominantly hypoglycaemia).
- **Meta-analysis [2011] of Intensive ↓ BG RCTs in T2DM**: 13 trials, n=34,500. Endpoints: mortality, no difference (RR=1.04, 99%CI 0.91-1.19); CV death, no difference (RR=1.11;0.86-1.43); non-fatal MI: ↓ (RR=0.85, 0.74-0.96);
  Severe hypoglycaemia: ↑↑ (RR=2.33, 1.62-3.36) 1.9-6.6% of patients required tx for severe hypoglycaemia over 5 years. If only high quality studies included, no longer a ↓ in non-fatal MI & there was an ↑ in HF.
  Microvascular effects: no difference, but heterogeneity; rate of retinopathy (0.85, 0.71-1.03); photocoagulation (0.91, 0.71-1.17), ↓ vision or blindness (1.00); neuropathy 0.99, 0.95-1.03); renal failure or 2x SCR (1.03, 0.98-1.08).
  Microalbuminuria: ↓ (0.90, 0.85-0.96), ARR 0.7%-3.1%; NNT=142-32. OVERALL: for hard clinical endpoints, no benefit, but increased severe hypoglycaemia requiring tx. However, note heterogeneity in trials, different tx approaches, different definitions of "intensive lowering", etc. Nevertheless, the more trials, the more evidence that just lowering BG does not equate automatically to beneficial clinical outcomes, but does carry hypoglycaemia risk.

There is some disconcordence between randomized trial outcome evidence and the frequently reported "1% A1C..." benefit. One thing that has growing certainty is that the risks and benefits of drug regimens that lower A1C is more complex than what was previously commonly accepted. While a high A1C is not good, some methods of lowering A1C in some patient groups, are also harmful. While we do not want to be lazy in addressing glucose control, the evidence suggests that we

not assume a net benefit for all A1C lowering interventions in all Type 2 diabetes patients. {*Let the target serve the patient, and not the patient the target.*} See also: Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. BMJ. 2011 Dec 28;343:d7995. http://www.bmj.com/content/343/bmj.d7995

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

See also RxFiles Landmark Trials Chart: Summary of Lipid, BP & ASA diabetes related trials: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-DIABETES-Landmark-Trials-Non-Glucose.pdf

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Blood Pressure Outcomes from RCTs Focusing on Patients with Diabetes

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Trial length of trial	Population mean age, risk, hx, etc.	Intervention	Results	Summary of RCTs: Blood Pressure
HOT [42] 3.8 yrs n=1,501 diabetic subgroup	entire cohort; age 62, BMI 28.5, smoker[16%], baseline BP [170/89]	felodipine RENEDIL 5-10 mg po daily, ± ACEI, ± beta-blocker, ± diuretic	target DBP of ≤80 mmHg vs ≤90 mmHg ◆ major CV events: 4.4 vs 9, NNT 20/3.8yrs [95% CI, 12.5 to 50] ◆ total mortality: 3.4 vs 6, NS	◆ subgroup of patients with diabetes did better with target DBP ≤ 80 mmHg, supporting aggressive BP lowering in these patients.
UKPDS-38 [43] UKPDS-39 [44] 8.4 yrs, n=1,148	T2DM; age 56, baseline BP[160/94], BMI 30	38: tight [<150/85] vs conventional[<180/105] BP control 39: captopril CAPOTEN 25-50 mg po twice daily vs atenolol TENORMIN 50-100 mg po once daily	◆death, diabetes related: 13.7 vs 20.3 per 1,000 person-yrs, NNT 152 patient-yrs ◆all-cause mortality, 22.4 vs 27.2 per 1,000 person-years, NS ◆stroke, 6.5 vs 11.6 per 1,000 person-years, NNT 196 patient-years ◆any diabetes-related complication 50.9 vs 67.4 per 1,000 person-years, NNT 61 patient-years	◆ tight BP control (~144/82) in hypertensive patients with T2DM reduces diabetes related morbidity & mortality. Captopril and atenolol were similarly effective (BP reduction, preserve renal function & proteinuria & CV complications).
ADVANCE [32] 4.3 yrs, n=11,140	T2DM, age 66, hx of major macrovascular ds[32%], HTN tx[68%], BMI 28	perindopril 2-4 mg po daily COVERSYL plus indapamide 0.625-1.25 mg po daily LOZIDE vs placebo	◆ 1°: macro & microvascular events, 15.5 vs 16.8, NNT 79/4.3yr ◆ 2° all-cause death: 7.3 vs 8.5, NNT 84/4.3yr ◆ BP 145/81 → 135/75 combo vs 140/77 placebo	◆ routine use of perindopril & indapamide vs placebo in patients with T2DM reduced combined macro & microvascular renal complications (but not individually significant). This combination decreases mortality in patients with T2DM. Treating T2DM to a lower blood pressure (BP 135/75) is beneficial.
ACCORD-BP [38] 4.7 yrs, n=4,733	T2DM, age 62, previous CV event [34%], BMI 32, HTN [139/76], smoker [13%], HbA1c ≥ 7.5%	non-blinded, intensive therapy {target SBP<120 mmHg} actual [119.3] vs standard therapy {target SBP <140 mmHg} actual [133.5]	◆ 1°: 1st major CV event: 8.8 vs 10.0, NS ◆ 2°: death from any cause: 6.3 vs 6.1, NS ◆ 2°: non-fatal MI: 5.3 vs 6.2, NS ◆ 2°: any stroke: 1.7 vs 2.6, NNT 84/4.7 yrs ◆ macroalbuminuria: 6.6 vs 8.7, NNT 47/4.7 yrs	◆ after 4.7 yrs, there was no significant difference between target SBP < 120 mmHg vs SBP < 140 mmHg in the primary outcome, with significantly more adverse events intensive vs standard 3.3 vs 1.3%; NNH 50/4.7 yrs ◆ targeting SBP <120 mmHg in patients with T2DM may be beneficial in reducing stroke and macroalbuminuria, with potentially more adverse effects, but did not reduce the primary composite endpoint of major CV events.
INVEST [45] f/u to 5.5 yrs, n=6,400 (diabetic subgrp) observational secondary analysis	diabetes, age 66, BMI 30, female [54%], established CAD	calcium antagonist verapamil or beta-blocker first line, followed by ACE inhibitor, diuretic or both to achieve a SBP <130 mmHg & DBP <85 mmHg	tight control = <130, usual control = 130 to <140, uncontrolled = ≥ 140 ◆ 1°: 1st occurrence of all-cause death, non-fatal MI or non-fatal stroke, 12.7 vs 12.6 tight vs usual, NS ◆ all-cause mortality (sub-grp of n=5,077 pts with extended 5 yr f/u), 22.8 vs 21.8 tight vs usual, NNH 100	◆ tight SBP control may not further improve CV outcomes and may increase mortality compared to usual control in patients with diabetes and coronary artery disease
ACCOMPLISH [33] 36 months, n=6,946 (diabetic cohort)	high-risk T2DM with hypertension [145/79 mmHg], age 68, Caucasian[80%], BMI 32, CAD hx [29%], stroke hx[8%], CKD[18%]	benazepril 40 mg [target] po daily LOTENSIN with either amlodipine NORVASC 5-10 mg po daily [BA] or HCTZ 12.5-25 mg po daily [BH]	BA vs BH, entire diabetic cohort (n=6,946) ◆ 1°: time to 1st CV event, 8.8 vs 11.0, NNT 46/36mon [95% CI, 30 to 120] ◆ 2°: CV death, MI or stroke, 4.9 vs 5.9, NS BA vs BH, 'very high-risk' diabetics (n=2,842) – hx of cardiac events, stroke or renal disease ◆ 1°: time to 1st CV event, 13.6 vs 17.3, NNT 28/36mon [95% CI, 18 to 91] ◆ 2°: CV death, MI or stroke, 6.9 vs 8.8 , NS	◆ overall trial was stopped early, similar results found in diabetic subgroup analysis - combination of BA was superior to BH in reducing cardiovascular events; 'very high-risk' subgroup was not a pre-specified analysis ◆ BA arm had greater BP reduction? BP reduction or specific drugs had greater impact on outcome. Mean achieved BPs: BA arm [131.5/72.6 mmHg] & BH arm [132.7/73.7 mmHg] ◆amlodipine more peripheral edema & HCTZ more hypokalemia & dizziness ◆ 1° composite findings suggest superiority of amlodipine vs HCTZ; but when endpoints were analyzed separately no significant improvements were noted[37]
CALM [31] 24 wks, n=199 4 wk placebo run-in	T2DM, microalbuminuria & hypertension~[162/96 mm Hg]; age 60	candesartan 16 mg po daily ATACAND, lisinopril 20 mg po daily ZESTRIL, or combination	24 wk results: ↓diastolic BP and urinary/albumin ratio ◆ combination therapy, 16.3 mmHg [95%CI, 13.6 to 18.9]; 50% [95% CI, 36 to 61] ◆ candesartan, 10.4 mmHg [95% CI, 7.7 to 13.1]; 24% [95% CI, 0 to 43] ◆ lisinopril, 10.7 mmHg [95% CI, 8.0 to 13.5]; 39% [95% CI, 20 to 54]	◆ lisinopril especially & candesartan ↓BP & microalbuminuria in T2DM. Combo ACEI & ARB may be more effective. [ON TARGET findings contradict this]
ON TARGET [50] 56 months, n=25,620 (n=6,391 patients with diabetes), 3 wk run-in	high-risk cohort: vascular disease or diabetes with end organ damage, but without HF; entire cohort: age 66, baseline BP [142/82], BMI 28	ramipril ALTACE [5mg dailiy x 2wk → 10 mg po daily], telmisartan MICARDIS 80mg po daily or combination of e	Ramipril: ◆ 1°: CV death, MI, stroke or hospitalization for heart failure: ◆ 2°: CV death, MI, or stroke: 2°: all-cause death: ◆ ramipril lowered BP less than comparators, but had equal clinical benefit. A substudy suggests ↑ CV death in diabetics with SBP<130. Another substudy, showed that more frequent achieved BP targets, had ↓ stroke & renal dx, but not MI or HF. (However, telmisartan fared no better than placebo on primary outcome, in TRANSCEND trial, n=5926, 56months pts at high risk of CV disease unable to tolerate ACEIs).	◆telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes & assoc. with less angioedema [NNT=500, 0.1 vs 0.3%] & cough [NNT=33 , 1.1 vs 4.2%], but more hypotension symptoms [NNH=112, 2.6 vs 1.7%]. ◆ combination of the two drugs was assoc. with more AEs leading to discontinuation [NNH=24] vs ramipril (hypotension [NNH=33], diarrhea, syncope, renal dysfunction [NNH=31, 13.5 vs 10.2%]. ◆was a treatment trial, not a "target trial"; thus groups were treated differently.
ALLHAT [34] 4.9 yrs, n= 13,101	T2DM cohort; age 66, African American [40%], smoker[13%], hx of atherosclerotic CVD[34%], hx CHD[20%], baseline BP [147/83 mmHg], BMI 31	chlorthalidone 12.5-25mg/d, amlodipine NORVASC 2.5-10 mg/d, or lisinopril ZESTRIL 10-40 mg/d	◆ Diabetes subgroup data (6 year rate/100; RR; 95% CI vs Chlorthalidone): CHD 1° / Stroke / Heart Failure Chlorthalidone 13.8 / 6.9 / 9.7 Amlodipine 13.7 RR=0.97 (0.86-1.10) / 6.4 RR=0.89 (0.74-1.06) / 13 RR=1.39 (1.22-1.59) Lisinopril 12.6 RR=0.97 (0.85-1.10) / 7.4 RR=1.06 (0.89-1.26) / 10.4 RR=1.15 (1.0-1.32)	◆ thiazide-type diuretic chlorthalidone at least as effective 1st line as ACEIs or CCBs ◆ both amlodipine and lisinopril associated with higher risk of heart failure ◆ no difference in end stage renal disease (trends favoured thiazide) or all cause death ◆ significant DM subgroup observations: black participants did worse on ACEI

Does statin use increase risk for diabetes?

- Vascular benefits from statin use outweigh potential risk for incident diabetes in patients with moderate to high CV risk or existing CV disease. {Outcome evidence trumps surrogate evidence. However, reasonable to be more cautious in lower risk, younger patients, many of whom may be on statins for 20-40 years with uncertain benefit/risk.}
- 2010 MetaAnalysis[21]: 13 RCTs, n=91,140, mean f/u = 4yrs. Conclusion: statins are associated with a 0.4% absolute increasein diabetes (NNH=255) over 4 years; treatment of 255 (95% CI 150-852) patients with a statin for 4 years resulted in 1 extra case of diabetes. {risk may be ↑'d in older individuals; equivalent between hydro- & lipophilic statins} ; 2008 MetaAnalysis suggested no risk.[23]
- Possible overestimation of risk due to 'survivor bias' - more pts living longer means more f/u time to screen for new diabetes. Also, pts in control arm who experience a non-fatal event are likely to implement lifestyle changes, such as weight loss and exercise. More events in control arm than statin arm suggests more opportunity to reduce diabetes risk amongst control arm.[22]
- Is risk influenced by the dose of statin?[30] 2011 MetaAnalysis included 5 trials, n=32,752 patients without diabetes at baseline, 2,749 pts developed diabetes over mean f/u of 4.9 yrs (1,449 intensive vs 1,300 moderate dose); there are an extra 2 cases of new diabetes compared to 6.5 fewer major CV events for every 1000 patients on high-dose instead of moderate-dose statin for a year.

RxFiles Links

CARDS Trial Overview: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-CARDS.pdf
Lipid Lowering Agents Overview: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid%20Agents-Header.pdf
Q & A Update on Statins: http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-QandA-Update-Oct04.pdf
ACCOMPLISH Trial Overview: http://www.rxfiles.ca/rxfiles/uploads/documents/HTN-QandA-Accomplish.pdf
ACCORD LIPID & BP Trial Overview: http://www.rxfiles.ca/rxfiles/uploads/documents/ACCORD-BP-Lipid-Trial-Overview.pdf

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Extras

- ASCEND (A Study of Cardiovascular Events iN Diabetes) and ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes). These are large, ongoing studies that will enrol up to 15,000 participants with anticipated completion dates of 2011 and 2013, respectively.

ETDRS 5 yrs, n=3,711	T1DM & T2DM plus diabetic retinopathy; ~50% of pts with hx of CV disease <10% hx of MI or stroke	aspirin 2 x 325mg/day vs placebo	◆ 1°: all-cause mortality, 12.1 vs 14.9, RR 0.91 [99% CI, 0.75 to 1.11, p=0.24] ◆ 2°: cardiovascular mortality, 9.3 vs 11.2, RR 0.87 [99% CI, 0.7 to 1.1, p=0.12] ◆ 2°: fatal or non-fatal MI, 9.1 vs 12.3, RR 0.83 [99% CI, 0.66 to 1.04] ◆ 2°: fatal or non-fatal stroke, 4.5 vs 3.8, RR 1.17 [99% CI, 0.79 to 1.28] -no evidence of harmful effects of aspirin

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- From Circulation 2010: Intervention patients experienced a decreased risk of nonfatal or fatal MI (RR 0.85, 95% CI 0.73–1.00). In contrast, stroke occurred more frequently with aspirin, although the difference was not statistically significant (RR 1.18, 99% CI 0.88 –1.58). Men appeared to derive more benefit from aspirin than women for prevention of MI (RR for men 0.74, 99% CI 0.54 –1.00; RR for women 0.91, 99% CI 0.65–1.28), but this difference was not statistically significant and could represent a chance finding.
- From CCS 2011: For the predetermined secondary endpoint of fatal or nonfatal MI, the difference was significant at 5 years (RR 0.72, 99% CI 0.55-0.95) but not at 7 years (RR 0.83, 99% CI 0.66-1.04).

Online Extras

NNTs in T2DM - (Standardized for 5 yrs)

- ↓ Mortality: Metformin 2550mg/d in obese NNT=$7_{/5yrs}$ UKPDS-34
- ↑ Mortality: intensive blood glucose control $_{(A1C\ target=6)}$; NNH=$66_{/5yrs}$ ACCORD
- Blood pressure control: ?HOT trial??
- Major CHD Event: Atorvastatin 10mg daily; NNT=$26_{/5yrs}$ CARDS

Considerations for patient during Ramadan.

- Ensure adequate fluid intake for safety, especially critical for some medications (metformin, insulin, ACEI, ARB)
- Metformin: 1000mg at sunset meal; 500mg at pre-dawn meal
- Sulfonylureas: if daily, dose given at sunset meal; if twice a day, give larger amount prior to sunset meal

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Weight Loss: Online Extras 💻

Mediterranean Diet

The Mediterranean Diet is of course variable, but see Table 1 for the diet used in one large RCT.[30]
The Mediterranean Diet is not a fat restriction diet - rather, the source of fat is changed.
Potential benefits of the Mediterranean Diet include reductions in overall mortality, cardiovascular mortality, cancer incidence, cancer mortality, and incidence of Parkinson's, and incidence of Alzheimer's.
Visit www.mayoclinic.com/health/mediterranean-diet/CL00011 for more details.

Table 1: Mediterranean Diet	
Olive Oil, especially for cooking and in salads	≥ 4 tablespoons per day
Tree nuts and peanuts	≥ 3 servings per week
Fresh fruits	≥ 3 servings per day
Vegetables	≥ 2 servings per day
Fish (especially fatty fish), seafood	≥ 3 servings per week
Legumes	≥ 3 servings per week
Sofrito (a sauce made with tomato and onion, often including garlic and aromatic herbs, and slowly simmered with olive oil)	≥ 2 servings per week
White meat	instead of red meat
Wine with meals (optional, for habitual drinkers)	≥ 7 glasses per week
Discouraged: soda drinks; commercial bakery goods, sweets, and pastries; spread fats; red and processed meats.	

Discontinued Weight Loss Medications:

Generic/TRADE g=generic avail	Rating given, but meds not generally recommended in pregnancy!	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	WEIGHT LOSS DOSE	$/30d
Sibutramine[31] **MERIDIA**, g 10, 15mg cap ✗ ⊗ (REDUCTIL[UK]) 🫀 **Anorexiant –** inhibits reuptake of norepinephrine, serotonin, >dopamine PL		• May help by ↑ fullness sensation or ↓ snacking. Additional benefit when sibutramine & orlistat combined. • **Weight loss**: **~4.2kg/1 yr** (95% CI -4.7 to -3.6kg) dose-related; peak weight loss at 6 months and maintained with continued treatment. • **AE**: **Common**: dry mouth, headache, constipation, dizziness (to ↓AE: med with plenty of water may help); insomnia, menstrual changes, dyspepsia, rash, nervousness; ↓HDL. **Serious**: ↑HR (4-5 beats/min), ↑BP (1-3mmHg) (in some); seizure, cholelithiasis, ↑LFT (↑stroke & MI nonfatal Scout 10 NNH=72/3.4yr). **Rare**: depression, abnormal bleeding, pulmonary hypertension, serotonin syndrome, ↑ QT interval • **CI**: anorexia nervosa, bulimia, **heart**/CVD/↑BP/liver dx; on central acting appetite suppressants/MAOIs, age >65 • **DI**: ergots, lithium, MAOI (2wk wash-out period), meperidine, SSRIs, tramadol & triptans (↑risk of serotonin syndrome); stimulants (↑BP & HR) • **M**: BP& HR (q2wks for first 12 wks; then q1-3months) • **Safety**: 2yr data Not studied in <12yrs. Limited in 12-16yrs.[32,33,34,35,36] • **Several non-Rx products found to contain sibutramine**[1]**:** ARMA - Sin Gang San, Chao Nongsu Qingzhi Jiaonang Slim Hong Kong, Dai Dai Hua Jiao Nang, Dan Bai Shou Shen Su, Detox Peptide, Energy II, Fat Rapid Loss (Xin Yan Zi Pai Mei Zi Jiao Nang, Lexscl), Hanguo shoushen Yihao, Karntien Easy to Slim, Lasmi, LiDa Daidaihua Slimming Caps, Miaozi Slimming Caps, More Slim, Qianweisu Slimming Herb, Qing Zhi, Reduce Weight, Slim 3in1, Soloslim, Super Fat Burning, Xin Yi Dai & Xian Zhi Wei II etc. **FDA**: http://www.fda.gov/bbs/topics/NEWS/2009/NEW01977.html **Health Canada List**: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php	*10mg daily*; *Reassess dose after 1-2mos* 10mg po daily 15mg po daily STORM {Europe- D/C 2010} Max 15mg/d (some trials up to 20mg/d)	**Withdrawn from market Oct 2010** Canada

Diets

Most diets have short-term (e.g. six month) results, but in the long-term weight is regained. See http://www.cfp.ca/content/57/8/894.full. Examples include:

- **Balanced**: Weight Watchers.
- **Low Fat**: Pritikin.
- **Low carbohydrate**: Atkins {initial limit 20g carbohydrate/day; can lead to ketosis & rapid short term wt loss}.
- DASH Hypertension - may not help with weight loss, but useful to reduce salt and lower blood pressure. See www.nhlbi.nih.gov/health/health-topics/topics/dash.

More Useful Websites

American Heart Association: Healthy Lifestyle http://www.heart.org/HEARTORG/HealthyLiving/HealthyEating/Nutrition/The-American-Heart-Associations-Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp
Centers for Disease Control and Prevention: Overweight and Obesity www.cdc.gov/nccdphp/dnpa/obesity/index.htm
Heart Healthy Diet(s): http://www.**mayoclinic**.com/health/**mediterranean**-diet/CL00011 ; http://www.**cfp**.ca/content/57/8/894.full
National Heart, Lung, and Blood Institute: Aim for a Healthy Weight! www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/index.htm
Surgeon General: Physical activity and health: A report of the Surgeon General www.cdc.gov/nccdphp/sgr/sgr.htm
UK multicentre obesity management project www.counterweight.org

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suicide during treatment with rimonabant, we recommend increased alertness by physicians to these potentially severe psychiatric adverse reactions. { InfoPOEMs Jan08: These authors searched several databases for double-blind randomized trials of rimonabant for weight loss in patients with a body mass index higher than 30 (27 if the patient also had an obesity-related comorbid condition such as diabetes). Two reviewers independently assessed the quality of the included studies using the Jadad score. The authors don't describe looking for unpublished studies. Four trials (4105 patients) were included in this analysis. After 1 year, patients taking rimonabant lost an average of 4.7 kg more than did those given placebo. Additionally, 25% of patients taking rimonabant lost at least 10% of their baseline weight compared with 7% of control patients (number needed to treat = 5.3; 95% CI, 4.8 - 6). However, patients taking rimonabant were more likely to have unspecified serious adverse events (4% vs 6%; number needed to treat to harm [NNTH] = 58; 95% CI, 33 - 295). Additionally, 3% of patients taking rimonabant developed depression compared with 1.4% of control patients (NNTH = 63; 95% CI, 41-150). Although it's not formally addressed in this study, the authors mention recent Food and Drug Administration reports of increased suicide risk in patients taking rimonabant.}

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FDA approves **Orlistat for OTC**, Pharmacist's Letter Mar 2007.

FDA Nov/08 Fashion Sanctuary announced a recall of **Zhen De Shou Fat Loss** Capsules because FDA analysis found the product to contain undeclared sibutramine, an FDA approved drug used as an appetite suppressant for weight loss.

FDA Jan/09 notified consumers not to take Venom **HYPERDRIVE 3.0**, a product sold as a dietary supplement but containing sibutramine.

FDA Mar/09 Herbal **Xenicol** (found to contain cetilistat, an obesity drug not approved in the U.S.) along with **Slimbionic** and **Xsvelten** (both containing sibutramine, a prescription-only weight loss drug) have been added to the list of tainted dietary supplements. There are now **72 products** on the list. http://www.fda.gov/bbs/topics/NEWS/2009/NEW01977.html

FDA Apr/09: **ABC Beauty Supply** & FDA notified consumers and healthcare professionals of a recall of 34 dietary supplement products. FDA lab analyses identified undeclared **sibutramine**, an FDA- approved drug, used as an appetite suppressant for weight loss. http://www.fda.gov/oc/po/firmrecalls/universalabc04_09.html **(34 products listed)**

FDA July/09 notified healthcare professionals that four weight loss dietary supplements sold and marketed by the firm (**Slimbionic, One Weight Loss Pill, SlimDemand Capsules, Botanical Weight Loss**) contain sibutramine.

FDA Aug/09 notified healthcare professionals and patients that it is reviewing new safety information regarding reports of liver-related adverse events in patients taking orlistat. **Orlistat** is marketed in the United States as a prescription product, Xenical, and as an over-the-counter (OTC) product, Alli. Between 1999 and October 2008, 32 reports of serious liver injury, including **6 cases of liver failure**, in patients using orlistat were submitted to FDA's Adverse Event Reporting System. The most commonly reported adverse events described in the 32 reports of serious liver injury were jaundice, weakness, and abdominal pain.

FDA Nov/09 & GMP Herbal Products notified consumers and healthcare professionals of a recall of **Pai You Guo**, a weight loss dietary supplement, due to the presence sibutramine & phenolphthalein **.**

FDA Jan/10 notified consumers and healthcare professionals about a counterfeit and potentially harmful version of **Alli 60 mg capsules** (120 count refill kit). The **counterfeit** version contained the controlled substance sibutramine and did not contain orlistat, the active ingredient.

FDA July/10 analysis of **Que She** found that it contains: fenfluramine – a stimulant drug withdrawn from the U.S. market in 1997 after studies demonstrated that it caused serious heart valve damage, propranolol – a prescription beta blocker drug that can pose a risk to people with bronchial asthma and certain heart conditions, sibutramine – a controlled substance and prescription weight loss drug, sibutramine was the subject of a recent study whose preliminary findings showed an association between sibutramine use and increased risk of heart attack and stroke in patients who have a history of heart disease, & ephedrine – a stimulant drug that is legally marketed over-the-counter for temporary relief of asthma but can pose a risk to people with certain cardiovascular conditions.

FDA Aug/10 lab analysis of **Solo Slim** was found to contain the undeclared drug ingredient Didesmethyl Sibutramine.

FDA July/10 lab analysis of **Slim-30** Herb Supplement distributed by the company was found to contain undeclared N-Desmethyl Sibutramine and traces of Sibutramine.

FDA July/10 lab analysis of this herb supplement, **Joyful Slim** Herb Supplement, was found to contain the undeclared drug, desmethyl sibutramine.

FDA Oct/10 notified consumers that **Slimming Beauty Bitter Orange Slimming Capsules** contain the active pharmaceutical ingredient sibutramine, a prescription-only drug which is a stimulant.

FDA Oct/10 Abbott Laboratories notified healthcare professionals and patients about the **voluntary withdrawal of Meridia (sibutramine)**, from the U.S. market because of clinical trial data indicating an increased risk of heart attack and stroke.

FDA Dec/10 has received multiple reports of adverse events associated with the use of **Fruta Planta**, including several cardiac events and one death. FDA laboratory analysis confirmed that Fruta Planta contains sibutramine.

FDA Jan/11 laboratory analysis confirmed that **Celerite Slimming Capsules** contain sibutramine

FDA Mar/11 lab analysis of **Svelte 30** orange & gray capsules determined that the product contains Sibutramine.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analyses of **Celerite Slimming Tea**: Recall - were found to contain undeclared Sibutramine.

FDA May/11 laboratory analysis confirmed that "**Slim Xtreme Herbal Slimming Capsule**" contains sibutramine.

FDA July/11 is advising consumers not to purchase or use "**Slim Forte Slimming Capsules**," "**Slim Forte Slimming Coffee**," and "**Botanical Slimming Soft Gel & Slim Forte Double Power Slimming Capsules**. FDA laboratory analysis confirmed that these products contain sibutramine.

FDA Dec/11 took joint action against several companies selling over-the-counter **hCG products** that falsely and illegally claim to promote weight loss. Labeled "homeopathic" by the seven companies who received the letters, the products contain human chorionic gonadotropin (hCG), a hormone produced during pregnancy by cells that form the placenta. 1. HCG Diet Direct LLC- HCG Diet Homeopathic Drops, 2. The hCG Drops LLC- Homeopathic HCG, 3. HCG Platinum LLC; RightWay Nutrition- HCG Platinum, HCG Platinum X-30, HCG Platinum X-14, 4. Nutri Fusion Systems LLC- HCG Fusion 30, HCG Fusion 43, 5. www.resetthebody.com; www.theoriginalhcgdrops.com-Homeopathic Original HCG, Homeopathic HCG, 6. Hcg-miracleweightloss.com- HCG Extra Weight Loss Homeopathic Drops, 7. Natural Medical Supply- Alcohol Free hCG Weight Loss Formula.

FDA Feb/12 **Healthy People Co.** notified the public of a recall of the company's dietary supplements sold under the brand names Healthy People Co. FDA lab analysis confirmed the presence of Sibutramine and Tadalafil, making these products unapproved new drugs. (**Mince Belle Dietary Supplement, PERFECT Men Dietary Supplement , EVERLAX Dietary Supplement, EVER Slim Dietary Supplement, Herbal Drink Acai-man Mangosteen Dietary Supplement, EVER SLIM Shake Mix Dietary Supplement**)

FDA Feb/12 is advising consumers not to purchase or use "**Japan Weight Loss Blue**," a product for weight loss sold on various websites, laboratory analysis confirmed that "Japan Weight Loss Blue" contains sibutramine, analogs of sibutramine, and ephedrine alkaloids.

FDA Apr/12 laboratory analysis confirmed that "**Japan Rapid Weight Loss Diet Pills Yellow**" contains sibutramine and phenolphthalein.

FDA Oct/12 is advising consumers not to purchase or use "**Ultimate Formula Bee Pollen Capsules (Ultimate Formula)**," or "**Zi Xiu Tang Bee Pollen Capsules**," also referred to as "**Zi Xiu Tang Beauty, Face & Figure Capsule**," products promoted and sold for weight loss because they contain sibutramine.

FDA Dec/12 is advising consumers not to purchase or use "**SLIMDIA Revolution**," a product promoted and sold for weight loss on various websites, including www.pinkfatty.com, and in some retail stores since it contains Sibutramine.

FDA Jan/13 is advising consumers not to purchase or use "**MAXILOSS** Weight Advanced," a product promoted and sold for weight loss on various websites, includingwww.dreamlifeweightloss.com, and in some retail stores since it contains sibutramine.

FDA Feb/13 Olaax Corp announced a nationwide recall of the company's dietary supplement sold under the brand name **Maxiloss Weight Advanced Softgels** to the user level, because FDA testing found the Maxiloss Weight Advanced product to contain Sibutramine.

FDA Jun/13 FDA laboratory analysis confirmed that **"Bethel 30", & "XIYOUJI QINGZHI CAPSULE**" & **JaDera** contains sibutramine. .

FDA Jun/13 A sample of **Extreme Body Slim, Fat Zero, Fruit & Plant Slimming, & Paiyouji Plus** all contains silbutramine.

FDA Jun/13 Beta Labs has recalled certain lots of **Oxyphen, Phentalene, Phen FX, and Red Vipers** because they contain 1,3 dimethylamylamine (DMAA), the FDA announced over the weekend. The products are used as pre-workout stimulants and for weight loss, but the agency has previously warned that DMAA can be dangerous: it can elevate blood pressure and lead to cardiovascular complications. One distributor, GNC, faces FDA seizure of over 3000 cases of two other DMAA-containing products, **Jack3d and OxyElitePro**. Although the manufacturer of those supplements has ceased production, GNC continues to sell its remaining stocks, according to the *New York Times*.

FDA July/13 **Meizi Revolution, Strawberry Balance** contains silbutramine.

FDA Aug/13 Herbal Give Care LLC issued a voluntarily recall of all lots of **Esbelin silouttete** and **Esbelin siloutte Herbal Blend with L-Carnitine** (30 Capsules), to the consumer level. The products have been found to contain undeclared Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine.

FDA Aug/13 Bethel Nutritional Consulting, Inc., New York, NY, is voluntarily recalling **Quick Thin and Bethel Advance** to the consumer level. These products have been found to contain Sibutramine and Phenolphthalein, and may pose a threat to consumers.

FDA Aug/13 CTV Best Group announced that it is conducting a voluntary nationwide recall of all lots of a dietary supplement products distributed by the company under the names **BEST SLIM 40 Pills** to the consumer level. Testing by FDA revealed the presence of Sibutramine in Best Slim.

FDA Aig/13 Herbal Give Care LLC is voluntarily recalling all lots of **Esbelder man (30 capsules), Esbelder fem (30 capsules) and Esbelder siloutte** (30 capsules) to the consumer level. The products have been found to contain undeclared Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine.

FDA Sep/13 laboratory analysis confirmed that **Shou Fu Ti Tun Guo Xiang Xing Jian Fei Jiao Nang** contains sibutramine.

FDA Oct/13: B@B Trade, Inc., Florida is voluntarily recalling all lots of **Slim Fortune, Lidiy, and Slim Expert** to the consumer level. The FDA laboratory analysis of these dietary supplements found to contain undeclared Sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Perfect Body Solutions or Burn 7**. FDA laboratory analyses confirmed that Perfect Body Solutions and Burn 7 contain sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Dr. Mao Slimming Capsules**. FDA laboratory analysis confirmed that Dr. Mao Slimming Capsules contain sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Bella Vi Insane Amp'd or Bella Vi Amp'd Up.** FDA laboratory analyses confirmed that Bella Vi Insane Amp'd and Bella Vi Amp'd Up contain sibutramine.

FDA Nov/13 **SlimExtra Herbal** capsules contain silbutramine.

FDA Dec/13 laboratory analysis found the **Burn 7 Capsules** to contain undeclared Sibutramine.

FDA Jan/14 is advising consumers not to purchase or use **Magic Slim or Dream Body Slimming Capsule**, products promoted and sold for weight loss and sold on various websites and in some stores, since FDA lab analysis confirmed they contains sibutramine.

FDA Jan/14 **Citrus Fit Gold, Hot Detox & Thinogenics** contains sibutramine. **Tonic Life BP** contains phenolphthalein.

FDA Feb/14: MyNicKnaxs, LLC notified the public it is recalling all lots of "**Reduce Weight Fruta Planta**". FDA lab analysis of the product found Reduce Weight Fruta Planta to contain 10.2 mg of Phenolphthalein.

FDA Mar/14 is advising consumers not to purchase or use **Vitaccino Coffee**, a product promoted and sold for weight loss. FDA laboratory analysis confirmed that Vitaccino Coffee contains sibutramine.

FDA Mar/14: New Life Nutritional Center is recalling all lots of "**Super Fat Burner capsules, Maxi Gold capsules and Esmeralda softgels**" to the user level after FDA analysis revealed the products contain undeclared active pharmaceutical ingredients: sibutramine, phenolphthalein or a combination of both sibutramine and phenolphthalein.

FDA Mar/14: **Bella Vi Insane Bee Pollen Capsules, Bella Vi BTrim Ultimate Boost, Bella Vi BTrim Max, Bella Vi Extreme Accelerator, Bella Vi Insane Amp'd, and Bella Vi Amp'd U**, contain silbutramine with or without phenolphthalein.

FDA Mar/14: GlaxoSmithKline (GSK) Consumer Healthcare is **voluntarily recalling** all alli weight loss products from U.S. and Puerto Rico retailers as the company believes that some packages of the product were tampered with and may contain product that is not authentic **Alli**.

FDA Apr/14: FDA analysis on **New You** contains silbutramine.

FDA Apr/14 has tested multiple **Zi Xiu Tang Bee Pollen** products from various distributors in the United States (US). All products that have been tested, including those that claim to be "genuine" and "anti-counterfeit," have been found to contain one or both of the undeclared drug ingredients sibutramine and Phenolphthalein.

FDA Apr/14 laboratory analysis confirmed that **Infinity & Lite Fit** USA contains sibutramine.

FDA Apr/14: Nature's Universe notified the public it is recalling all lots of **Thinogenics** product sold prior to February 6, 2014 to the user level after FDA analysis revealed that the affected product contained undeclared sibutramine.

FDA May/14 laboratory analysis confirmed that **Slim Trim U & Natural Body Solution** contains sibutramine.

FDA May/14 is advising consumers not to purchase or use **Asset Bee Pollen**, a product promoted and sold for weight loss because it contains sibutramine.

FDA May/14 is advising consumers not to purchase or use **Asset Bold**, a product promoted and sold for weight loss. FDA laboratory analysis confirmed that Asset Bold contains sibutramine.

FDA Jun/14 laboratory analysis confirmed that **La Jiao Shou Shen** contains sibutramine

FDA Jun/14 laboratory analysis confirmed that **Sliming Diet** contains sibutramine.

FDA July/14 laboratory analysis confirmed that **Mix Fruit Slimming, Lingzhi Cleansed Slim Tea, 24 Ince, Lipo 8 Burn Slim, Sliming (sic) Diet By Pretty, & Trim-Fast Slimming Softgel** contains sibutramine.

FDA July/14: **Vitaccino Coffee, Collagen Slim, & Sulami** contains sibutramine.

FDA July/14: **Fruta Bio, Jianfeijindan Activity Girl, & LTD Japanese Chinese Formula pill** for weight reduction contains sibutramine and/or phenolphthalein.

FDA Aug/14 Regeneca Worldwide a division of VivaCeuticals, Inc., is conducting a voluntary nationwide recall of its **RegenESlim appetite control dietary supplement**, lot # EX0616R15814 and lot #11414RE5516, because FDA analysis confirmed the presence of DMAA.

FDA Sep/14 laboratory analysis confirmed that **Best Line Suplemento Alimenticio Capsules** contains sibutramine.

FDA Sep/14 laboratory analysis confirmed that **Japan Hokkaido Slimming Weight Loss Pills** contain sibutramine, benzocaine, phenolphthalein and diclofenac.

FDA Sep/14 laboratory analysis confirmed that **Mezo** contains benzylsibutramine, a substance structurally similar to sibutramine.

FDA Sep/14 laboratory analysis confirmed that **Mezo** contains benzylsibutramine, a substance structurally similar to sibutramine.

FDA Oct/14 laboratory analysis confirmed that **Sit and Slim II** contains sibutramine.

FDA Nov/14 is advising consumers not to purchase or use **V26 Slimming Coffee**. FDA laboratory analysis confirmed that V26 Slimming Coffee contains sibutramine.

FDA Nov/14: REFA Enterprises is voluntarily recalling one lot each of: **Forever Beautiful Bee Pollen** (UPC # 6333090804632), **Forever Beautiful Infinity** (UPC # 633090804649). The products have been found to contain undeclared Sibutramine or a combination of both Sibutramine and Phenolphthalein through FDA laboratory analyses.

FDA Nov/14 is advising consumers not to purchase or use **Bee Slim, Bee Thin & Super Extreme Accelerator**. FDA laboratory analysis confirmed that they contain sibutramine.

FDA Nov/14 laboratory analysis confirmed that **Slim-Vie** containssibutramine.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **SLIM-K Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of SLIM-K collected and tested by the FDA was found to contain sibutramine, desmethylsibutramine, and phenolphthalein.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **B-Lipo Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of B-Lipo Capsules collected and tested by the FDA was found to contain lorcaserin.

FDA Feb/15 laboratory analysis confirmed that **Lean Body Extreme** contains sibutramine, desmethyl sibutramine, phenolphthalein, and sildenafil.

FDA Feb/15 laboratory analysis confirmed that **Nine Slim, & Seven Slim** contains phenolphthalein.

FDA Mar/15 laboratory analysis confirmed that **Elimulating Weight & Toxin Keeping Beauty** contains sibutramine

FDA Mar/15 laboratory analysis confirmed that **Black Mamba Hyperrush & L-Carnitine Sob Strengthening Version Slimming Miracle Capsule** contains sibutramine.

FDA Mar/15 laboratory analysis confirmed that **Green Algae** Combination by Crane Beauty contains lorcaserin.

FDA May/15 laboratory analysis confirmed that **Li Da Dai Dai Hua Slimming Capsule** contains sibutramine.

FDA May/15 laboratory analysis confirmed that **Slim Forte Slimming Capsule** contains sibutramine.

FDA Apr/15 laboratory analysis confirmed that **Superior** contains sibutramine.

FDA May/15 **Yanhee Slim & iNSANE Bee Pollen** contains undeclared lorcaserin; **EDGE Amplified Weight Release** contains undeclared phenolphthalein and fluoxetine; **iNDiGO & BtRim Max** contains undeclared phenolphthalein.

FDA May/15: **Nine Slim & Seven Slim** contains undeclared phenolphthalein.

FDA May/15: **Oxy ELITE Pro Super Thermogenic** contains undeclared fluoxetine.

FDA May/15: **Elimulating Weight & Toxin Keeping Beauty & L-Carnitine Sob Strengthening Version Slimming Miracle Capsule** contains undeclared sibutramine.

FDA May/15: **Lean Body Extreme** contains undeclared sibutramine, desmethyl sibutramine, phenolphthalein & sildenafil.

FDA May/15: **Diablos Eca Fire Caps** contains undeclared sildenafil, phenolphthalein, sibutramine & deisobutylbenzylsibutramine.

FDA July 15: **Black Mamba Hyperrush & Ultra ZX** contains Undeclared sibutramine and phenolphthalein.

FDA July 15:**Botanical Slimming (Red) & Xcel** contains Undeclared fluoxetine.

FDA July 15:**Green Algae Combination** by Crane Beauty contains Undeclared lorcaserin.

FDA July 15:**Natural Max Slimming** contains Undeclared sildenafil, fluoxetine, and sibutramine.

FDA July 15: **Ultimate Boost & Xcel Advanced** contains Undeclared phenolphthalein.

FDA Sep/15: **Miracle Diet 30** has been found to contain undeclared **phenolphthalein.**

FDA Oct/15 **Lida DaiDaiHua** contains undeclared sibutramine & phenolphthalein.

FDA Sep/15: **Miracle Diet 30** has been found to contain undeclared phenolphthalein.

FDA Oct/15 laboratory analysis confirmed that **Xtreme Fat Burner Capsules** contains phenolphthalein.

FDA Oct/15 laboratory analysis confirmed that **Tip-Top Shape, Lishou Slimming Coffee, & Basha Nut 100% Fruit Soft Gel Capsules** contains sibutramine.

FDA Nov/15 laboratory analysis confirmed that **Super Herbs** contains sibutramine and desmethylsiburamine.

FDA Nov/15 laboratory analysis confirmed that **Zero Fat & SPCARET Princess Diet** contains sibutramine.

FDA Dec/15 laboratory analysis confirmed that **Thirty Plus** contains sibutramine.

FDA Dec/15 Lipo Escultura Corp. of Brooklyn, NY (dba JAT Productos Naturales Corp., and JAT Natural Products Corp.): recalling all **Lipo Escultura** within expiry to the consumer level since contains sibutramine and diclofenac..

FDA Dec/15 laboratory analysis confirmed that **Evolve Bee Pollen, Jenesis, Prime Bee Pollen & Oasis Bee Pollen** contains sibutramine.

FDA Dec/15: laboratory analysis confirmed that **La'Trim Plus** contains sibutramine.

FDA's Dec/15 analysis found the **Smart Lipo** products to contain undeclared sibutramine, desmethylsibutramine, and phenolphthalein.

FDA Dec/15 BeeXtreme LLC is recalling all lots of **La' Trim Plus, Jenesis and Oasis products** from the market. Recent Analysis by the Food and Drug Administration has found undeclared Sibutramine and Phenolphthalein.

FDA Jan/16 analysis of **Pink Bikini** (white capsules, blue capsules and gold capsules) and **Shorts on the Beach** (blue capsules and gold capsules) found these products to be tainted with Sibutramine, Phenolphthalein, and/or Diclofenac.

FDA Mar/16 laboratory analysis confirmed that **Propell Platinum** contains sibutramine.

FDA Mar/16 laboratory analysis confirmed that **ENVY BP** contains sibutramine.

FDA Apr/16 Super Herbs is voluntarily recalling all bottles of **SUPER HERBS**, light green and dark green capsules to the consumer level after FDA laboratory testing found SUPER HERBS to contain sibutramine, desmethylsibutramine, and/or phenolphthalein.

FDA May/16 laboratory analysis confirmed that **3rd Degree & Black Gold X** contains sibutramine.

FDA May/16 laboratory analysis confirmed that **Black Label X** contains sildenafil.

FDA May/16 laboratory analysis confirmed that **Step 2 contains** sibutramine.

FDA June/16: The Body Shot Bar is voluntarily recalling all lots distributed March 1- May 6 2016 of **Step 2 60 gold capsule** (350MG per) capsules to the consumer level. Step 2 has been found positive for Sibutramine.

FDA July/16: FDA laboratory analysis confirmed that **Dream Body Extreme Gold** contains sibutramine, fluoxetine and sildenafil.

FDA July/16: FDA laboratory analysis confirmed that **Dream Body Original Formula, SBF Bee Pollen & Extra Slim Plus Acai Berry Weight Loss Formula** contains sibutramine.

FDA July/16: Dream Body Weight Loss is voluntarily recalling all lots of **Dream Body Extreme Gold 800mg 30 gold capsules, Dream Body 450mg 30 white capsules, and Dream Body Advanced 400mg 30 purple capsules** to the consumer level. The **Dream Body Extreme 800mg Gold, Dream Body 450mg and Dream Body Advanced 400mg** have been found to contain sibutramine.

FDA July 16 laboratory analysis confirmed that **Slim Fit X, & Mang Luk Power Slim Detox** contains sibutramine and desmethylsibutramine.

FDA July 16 laboratory analysis confirmed that **Mang Luk Power Slim, Maxx Easy** contains sibutramine.

FDA July/16 laboratory analysis confirmed that **Xcelerated Weight Loss Charged Up, Xcelerated Weight Loss Turbo Charge** contains sibutramine.

FDA July/16 laboratory analysis confirmed that **Xcelerated Weight Loss Ultra Max** contains phenolphthalein and sildenafil.

FDA Jul/16 laboratory analysis confirmed that **Zi Xiu Tang Beauty Face & Figure Capsule** contains phenolphthalein and fluoxetine.

FDA Jul/16 laboratory analysis confirmed that **Ultimate Lean** contains sibutramine and desmethylsibutramine.

FDA Aug/16 laboratory analysis confirmed that **Natural Eruption** contains sibutramine.

FDA Aug/16 laboratory analysis confirmed that **Citrus' Fit** contains sibutramine and desmethylsibutramine.

FDA Aug/16 laboratory analysis confirmed that **Adelgazantes R-II** contains sibutramine.

FDA Oct/16 laboratory analysis confirmed that **Zi Su Body Fat Health II** contains sibutramine and phenolphthalein.

FDA Nov/16 laboratory analysis confirmed that **ABX Weight Loss** contains sibutramine.

FDA Nov/16 Love My Tru Body is voluntarily recalling all of **Skinny Bee Diet 500 mg** to the consumer level after FDA laboratory testing found Skinny Bee Diet to contain sibutramine, desmethylsibutramine, and/phenolphthalein.

FDA Dec/16 Ultimate Body–Tox is voluntarily recalling all lots of **Ultimate Body Tox PRO** capsules to the consumer level. FDA analyses of this product found it to contain undeclared sibutramine.

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Health Canada Apr/07 is warning consumers about **Bitter orange** & cardiovascular reactions in the Canadian Adverse Reactions April 2007 Newsletter.
Health Canada Apr/07 is warning consumers from the Hong Kong Department of Health found **Lexscl Fat Rapid Loss capsules to be adulterated with sibutramine** and thyroid hormones.
Health Canada via July/07 Medsafe also advised the public not to use the product **Dai Dai Hua Jiao Nang** because it was found to contain sibutramine.
Health Canada Aug/07 is advising Canadians of a recall in the United States of one lot of **Metaboslim Apple Cider Vinegar**, which is marketed as a dietary supplement, because it has been found to contain sibutramine, a prescription medication that should only be taken under medical supervision.
Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang**, **J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.
Health Canada Jan/08 is warning Canadians not to use the unauthorized product **Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules** (batch number 28012007 / expiration date: Jan 2009). This product is promoted for weight loss and has been found to contain a derivative of the prescription drug sibutramine.
Health Canada April/08 is advising consumers not to use **Xian Zhi Wei II** was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.
Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Dan Bai Shou Shen Su** was found to contain undeclared thyroid hormones and sibutramine. **Karntien and Karntien Easy to Slim** were adulterated with sibutramine and a compound that is similar in structure to sibutramine (N-desmethylsibutramine). **More Slim** was found to contain the undeclared pharmaceutical ingredient sibutramine. **Soloslim** was found to contain an undeclared substance similar in structure to the prescription drug sibutramine. It also contains the prescription drug L-carnitine, as well as synephrine, which is not authorized for sale in weight loss products in Canada.
Health Canada Aug/08 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of Natural (Xin Yi Dai) and Lasmi because Natural (Xin Yi Dai) was found to contain sibutramine and phenolphthalein, and Lasmi was found to contain sibutramine and spironolactone. The Hong Kong Department of Health warned against the use of AA Qu Feng Shu Jin Wan because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. Apisate contained fenfluramine and Energy ll contained sibutramine. Obat Asam Urat and Asam Urat both contained dexamethasone, phenylbutazone and piroxicam. The Hong Kong Department of Health warned against the use of Slim 3in1 (Xiao Nan zhi Bao) because it was found to contain the undeclared pharmaceutical ingredients sibutramine and phenolphthalein.
Health Canada Sep/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of **Hanguo shoushen yihao** (meiti xing) because it was found to contain the undeclared pharmaceutical ingredient sibutramine. The Hong Kong Department of Health warned against the use of **ARMA - Sin Gang San** and New ARMA - Sin Gang San because they were found to contain the undeclared pharmaceutical ingredients sibutramine and fenfluramine.
Health Canada Nov/08 is advising that the Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine.
Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains sibutramine.
Health Canada Mar/09 Foreign Product: **68 Weight Loss Products**; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien & Relacore. Plus Lami, Linglongquxian, Menergy M-Essence, Nyal Day & Night Cold & Flu Fighter (AUST L 146264), Nyal Cold & Flu Fighter (AUST L 146263), 999 Radix Notoginseng, Batch no. 0807021, Slim Pure, Carbohydrate, Kalomee, K Carbohydrate, K Tighten Slim, & K Slimming Pills. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php
Health Canada June/09 Foreign Product Alerts: **Jia Yi Jian** (undeclared sibutramine & tadalafil); **Shan Dian Qiang Xiao Shou** (undeclared sibutramine & phenolphthalein).
Health Canada June/09 is warning consumers not to use the unauthorized product **Slim Magic Herbal**, which is promoted as a weight-loss product, as it was found to contain an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning consumers not to use the unauthorized product **Nutural Slim**, which is promoted as a weight-loss product, as it was found to contain the undeclared pharmaceutical ingredient sibutramine and also an undeclared pharmaceutical ingredient similar to sibutramine.

Health Canada June/09 warns of foreign Product Alerts: ***Herbal Xenicol*** because it contains undeclared cetilistat. ***BioEmagrecim***, which the FDA had previously warned contained sibutramine, was also found to contain fluoxetine, furosemide and fenproporex. Products: ***Slimbionic***, ***Xsvelten***, ***999 Fitness Essence***, ***24" ince***, ***Light Some***, ***Paiyouji***, ***Pearl White Slimming***, & ***Reducing Weight Easily*** contain undeclared pharmaceutical ingredients (sibutramine and/or phenolphthalein) and/or excessive levels of lead, and may cause serious health effects..

Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is warning consumers not to use "**RevolutionDS Weight Loss**", an unauthorized health product promoted for weight loss, because it contains benzylpiperazine (BZP), and may pose serious health risks.

Health Canada Jan/10 informs that U.S. FDA: **Pai You Guo** contains sibutramine and phenolphthalein. Hong Kong Department of Health: **Ku Xiu Ba Xiang Jian Fei Wan** contains sibutramine and an unauthorized substance similar to sibutramine; **Super Slim (Yani)** contains sibutramine and phenolphthalein; **SHoufsy** contains sibutramine & **MIGAC (sic) FAT BURMING (sic) FACTOR** contains sibutramine.

Health Canada Jan/10 is warning consumers not to use the unauthorized product "**The Slimming Coffee**," which was previously sold as "**Lose Weight Coffee**," because it was found to contain sibutramine.

Health Canada Mar/10 is warning Canadians that an unauthorized health product, "**Herbal Diet Natural**" has been found on the Canadian market and contains an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning Canadians that an unauthorized health product, "**West Pharm Therma Lean Fat Burner Energizer**" was found on the Canadian market. West Pharm Therma Lean Fat Burner Energizer contains Ephedrine and caffeine, which combined together, may cause serious and possibly fatal adverse effects.

Health Canada Apr/10 is warning Canadians that an unauthorized health product, "Slim-30" distributed in Ontario and Quebec by Duxx Enterprises Inc., contains an undeclared pharmaceutical ingredient similar to the prescription drug, sibutramine.

Health Canada May/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Ba Bao Xiao Ke Dan** The Hong Kong Department of Health warned consumers not to buy or use Ba Bao Xiao Ke Dan after it was found to contain undeclared glibenclamide. 2. **Seven Slim 7 Seshou** (Qingchun Shaonüxing, Jieshixing, Guifurenxing, Songchixing), Shoushen Jiaoguan-Tinei Yundong Wan (Jian Xiabanshen, Jian Quanshen Feipang) The Hong Kong Department of Health warned consumers not to buy or use the six products listed above after they were found to contain undeclared sibutramine and phenolphthalein.

Health Canada May/10 is advising consumers not to use 1. **Botanical Slimming 100% Natural Soft Gel, also sold as Meizitang** The Australian Therapeutic Goods Administration warned consumers not to buy or use this product after it was found to contain undeclared sibutramine. 2. **Marsha Slim Plus** The Hong Kong Department of Health warned consumers not to buy or use Marsha Slim Plus after it was found to contain undeclared sibutramine, an unauthorized substance similar to sibutramine and phenolphthalein. 3**. S&S Super Slender** The Hong Kong Department of Health warned consumers not to buy or use S&S Super Slender after two samples were found to contain agent similar to sibutramine. One of the tested samples also contained undeclared sibutramine and phenolphthalein.

Health Canada June/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **COMECOO, ZHONGCAOYAO-JIANKANGJIANFEI** The Hong Kong Department of Health warned consumers not to buy or consume these two products after they were found to contain undeclared phenolphthalein, sibutramine and two unauthorized substances similar to sibutramine. 2. **Qingzhi Santian Shou** The Hong Kong Department of Health warned consumers not to buy or consume Qingzhi Santian Shou after it was found to contain undeclared sibutramine and an unauthorized substance similar to sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) 1.. **Po Chai Pills** (capsule form) The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain undeclared sibutramine and phenolphthalein. Sibutramine is a prescription drug and should only be used under the supervision of a health care practitioner while phenolphthalein is no longer authorized for sale in Canada because it may cause cancer. Po Chai Pills (capsule form) has been recalled by the manufacturer. 2. **LiPO-8 Cap and Glucomi 600 Cap** Hong Kong Department of Health warned consumers not to buy or use these products because they contain undeclared sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume *1 Body Beautiful* after it was found to contain undeclared phenolphthalein and sibutramine. 2. **USA Yaku Cell Slimming Capsules, Dong Gua Pai You Su, Qing Gua Pai You Su, and Mu Gua Pai You Su** The Hong Kong Department of Health warned consumers not to buy or consume these four products after they were found to contain undeclared phenolphthalein, sibutramine and an unauthorized substance similar to sibutramine.

Health Canada Aug/10 is advising consumers not to use the following foreign health product(s): **Que She** The U.S. FDA warned consumers not to buy or use Que She after it was found to contain undeclared fenfluramine, propranolol, sibutramine and ephedrine. **Sheng Yuan Fang** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use Sheng Yuan Fang after it was found to contain undeclared phenolphthalein and sibutramine.

Health Canada Sep/10 is advising consumers not to use : **Joyful Slim Herb** Supplement The U.S. FDA informed consumers of a recall of one lot (#101408) of Joyful Slim Herb Supplement after FDA tests found it to contain undeclared desmethyl sibutramine. The lot is being voluntarily recalled nationwide in the U.S. by the company J & H Besta Corp.

Health Canada Oct/10 is informing healthcare practitioners and Canadians that Abbott Laboratories is **voluntarily withdrawing the prescription weight-loss drug sibutramine**, which is marketed as Meridia®, from the Canadian market.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Goya–Bitter Melon - Miyura Fit'x Capsules** contained undeclared phenolphthalein and sibutramine **2. Solo Slim Extra Strength - Revivexxx Extra Strength** contained undeclared didesmethyl sibutramine.

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Slimming Beauty Bitter Orange Slimming Capsule (Slimming Beauty)** The U.S. Food and Drug Administration warned consumers not to buy or use Slimming Beauty after FDA lab tests revealed that this product contains undeclared sibutramine.

Health Canada Jan/11 The product **Synerate**, manufactured for Strive and distributed by Upper 49th, is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. Synerate, a product used for weight loss or body building, contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Feb/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Fruta Planta, Reduce Weight Fruta Planta** The U.S. FDA warned consumers not to buy or use Fruta Planta and Reduce Weight Fruta Planta after FDA lab tests revealed that this product contains undeclared sibutramine. **2. Slimming Factor** The Australian TGA warned consumers not to buy or use Slimming Factor after TGA lab tests confirmed the presence of the undeclared substances sibutramine, fenfluramine and phenolphthalein. According to the TGA release, the product is sold over the Internet.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Celerite Slimming Capsules**: The U.S. FDA informed consumers of a company recall of CeleriteTM Slimming

Capsules after it was found to contain undeclared sibutramine. 2. **Herbal Flos Lonicerae** (Herbal Xenicol) Natural Weight Loss Formula: The product was found to contain undeclared sibutramine at more than twice the dose that was normally prescribed before sibutramine was removed from the UK market in 2010.

Health Canada May/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Dr. Health Series CM Factor** The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain an unauthorized substance similar to sibutramine that may pose similar health risks.

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Slim Xtreme Herbal Slimming Capsules** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *Slim Xtreme Herbal Slimming Capsules* was found to contain undeclared sibutramine.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Celerite Slimming Tea** The U.S. FDA informed consumers of a company recall of Celerite Slimming Tea after it was found to contain undeclared sibutramine. **2. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet. **3. Fifteen products promoted for weight loss** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use these 15 products after they were found to contain at least one of the following undeclared substances: phenolphthalein, sibutramine, and/or an unauthorized substance similar to sibutramine.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **Slim Forte Slimming Capsules**, **Slim Forte Double Power Slimming Capsules**, **Slim Forte Slimming Coffee** and **Meizitang Botanical Slimming Soft Gel**-The U.S. Food and Drug Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **OxyELITE Pro capsules and Pure Fat Three Days Reduce Weight capsules**-The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine), or a prescription drug (yohimbine).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. 1. **Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones). 2. **Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al,** and **Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine). 3. **Slimming Kapsul** The Hong Kong Department of Health warned that this weight-loss product contains an unauthorized drug (sibutramine) and a prescription drug (spironolactone). 4. **Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a prescription drug (glyburide).

Health Canada Jan/12 advises: 1)**17 weight loss products (see Alert for a complete list)** A-Slim 100% Natural Slimming Capsule, Acai Berry Soft Gel ABC, Advanced Slim 5 >DaiDaiHuaJiaoNang, Dream Body Slimming Capsule, Fruit Plant Lossing Fat Capsule, Health Slimming Coffee, Ja Dera 100% Natural Weight Loss Supplement, Leisure 18 Slimming Coffee, Lishou, Magic Slim Tea, Magic Slim Weight Reduction Capsule, P57 Hoodia, Pai You Guo Slim Tea, PhentraBurn Slimming Capsules, Slender Slim 11 Tengda. The U.S. Food and Drug Administration warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Slimina weightloss capsules, S-shape slim capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain prescription drugs (propranolol, nifedipine) and/or unauthorized drugs (sibutramine, fenfluramine, phenolphthalein). **3. Cardiotium, Paidusu, SlimEasy Herbs Capsule, Tianran Zuanshi Xianweisu** The Hong Kong Department of Health warned that these health products contain prescription drugs (losartan, atorvastatin, thyroxine) and/or unauthorized drugs (sibutramine, phenolphthalein).

Health Canada May/12 1. **CanSui; Lexscl Fat Rapid Loss Capsule; The Extreme-thin Fat Burning Bomb; Xiu Zhi Su L-Carnitine Slimming Capsule** The Hong Kong Department of Health warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). 2. **Lipro Diet Pills; Xiyouji Qingzhi** weight loss capsules The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine).

Health Canada June/12 **1. Japan Weight Loss Blue, Japan Rapid Weight Loss Diet Pills Green; Japan Rapid Weight Loss Diet Pills Yellow:** The U.S. Food and Drug Administration warned that these weight loss products contain prescription drugs (sibutramine, ephedrine alkaloids) and unauthorized drugs (phenolphthalein, and substances similar to sibutramine). **2. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil).

Health Canada Jun/12 testing has identified that the weight loss product "**ZXT Gold**" bee pollen capsules contain hidden pharmaceutical ingredients (sibutramine and phenolphthlalein).

Health Canada Aug/12: Burnaby, B.C. Store (**U-Box**) Selling Potentially Dangerous Weight Loss Products. Further to our previous communications, Health Canada is advising Canadians that four products promoted for weight loss have been seized from "U-Box," a store in Burnaby, B.C. Health Canada testing has identified they contain hidden drug ingredients (sibutramine and phenolphthalein) that may pose serious health risks. Caffeine was also found in some of the products and was not listed on the product label.

Health Canada is advising Canadians that three unauthorized products **"Goya Bittermelon", "S-organic Cocoa+L-carnitine", or "KaBaNa L-Carnitine 360 Slimming Coffee**", promoted for weight loss have been seized from "Cube Inc.", a box-store in Richmond, B.C. These products contain hidden drug ingredients (sibutramine and phenolphthalein) that may pose serious health risks. Caffeine was also found in two products and was not listed on the product label.

Health Canada Apr/13 **1. Diet Garcinia Forte; Shan Dian Shou; Aulura Energy Dietary Supplement** The Hong Kong Department of Health has advised consumers not to use these products after they were found to contain sibutramine and phenolphthalein, drug ingredients that were not declared on their product label.

Health Canada Aug/13 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Brazilian Slimming Coffee, Leisure 18 Slimming Coffee, 7 Days Slimming Coffee, Brazilian 7 Days Slimming Coffee, Beauty Secret Slimming Coffee, Body Beauty 5 Days Slimming Coffee, Leisure 18 Slimming Mango Juice, Leisure 18 Slimming Orange Juice, Authentic Leisure 18 Slimming Orange Juice, Super Slim Orange Juice, Coffee Fashion Slimming** The Hong Kong Department of Health has advised consumers not to use these products after they were found to contain the undeclared drug ingredients sibutramine and/or phenolphthalein. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34859a-eng.php **5. Best Slim capsules, Meizi Evolution Botanical Slimming soft gel capsules** The Australian Therapeutic Goods Administration warned consumers not to use these products after they were found to contain the undeclared drug sibutramine.

Health Canada Nov/13 is advising Canadians not to use these foreign health products as they may pose a health risk. These products have been found by regulators in other countries to contain drug ingredients or soy milk allergens that are not declared on the product labels, or a high level of microbial contamination. Prescription drugs should only be taken under the supervision of a healthcare professional. These products are not authorized for sale in Canada and have not been found on the Canadian market, but they may have been brought into the country by travellers or purchased over the Internet:

1. **Aisiyuan V26 Slimming Granules, AcaiBerry Living-XS, and 4C Cosmoslim** , http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36269a-eng.php ;

2**. MAXILOSS Weight Advanced** http://healthycanadians.gc.ca/recall-alert- rappel-avis/hc-sc/2013/36197a-eng.php;

3. **ESV Extra Strong Version, MSV Strong Version, RL Rapid Loss, My Slimmer Me (MSM) soft gel capsules, Natural Miaotiaoyishen capsules, and Paiyouji Natural Slimming Capsules** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36521a-eng.php.

Health Canada Feb/14: 1. **Lightning 10.0+, LV Shou Reduces Fat, and STB Summit of the Thin Body S Woman Degreasing Burning Pill** The Hong Kong Department of Health warned consumers not to use this product after it was found to contain sibutramine, phenolphthalein, and indomethacin.

Health Canada Apr/14 has seized the unauthorized drug, "**L-Showm Weight Loss Pills**", being sold at the U-Box store, located at 2809-4500 Kingsway, Burnaby, BC. Health Canada testing: contained an undisclosed ingredient, phenolphthalein.

Health Canada Apr/14: Four unauthorized drugs being sold at two SVN FUEL stores - one in Burnaby and one in Coquitlam, B.C. - were seized by Health Canada as they contain ingredients that are potentially dangerous to the health of consumers. The products, and the unapproved ingredients they contain, include **Jack3d** (DMAA (1, 3-dimethylamylamine), **Red Rockets** (ephedrine and caffeine), **West Pharm Therma Lean** (ephedrine and caffeine), and **OxyElite Pro** (1, 3-dimethylamylamine HCl and Yohimbe Bark extract). They were being promoted for weight management.

Health Canada May/14 **Esbelin siloutte te, Esbelin Siloutte Herbal blend with L-Carnitine, Esbelder man, Esbelder fem, Esbelder siloutte** contains Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine; **Instant Slim** contains sibutramine and phenolphthalein.

Health Canada May/14 One lot of **Lite Fit USA** (Lot Number 13165, Exp. 05/17) is being voluntarily recalled in the U.S. after analysis by the U.S. Food and Drug Administration revealed the lot contains the undeclared prescription drug sibutramine.

Health Canada May/14: 1. **Slim Fortune, Lidiy & Slim Expert:** FDA found sibutramine; 2. **Dr. Mao Slimming capsules, Perfect Body Solutions, Burn 7**: FDA found sibutramine; **Bella Vi Insane Amp'd Up, Be Inspired, Goodliness Fat Reducing capsules, Jimpness Beauty Fat Loss capsules**: FDA found sibutramine and phenolphthalein.

Health Canada June/14: **Asset Extreme, Asset Extreme Plus, Meizitang Citrus, Slimming Diet Berry Plus, Citrus Fit Gold, Hot Detox, Thinogenics** contains sibutramine. **Tonic Life BP & Slimfast** capsules contains phenolphthalein . **Dr. Ming's Chinese Capsule, Magic Slim and Apple's Quick Impact Weight Loss** contains sibutramine and phenolphthalein.

Health Canada July/14: **Bella Vi Insane Bee Pollen Capsules, Bella Vi BTrim Ultimate Boost, Bella Vi BTrim Max, Bella Vi Extreme Accelerator**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and/or phenolphthalein. **Super Fat Burner capsules, Maxi Gold capsules, and Esmeralda softgels**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and phenolphthalein. **Powerful leg-slimming capsules, Pink grain herbal slimming capsules, and Night fat-burning capsules**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain undeclared phenolphthalein and diclofenac. The product, Night fat-burning slimming capsules, was also found to contain undeclaredtheophylline. **Zi Xiu Tang Pollen capsule and Zi Xiu Tang Beauty Face and Figure capsule**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain undeclared sibutramine, phenolphthalein, diclofenac, and ibuprofen. The product, Zi Xiu Tang Beauty Face and Figure capsule, was also found to contain undeclared glibenclamide, and indomethacin.

Heath Canada Aug/14: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use the product **Sanovera Starter capsules**, the Hong Kong Department of Health warned consumers not to use the product **Yanhee Slim** and the United States Food and Drug Administration (FDA) warned consumers not to use the products **Infinity, Asset Bee Pollen, Asset Bold, Slim Trim U, and Natural Body Solution** after they were found to contain undeclared sibutramine. The Australian Therapeutic Goods Administration (FDA) warned consumers not to use **3x Slimming Powder Capsules** after it was found to contain undeclared sibutramine and phenolphthalein.

Health Canada Sep/14: **La Jiao Shou Shen, B-Perfect, Diet Master, Super Slim, Slim Max**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and phenolphthalein.

Health Canada Dec/14 is following up with Rapha Biotech Inc. **RAPHA Vitamin B1** (NPN: 80036493) -- undeclared ingredients: sibutramine, desmethyl sibutramine.

Health Canada Dec/14: The United States Food and Drug Administration (FDA) warned consumers not to use the products **Lingzhi Cleansed Slim Tea, Trim-Fast Slimming Softgel, Sliming Diet By Pretty White, Lipo 8 Burn Slim, and Best Line Suplemento Alimenticio Capsules**. Tthe Hong Kong Department of Health warned consumers not to use the products **Slim Perfect Arm and Slim Perfect Legs** and the Australian Therapeutics Goods Administration (TGA) warned consumers not to use the product **Slyn Both Green capsules** after they were found to contain undeclaredsibutramine. The United States Food and Drug Administration (FDA) also warned consumers not to use the product **Mezo** after it was found to contain benzylsibutramine. **Mix Fruit Slimming**: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain undeclared sibutramine and phenolphthalein.

Health Canada Jan/15: **Star Majestic Slimming-** Undeclared sibutramine & phenolphthalein via Australian Therapeutic Goods Administration. **Sit and Slim II**-Undeclared sibutramine & phenolphthalein via FDA.

Health Canada Mar/15 advises- FDA Mar/15 **Bee Slim** & **Bee Thin** has undeclaried silbutramine. Singapore Health Sciences Authority Mar/15 **Nutri Drops Grapefruit Diet**: Undeclared sibutramine, benzyl sibutramine & phenolphthalein.

Health Canada Mar/15 advisory regarding "**Altimate Fat Burner Maximum Burn" being sold by Nature's** Source in Vaughan, Ont., the Department received a complaint about the product also being sold at Nature's Source, 2391 Trafalgar Rd., Unit #6 in Oakville, Ont. Altimate Fat Burner Maximum Burn is an unauthorized health product labelled to contain DHEA, yohimbe, caffeine and ephedrine.

Health Canada Jun/15 requests quarantine of drugs linked to **Zhejiang Hisun Pharma** due to data integrity concerns.

Health Canada Aug/15-FDA has **Akttive Capsules & Zero Xtreme Capsules** with undeclared silbutramine.

Health Canada Mar/16 says A**sia Black, Black Widow 25, Burn Fat Now, Extreme Stack, Fataway Ultimate Stack, MaxOut Body, Metabolic Accelerator, Methyldrene Original 25 Dietary Supplements, ThermoFX, Thermogenic Fat Burner & Thin and Slim Naturally** by FDA contains undeclared salicylic acid.

Health Canada Mar/16 says **BASCHI Quick Slimming capsules** by Australian Therapeutic Goods Administration contains undeclared sibutramine.

Health Canada Mar/16 says **Basha Nut 100% Fruit Soft Gel Capsules, Ultimate Herbal Slimcap, Lishou Slimming Coffee, Meizi Super Power Fruits Herbal Slimming Formula, NATUREAL & Tip-Top Shape by FDA** contains undeclared sibutramine.

Health Canada Mar/16 says **Miracle Diet 30 & Xtreme Fat Burner Capsules** by FDA contains undeclared phenolphthalein.

Health Canada Mar/16 says **New Queen Slimming soft gel capsules** by Australian Therapeutic Goods Administration contains undeclared sibutramine.

Health Canada Mar/16 says **Perfect Slim Fast Track Slim & Slyn Both** by FDA contains undeclared fluoxetine

Health Canada Mar/16 says **Pink Bikini and Shorts on the Beach Blue Edition & Pink Bikini and Shorts on the Beach Blue Gold Edition** by FDA contains undeclared sibutramine and phenolphthalein.

Health Canada Mar/16 says **Super Herbs** by FDA contains undeclared sibutramine and desmethylsibutramine

Health Canada June/16: Australian Therapeutic Goods Administration-**Excellence Losing Weight** capsules contains undeclared silbutramine.

Health Canada June/16: Australian Therapeutic Goods Administration- **Natural Model capsules** contains undeclared sibutramine and phenolphthalein

Health Canada July/16: FDA says **Dynamizm Capsules, ENVY BP, Propell Platinum, Xerophagy Capsules, & Sextra** contains undeclared sibutramine.
Health Canada July/16: FDA says **Eradicate Capsules** undeclared sibutramine and desmethylsibutramine.
Health Canada July/16: Australian Therapeutic Goods Administration says **Leisure Slimming capsules** contains undeclared sibutramine and phenolphthalein.
Health Canada July/16: Australian Therapeutic Goods Administration says **U Slimming and U Plus Slimming capsules** undeclared sibutramine, phenolphthalein, diclofenac, and lignocaine.
Health Canada Aug/16 is advising consumers not to use the weight loss product **AlgoSlim**, distributed via mail order by E Sélection. The package does not contain unauthorized AlgoSlim and instead contains an authorized product, Slite-T, from a lot that expired in June 2012.
Health Canada July/16 **Exhilarate** undeclared sibutramine, desmethylsibutramine, phenolphthalein.
Health Canada Aug/16: FDA- **Dream Body 450mg, Dream Body Original Formula, Dream Body Advanced 400mg, Extra Slim Plus Acai Berry Weight Loss Formula, Lose Weight Coffee & SBF Bee Pollen** undeclared silbutramine.
Health Canada Aug/16: Hong Kong Department of Health- **Lose Weight Coffee** undeclared silbutramine.
Health Canada Aug/16: FDA- **Dream Body Advanced + Acai Weight Loss & Cleanse, & Dream Body Extreme Gold** undeclared sibutramine, fluoxetine, and sildenafil.
Health Canada Oct/16: **Adelganzantes R-II, Mang Luk Power Slim, Xcelerated Weight Loss Charged Up, & Xcelerated Weight Loss Turbo Charge**-Undeclared sibutramine by United States Food and Drug Administration.
Health Canada Oct/16: **B-finn**- Undeclared orlistat and 2-(diphenylmethyl)pyrrolidine (desoxy-D2PM)by Hong Kong Department of Health.
Health Canada Oct/16: **Citrus' Fit, Mang Luk Power Slim Detox, Slim Fit X, & Ultimate Lean** -Undeclared sibutramine and desmethylsibutramine by United States Food and Drug Administration.
Health Canada Oct/16: **Double S**- Undeclared sibutramine by Hong Kong Department of Health.
Health Canada Oct/16: **Maxx Easy**-Undeclared sibutramine and lorcaserin, and orlistat by United States Food and Drug Administration.
Health Canada Oct/16: **Mi Show Slimming capsules**- Undeclared sibutramine by Australian Therapeutic Goods Administration.
Health Canada Oct/16: **Xcelerated Weight Loss Ultra Max**- Undeclared phenolphthalein and sildenafil by United States Food and Drug Administration.
Health Canada Oct/16: **Zi Xiu Tang Beauty Face and Figure Capsule**- Undeclared phenolphthalein and fluoxetine by United States Food and Drug Administration.
Health Canada Nov/16: **Natural Eruption** has undeclared sibutramine by the United States Food and Drug Administration.
Health Canada Dec/16 reports: Australian Therapeutic Goods Administration: **Bee Sexy Slimming capsules** undeclared sibutramine; Australian Therapeutic Goods Administration: **Biolo World Slimming capsules**-undeclared sibutramine and phenolphthalein; Hong Kong Department of Health: **ele Slim Shot**-undeclared orlistat.

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MHRA Feb/12 Herbal sliming products found to contain potentially dangerous undeclared pharmaceuticals: **Expelling Grease Slimming Abdomen, V12 Fruit Slimming, 100% Natural Weight Loss Coffee, Leisure 18 Slimming Orange Juice, Fashion Slimming Milk Shake, Langli, Ya Buk & Fruit and vegetables lose weight**. MHRA has received advice from the Danish Medicines Agency that these unlicensed products have been tested and found to contain the Prescription Only Medicine Sibutramine.

MHRA Feb/12 Following a safety alert issued in October 2010 about slimming products containing Paiyouji the Agency has received a further complaint about a product called **'Paiyouji Plus - Fast Acting Slimming Tea'**. This product has been tested by the Agency and, as in the case of other Paiyouji products, found to contain sibutramine.

MHRA Nov/12 has received advice from the Danish Medicines Agency that this unlicensed product, **Ultra Slim** has been tested and found to contain the Prescription Only Medicine Sibutramine.

MHRA Feb/13 is advising consumers not to use the products specified below due to sibutramine content. Product: **Fashion Slimming Coffee, L-Carnitine + P57, L-CarnitinL 360 Slimming Coffee, Brazil Potent Slimming Coffee sachets, Coffee 26 Original sachets, Coffee Nature Fashion Slimming sachets, Slender Capsule, Slim-1.**

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raised blood pressure and pulse rate. Rimonabant improved concentrations of high density lipoprotein cholesterol and triglycerides, blood pressure, and glycaemic control in patients with diabetes but increased the risk of mood disorders. Orlistat, sibutramine, and rimonabant modestly reduce weight, have differing effects on cardiovascular risk profiles, and have specific adverse effects.

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Extras (RxFiles Herbal Weight Loss

Energy Drinks

Health Canada: Safe Use of Energy Drinks. Accessed online at http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/food-aliment/boissons-energ-drinks-eng.php. {Excessive drinking of energy drinks or mixing them with alcohol can have serious health effects. Energy drinks are meant to supply mental and physical stimulation for a short period of time. They usually contain caffeine, taurine (an amino acid, one of the building blocks of protein), vitamins and glucuronolactone, a carbohydrate. Energy drinks should not be confused with sports drinks such as Gatorade® or Powerade®. Sports drinks re-hydrate the body and provide sugars, which the body burns to create energy and replenish electrolytes.}

Glucomannan (in PGX PolyGlycopleX) Plant fibre water-soluble: unabsorbable polysaccharide (glucose + mannose). May ↓LDL, ↓gastric emptying & improve BG control. Conflicting evidence. SE: gas, bloating, etc.

◆General References 7,8,9,10,11,12

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FDA Dec/08 alerted consumers nationwide not to purchase or consume more than **25 different products** marketed for weight loss because they contain undeclared, active pharmaceutical ingredients that may put consumers' health at risk. The undeclared active pharmaceutical ingredients in some of these products include sibutramine (a controlled substance), rimonabant (a drug not approved for marketing in the United States), phenytoin (an anti-seizure

medication), and phenolphthalein (a solution used in chemical experiments and a suspected cancer causing agent). The weight loss products, some of which are marked as "dietary supplements," are promoted and sold on various web sites and in some retail stores. FDA advises consumers who use the products to stop taking them and consult their healthcare professional immediately as the health risks posed by these products can be serious (for example, high blood pressure, seizures, tachycardia, palpitations, heart attack or stroke). FDA also encourages consumers to seek guidance from healthcare professional before purchasing weight loss products. See the FDA News Release for a listing of the names of the 25 referenced products. Read the MedWatch 2008 safety summary, including links to http://www.fda.gov/medwatch/safety/2008/safety08.htm#Weight

FDA May/09 warned consumers to immediately stop using **Hydroxycut products by Iovate Health Sciences**, Inc. Hydroxycut products are associated with a number of **serious liver injuries**. Hydroxycut products are dietary supplements that are marketed for weight-loss, as fat burners, as energy-enhancers, as low carb diet aids, and for water loss under the Iovate and MuscleTech brand names. FDA has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, an indicator of potential liver injury, to liver damage requiring liver transplant. One death due to liver failure has been reported to FDA. Other health problems reported include seizures; cardiovascular disorders; and rhabdomyolysis, a type of muscle damage that can lead to other serious health problems such as kidney failure.

FDA Jan/10 notified consumers and healthcare professionals about a counterfeit and potentially harmful version of **Alli 60 mg capsules** (120 count refill kit). The **counterfeit version** contained the controlled substance sibutramine and did not contain orlistat, the active ingredient.

FDA July/10 analysis of **Que She** found that it contains: fenfluramine – a stimulant drug withdrawn from the U.S. market in 1997 after studies demonstrated that it caused serious heart valve damage, propranolol – a prescription beta blocker drug that can pose a risk to people with bronchial asthma and certain heart conditions, sibutramine – a controlled substance and prescription weight loss drug, sibutramine was the subject of a recent study whose preliminary findings showed an association between sibutramine use and increased risk of heart attack and stroke in patients who have a history of heart disease, & ephedrine –a stimulant drug that is legally marketed over-the-counter for temporary asthma relief but can pose a risk to people with cardiovascular disease.

FDA Aug/10 lab analysis of **Solo Slim** was found to contain the undeclared drug ingredient Didesmethyl Sibutramine.

FDA July/10 lab analysis of **Slim-30** Herb Supplement distributed by the company was found to contain undeclared N-Desmethyl Sibutramine & Sibutramine.

FDA July/10 lab analysis of this herb supplement, **Joyful Slim** Herb Supplement, was found to contain the undeclared drug, desmethyl sibutramine.

FDA Oct/10 notified consumers that **Slimming Beauty Bitter Orange Slimming Capsules** contain sibutramine, a prescription-only drug which is a stimulant.

FDA Dec/10 has received multiple reports of adverse events associated with the use of **Fruta Planta**, including several cardiac events and one death. FDA lab analysis confirmed that Fruta Planta contains sibutramine.

FDA Jan/11 laboratory analysis confirmed that **Celerite Slimming Capsules** contain sibutramine

FDA Mar/11 lab analysis of **Svelte 30** orange & gray capsules determined that the product contains Sibutramine.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analyses of **Celerite Slimming Tea**: Recall - were found to contain undeclared Sibutramine.

FDA May/11 laboratory analysis confirmed that "**Slim Xtreme Herbal Slimming Capsule**" contains sibutramine.

FDA July/11 is advising consumers not to purchase or use "**Slim Forte Slimming Capsules**," "**Slim Forte Slimming Coffee**," and "**Botanical Slimming Soft Gel & Slim Forte Double Power Slimming Capsules**. FDA laboratory analysis confirmed that these products contain sibutramine.

FDA Dec/11 took joint action against several companies selling over-the-counter **hCG products** that falsely and illegally claim to promote weight loss. Labeled "homeopathic" by the seven companies who received the letters, the products contain human chorionic gonadotropin (hCG), a hormone produced during pregnancy by cells that form the placenta. 1. HCG Diet Direct LLC- HCG Diet Homeopathic Drops, 2. The hCG Drops LLC- Homeopathic HCG, 3. HCG Platinum LLC; RightWay Nutrition- HCG Platinum, HCG Platinum X-30, HCG Platinum X-14, 4. Nutri Fusion Systems LLC- HCG Fusion 30, HCG Fusion 43, 5. www.resetthebody.com; www.theoriginalhcgdrops.com-Homeopathic Original HCG, Homeopathic HCG, 6. Hcg-miracleweightloss.com- HCG Extra Weight Loss Homeopathic Drops, 7. Natural Medical Supply- Alcohol Free hCG Weight Loss Formula.

FDA Feb/12 is advising consumers not to purchase or use "**Japan Weight Loss Blue**," a product for weight loss sold on various websites, laboratory analysis confirmed that "Japan Weight Loss Blue" contains sibutramine, analogs of sibutramine, and ephedrine alkaloids.

FDA Apr/12 laboratory analysis confirmed that "**Japan Rapid Weight Loss Diet Pills Yellow**" contains sibutramine and phenolphthalein.

FDA Dec/12 is advising consumers not to purchase or use "SLIMDIA Revolution," a product promoted and sold for weight loss on various websites, including www.pinkfatty.com, and in some retail stores since it contains Sibutramine.

FDA Jan/13 is advising consumers not to purchase or use "**MAXILOSS** Weight Advanced," a product promoted and sold for weight loss on various websites, includingwww.dreamlifeweightloss.com, and in some retail stores since it contains sibutramine.

FDA Feb/13 Olaax Corp announced a nationwide recall of the company's dietary supplement sold under the brand name **Maxiloss Weight Advanced Softgels** to the user level, because FDA testing found the Maxiloss Weight Advanced product to contain Sibutramine.

FDA Jun/13 FDA laboratory analysis confirmed that "**Bethel 30", & "XIYOUJI QINGZHI CAPSULE**" & **JaDera** contains sibutramine. .

FDA Jun/13 A sample of **Extreme Body Slim, Fat Zero, Fruit & Plant Slimming, & Paiyouji Plus** all contains silbutramine.

FDA Jun/3 Beta Labs has recalled certain lots of **Oxyphen, Phentalene, Phen FX, and Red Vipers** because they contain 1,3 dimethylamylamine (DMAA), the FDA announced over the weekend. The products are used as pre-workout stimulants and for weight loss, but the agency has previously warned that DMAA can be dangerous: it can elevate blood pressure and lead to cardiovascular complications. One distributor, GNC, faces FDA seizure of over 3000 cases of two other DMAA-containing products, **Jack3d and OxyElitePro**. Although the manufacturer of those supplements has ceased production, GNC continues to sell its remaining stocks, according to the New York Times.

FDA July/13 **Meizi Revolution, Strawberry Balance** contains silbutramine.

FDA Aug/13 Herbal Give Care LLC issued a voluntarily recall of all lots of **Esbelin silouttete** and **Esbelin siloutte Herbal Blend with L-Carnitine** (30 Capsules), to the consumer level. The products have been found to contain undeclared Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine.

FDA Aug/13 Bethel Nutritional Consulting, Inc., New York, NY, is voluntarily recalling **Quick Thin and Bethel Advance** to the consumer level. These products have been found to contain Sibutramine and Phenolphthalein, and may pose a threat to consumers.

FDA Aug/13 CTV Best Group announced that it is conducting a voluntary nationwide recall of all lots of a dietary supplement products distributed by the company under the names **BEST SLIM 40 Pills** to the consumer level. Testing by FDA revealed the presence of Sibutramine in Best Slim.

FDA Aig/13 Herbal Give Care LLC is voluntarily recalling all lots of **Esbelder man (30 capsules), Esbelder fem (30 capsules) and Esbelder siloutte** (30 capsules) to the consumer level. The products have been found to contain undeclared Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine.

FDA Sep/13 laboratory analysis confirmed that **Shou Fu Ti Tun Guo Xiang Xing Jian Fei Jiao Nang** contains sibutramine.

FDA Oct/13: B@B Trade, Inc., Florida is voluntarily recalling all lots of **Slim Fortune, Lidiy, and Slim Expert** to the consumer level. The FDA laboratory analysis of these dietary supplements found to contain undeclared Sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Perfect Body Solutions or Burn 7.** FDA laboratory analyses confirmed that Perfect Body Solutions and Burn 7 contain sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Dr. Mao Slimming Capsules**. FDA laboratory analysis confirmed that Dr. Mao Slimming Capsules contain sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Bella Vi Insane Amp'd or Bella Vi Amp'd Up.** FDA laboratory analyses confirmed that Bella Vi Insane Amp'd and Bella Vi Amp'd Up contain sibutramine.

FDA Nov/13 **SlimExtra Herbal** capsules contain silbutramine.

FDA Dec/13 laboratory analysis found the **Burn 7 Capsules** to contain undeclared Sibutramine.

FDA Jan/14 is advising consumers not to purchase or use **Magic Slim or Dream Body Slimming Capsule**, products promoted and sold for weight loss and sold on various websites and in some stores, since FDA lab analysis confirmed they contains sibutramine.

FDA Jan/14 **Citrus Fit Gold, Hot Detox & Thinogenics** contains sibutramine. **Tonic Life BP contains** phenolphthalein.

FDA Mar/14 is advising consumers not to purchase or use **Vitaccino Coffee**, a product promoted and sold for weight loss. FDA laboratory analysis confirmed that Vitaccino Coffee contains sibutramine.

FDA Mar/14: New Life Nutritional Center is recalling all lots of "**Super Fat Burner capsules, Maxi Gold capsules and Esmeralda softgels**" to the user level after FDA analysis revealed the products contain undeclared active pharmaceutical ingredients: sibutramine, phenolphthalein or a combination of both sibutramine and phenolphthalein.

FDA Mar/14: **Bella Vi Insane Bee Pollen Capsules, Bella Vi BTrim Ultimate Boost, Bella Vi BTrim Max, Bella Vi Extreme Accelerator, Bella Vi Insane Amp'd, and Bella Vi Amp'd U**, contain silbutramine with or without phenolphthalein.

FDA Apr/14: FDA analysis on **New You** contains silbutramine.

FDA Apr/14 has tested multiple **Zi Xiu Tang Bee Pollen** products from various distributors in the United States (US). All products that have been tested, including those that claim to be "genuine" and "anti-counterfeit," have been found to contain one or both of the undeclared drug ingredients sibutramine and Phenolphthalein.

FDA Apr/14 laboratory analysis confirmed that **Infinity & Lite Fit** USA contains sibutramine.

FDA Apr/14: Nature's Universe notified the public it is recalling all lots of **Thinogenics** product sold prior to February 6, 2014 to the user level after FDA analysis revealed that the affected product contained undeclared sibutramine.

FDA May/14 laboratory analysis confirmed that **Slim Trim U & Natural Body Solution** contains sibutramine.

FDA May/14 is advising consumers not to purchase or use **Asset Bee Pollen**, a product promoted and sold for weight loss because it contains sibutramine.

FDA May/14 is advising consumers not to purchase or use **Asset Bold**, a product promoted and sold for weight loss. FDA laboratory analysis confirmed that Asset Bold contains sibutramine.

FDA Jun/14 laboratory analysis confirmed that **La Jiao Shou Shen** contains sibutramine.

FDA Jun/14 laboratory analysis confirmed that **Sliming Diet** contains sibutramine.

FDA July/14 laboratory analysis confirmed that **Mix Fruit Slimming, Lingzhi Cleansed Slim Tea, 24 Ince, Lipo 8 Burn Slim, Sliming (sic) Diet By Pretty, & Trim-Fast Slimming Softgel** contains sibutramine.

FDA July/14: **Vitaccino Coffee, Collagen Slim, & Sulami** contains sibutramine.

FDA July/14: **Fruta Bio, Jianfeijindan Activity Girl, & LTD Japanese Chinese Formula** pill for weight reduction contains sibutramine and/or phenolphthalein.

FDA Aug/14 Regeneca Worldwide a division of VivaCeuticals, Inc., is conducting a voluntary nationwide recall of its **RegenESlim appetite control dietary** supplement, lot # EX0616R15814 and lot #11414RE5516, because FDA analysis confirmed the presence of DMAA.

FDA Sep/14 laboratory analysis confirmed that **Best Line Suplemento Alimenticio Capsules** contains sibutramine.

FDA Sep/14 laboratory analysis confirmed that **Japan Hokkaido Slimming Weight Loss Pills** contain sibutramine, benzocaine, phenolphthalein and diclofenac.

FDA Sep/14 laboratory analysis confirmed that **Mezo** contains benzylsibutramine, a substance structurally similar to sibutramine.

FDA Oct/14 laboratory analysis confirmed that **Sit and Slim II** contains sibutramine.

FDA Nov/14 is advising consumers not to purchase or use **V26 Slimming Coffee**. FDA laboratory analysis confirmed sibutramine.

FDA Nov/14: REFA Enterprises is voluntarily recalling one lot each of: **Forever Beautiful Bee Pollen** (UPC # 6333090804632), **Forever Beautiful Infinity** (UPC # 633090804649). The products have been found to contain undeclared Sibutramine or a combination of both Sibutramine and Phenolphthalein through FDA laboratory analyses.

FDA Nov/14 is advising consumers not to purchase or use **Bee Slim, Bee Thin & Super Extreme Accelerator**. FDA laboratory analysis confirmed that they contain sibutramine.

FDA Nov/14 laboratory analysis confirmed that **Slim-Vie** containssibutramine.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **SLIM-K Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of SLIM-K collected and tested by the FDA was found to contain sibutramine, desmethylsibutramine, and phenolphthalein.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **B-Lipo Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of B-Lipo Capsules collected and tested by the FDA was found to contain lorcaserin.

FDA Feb/15 laboratory analysis confirmed that **Lean Body Extreme** contains sibutramine, desmethyl sibutramine, phenolphthalein, and sildenafil.

FDA Feb/15 laboratory analysis confirmed that **Nine Slim, & Seven Slim** contains phenolphthalein.

FDA Mar/15 laboratory analysis confirmed that **Elimulating Weight & Toxin Keeping Beauty** contains sibutramine

FDA Mar/15 laboratory analysis confirmed that **Black Mamba Hyperrush & L-Carnitine Sob Strengthening Version Slimming Miracle Capsule** contains sibutramine.

FDA May/15 laboratory analysis confirmed that **Li Da Dai Dai Hua Slimming Capsule** contains sibutramine.

FDA May/15 laboratory analysis confirmed that **Slim Forte Slimming Capsule** contains sibutramine.

FDA Apr/15 laboratory analysis confirmed that **Superior** contains sibutramine.

FDA May/15: **Nine Slim & Seven Slim** contains undeclared phenolphthalein.

FDA May/15: **Oxy ELITE Pro Super Thermogenic** contains undeclared fluoxetine.

FDA May/15: **Elimulating Weight & Toxin Keeping Beauty & L-Carnitine Sob Strengthening Version Slimming Miracle Capsule** contains undeclared sibutramine.

FDA May/15: **Lean Body Extreme** contains undeclared sibutramine, desmethyl sibutramine, phenolphthalein & sildenafil.

FDA May/15: **Diablos Eca Fire Caps** contains undeclared sildenafil, phenolphthalein, sibutramine & deisobutylbenzylsibutramine.

FDA July 15: **Black Mamba Hyperrush & Ultra ZX** contains Undeclared sibutramineand phenolphthalein.

FDA July 15:**Botanical Slimming (Red) & Xcel** contains Undeclared fluoxetine.

FDA July 15:**Green Algae Combination** by Crane Beauty contains Undeclared lorcaserin.

FDA July 15:**Natural Max Slimming** contains Undeclared sildenafil, fluoxetine, andsibutramine.

FDA July 15: **Ultimate Boost & Xcel Advanced** contains Undeclared phenolphthalein.

FDA Oct/15 **Kaboom Action Strips** 12 Pack contains undeclared sulfoaildenafil.

FDA Oct/15 **Lida DaiDaiHua** contains undeclared sibutramine & phenolphthalein.

FDA Sep/15: **Miracle Diet 30** has been found to contain undeclared phenolphthalein.

FDA Oct/15 laboratory analysis confirmed that **Xtreme Fat Burner Capsules** contains phenolphthalein.

FDA Oct/15 laboratory analysis confirmed that **Tip-Top Shape, Lishou Slimming Coffee, & Basha Nut 100% Fruit Soft Gel Capsules** contains sibutramine.
FDA Dec/15 laboratory analysis confirmed that **Evolve Bee Pollen, Jenesis, Prime Bee Pollen & Oasis Bee Pollen** contains sibutramine.
FDA Dec/15: laboratory analysis confirmed that **La'Trim Plus** contains sibutramine.
FDA's Dec/15 analysis found the **Smart Lipo** products to contain undeclared sibutramine, desmethylsibutramine, and phenolphthalein.
FDA Dec/15 BeeXtreme LLC is recalling all lots of **La' Trim Plus, Jenesis and Oasis products** from the market. Recent Analysis by the Food and Drug Administration has found undeclared Sibutramine and Phenolphthalein.

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Folkvord F, Anschütz DJ, Nederkoorn C, et al. **Impulsivity, "Advergames**," and Food Intake. Pediatrics. 2014 May 5.
Grasser EK, Dulloo AG, Montani JP. Cardiovascular and cerebrovascular effects in response to red bull consumption combined with mental stress. Am J Cardiol. 2015 Jan 15;115(2):183-9.
Health Canada April 2007: The **Safe Use of Health Products** for Weight Loss. http://www.hc-sc.gc.ca/iyh-vsv/med/weight-amaigr_e.html
Health Canada Apr/07 is warning consumers about **Bitter orange** & cardiovascular reactions in the Canadian Adverse Reactions April 2007 Newsletter.
Health Canada Apr/07 is warning consumers from the Hong Kong Department of Health found **Lexscl Fat Rapid Loss capsules to be adulterated with sibutramine** and thyroid hormones.
Health Canada via July/07 Medsafe also advised the public not to use the product **Dai Dai Hua Jiao Nang** because it was found to contain sibutramine.
Health Canada Aug/07 is advising Canadians of a recall in the United States of one lot of **Metaboslim Apple Cider Vinegar**, which is marketed as a dietary supplement, because it has been found to contain sibutramine, a prescription medication that should only be taken under medical supervision.
Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang**, **J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.
Health Canada Jan/08 is warning Canadians not to use the unauthorized product **Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules** (batch number 28012007 / expiration date: Jan 2009). This product is promoted for weight loss and has been found to contain a derivative of the prescription drug sibutramine.
Health Canada April/08 is advising consumers not to use **Xian Zhi Wei II** was found to contain sibutramine and phenolphthalein, which are not meant for self-care and may cause serious side effects.
Health Canada Aug/08 is advising consumers not to use 9 foreign health products due to concerns about possible side-effects: **Dan Bai Shou Shen Su** was found to contain undeclared thyroid hormones and sibutramine. **Karntien and Karntien Easy to Slim** were adulterated with sibutramine and a compound that is similar in structure to sibutramine (N-desmethylsibutramine). **More Slim** was found to contain the undeclared pharmaceutical ingredient sibutramine. **Soloslim** was found to contain an undeclared substance similar in structure to the prescription drug sibutramine. It also contains the prescription drug L-carnitine, as well as synephrine, which is not authorized for sale in weight loss products in Canada.
Health Canada Aug/08 is advising consumers not to use 8 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of Natural (Xin Yi Dai) and Lasmi because Natural (Xin Yi Dai) was found to contain sibutramine and phenolphthalein, and Lasmi was found to contain sibutramine and spironolactone. The Hong Kong Department of Health warned against the use of AA Qu Feng Shu Jin Wan because it was found to contain the undeclared pharmaceutical ingredient dexamethasone. Apisate contained fenfluramine and Energy ll contained sibutramine. Obat Asam Urat and Asam Urat both contained dexamethasone, phenylbutazone and piroxicam. The Hong Kong Department of Health warned against the use of Slim 3in1 (Xiao Nan zhi Bao) because it was found to contain the undeclared pharmaceutical ingredients sibutramine and phenolphthalein.
Health Canada Sep/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned against the use of **Hanguo shoushen yihao** (meiti xing) because it was found to contain the undeclared pharmaceutical ingredient

sibutramine. The Hong Kong Department of Health warned against the use of **ARMA - Sin Gang San** and New ARMA - Sin Gang San because they were found to contain the undeclared pharmaceutical ingredients sibutramine and fenfluramine.

Health Canada Nov/08 is advising that the Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine.

Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains sibutramine.

Health Canada Mar/09 Foreign Product: **68 Weight Loss Products**; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien & Relacore. Plus Lami, Linglongquxian, Menergy M-Essence, Nyal Day & Night Cold & Flu Fighter (AUST L 146264), Nyal Cold & Flu Fighter (AUST L 146263), 999 Radix Notoginseng, Batch no. 0807021, Slim Pure, Carbohydrate, Kalomee, K Carbohydrate, K Tighten Slim, & K Slimming Pills. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php

Health Canada June/09 Foreign Product Alerts: **Jia Yi Jian** (undeclared sibutramine & tadalafil); **Shan Dian Qiang Xiao Shou** (undeclared sibutramine & phenolphthalein).

Health Canada June/09 is warning consumers not to use the unauthorized product **Slim Magic Herbal**, which is promoted as a weight-loss product, as it was found to contain an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning consumers not to use the unauthorized product **Nutural Slim**, which is promoted as a weight-loss product, as it was found to contain the undeclared pharmaceutical ingredient sibutramine and also an undeclared pharmaceutical ingredient similar to sibutramine.

Health Canada June/09 warns of foreign Product Alerts: ***Herbal Xenicol*** because it contains undeclared cetilistat. ***BioEmagrecim***, which the FDA had previously warned contained sibutramine, was also found to contain fluoxetine, furosemide and fenproporex. Products: ***Slimbionic***, ***Xsvelten***, ***999 Fitness Essence***, ***24" ince***, ***Light Some***, ***Paiyouji***, ***Pearl White Slimming***, & ***Reducing Weight Easily*** contain undeclared pharmaceutical ingredients (sibutramine and/or phenolphthalein) and/or excessive levels of lead, and may cause serious health effects..

Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is warning consumers not to use "**RevolutionDS Weight Loss**", an unauthorized health product promoted for weight loss, because it contains benzylpiperazine (BZP), and may pose serious health risks.

Health Canada Dec/09 is advising consumers not to use **Show Party**: Hong Kong Department of Health warned consumers not to buy or consume [shou-shen pai] after it was found to contain undeclared sibutramine and phenolphthalein.

Health Canada Jan/10 informs that U.S. FDA: **Pai You Guo** contains sibutramine and phenolphthalein. Hong Kong Department of Health: **Ku Xiu Ba Xiang Jian Fei Wan** contains sibutramine and an unauthorized substance similar to sibutramine; **Super Slim (Yani)** contains sibutramine and phenolphthalein; **SHoufsy** contains sibutramine & **MIGAC (sic) FAT BURMING (sic) FACTOR** contains sibutramine.

Health Canada Jan/10 is warning consumers not to use the unauthorized product "**The Slimming Coffee**," which was previously sold as "**Lose Weight Coffee**," because it was found to contain sibutramine.

Health Canada Mar/10 is warning Canadians that an unauthorized health product, "**Herbal Diet Natural**" has been found on the Canadian market and contains an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning Canadians that an unauthorized health product, "**West Pharm Therma Lean Fat Burner Energizer**" was found on the Canadian market. West Pharm Therma Lean Fat Burner Energizer contains Ephedrine and caffeine, which combined together, may cause serious and possibly fatal adverse effects.

Health Canada Apr/10 is warning Canadians that an unauthorized health product, "**Slim-30**" distributed in Ontario and Quebec by Duxx Enterprises Inc., contains an undeclared pharmaceutical ingredient similar to the prescription drug, sibutramine.

Health Canada May/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Ba Bao Xiao Ke Da**n The Hong Kong Department of Health warned consumers not to buy or use Ba Bao Xiao Ke Dan after it was found to contain undeclared glibenclamide. 2. **Seven Slim 7 Seshou** (Qingchun Shaonüxing, Jieshixing, Guifurenxing, Songchixing), Shoushen Jiaoguan-Tinei Yundong Wan (Jian Xiabanshen, Jian Quanshen Feipang) The Hong Kong Department of Health warned consumers not to buy or use the six products listed above after they were found to contain undeclared sibutramine and phenolphthalein.

Health Canada May/10 is advising consumers not to use 1. **Botanical Slimming 100% Natural Soft Gel, also sold as Meizitang** Australian Therapeutic Goods

Administration warned consumers not to buy or use this product after it was found to contain undeclared sibutramine. 2. **Marsha Slim Plus** Hong Kong Department of Health warned consumers not to buy or use Marsha Slim Plus after it was found to contain undeclared sibutramine, an unauthorized substance similar to sibutramine and phenolphthalein. 3. **S&S Super Slender** The Hong Kong Department of Health warned consumers not to buy or use S&S Super Slender after two samples were found to contain agent similar to sibutramine. One of the tested samples also contained undeclared sibutramine and phenolphthalein.

Health Canada June/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **COMECOO**, **ZHONGCAOYAO-JIANKANGJIANFEI** The Hong Kong Department of Health warned consumers not to buy or consume these two products after they were found to contain undeclared phenolphthalein, sibutramine and two unauthorized substances similar to sibutramine. 2. **Qingzhi Santian Shou** The Hong Kong Department of Health warned consumers not to buy or consume Qingzhi Santian Shou after it was found to contain undeclared sibutramine and an unauthorized substance similar to sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) 1. **Po Chai Pills** (capsule form) The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain undeclared sibutramine and phenolphthalein. Sibutramine is a prescription drug and should only be used under the supervision of a health care practitioner while phenolphthalein is no longer authorized for sale in Canada because it may cause cancer. Po Chai Pills (capsule form) has been recalled by the manufacturer. 2. **LiPO-8 Cap and Glucomi 600 Cap** The Hong Kong Department of Health warned consumers not to buy or use these products because they contain undeclared sibutramine.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume *1 Body Beautiful* after it was found to contain undeclared phenolphthalein and sibutramine. 2. **USA Yaku Cell Slimming Capsules, Dong Gua Pai You Su, Qing Gua Pai You Su, and Mu Gua Pai You Su** The Hong Kong Department of Health warned consumers not to buy or consume these four products after they were found to contain undeclared phenolphthalein, sibutramine and an unauthorized substance similar to sibutramine.

Health Canada Aug/10 is advising consumers not to use the following foreign health product(s): **Que She** The U.S. FDA warned consumers not to buy or use Que She after it was found to contain undeclared fenfluramine, propranolol, sibutramine and ephedrine. **Sheng Yuan Fang** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use Sheng Yuan Fang after it was found to contain undeclared phenolphthalein and sibutramine.

Health Canada Sep/10 is advising consumers not to use : **Joyful Slim** Herb Supplement The U.S. FDA informed consumers of a recall of one lot (#101408) of Joyful Slim Herb Supplement after FDA tests found it to contain undeclared desmethyl sibutramine. The lot is being voluntarily recalled nationwide in the U.S. by the company J & H Besta Corp.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Goya–Bitter Melon - Miyura Fit'x Capsules** contained undeclared phenolphthalein and sibutramine **2. Solo Slim Extra Strength - Revivexxx Extra Strength** contained undeclared didesmethyl sibutramine

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Slimming Beauty Bitter Orange Slimming Capsule (Slimming Beauty)** The U.S. Food and Drug Administration warned consumers not to buy or use Slimming Beauty after FDA lab tests revealed that this product contains undeclared sibutramine.

Health Canada Jan/11 The product **Synerate**, manufactured for Strive and distributed by Upper 49th, is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. Synerate, a product used for weight loss or body building, contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Feb/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Fruta Planta, Reduce Weight Fruta Planta** The U.S. FDA warned consumers not to buy or use Fruta Planta and Reduce Weight Fruta Planta after FDA lab tests revealed that this product contains undeclared sibutramine. **2. Slimming Factor** The Australian TGA warned consumers not to buy or use Slimming Factor after TGA lab tests confirmed the presence of the undeclared substances sibutramine, fenfluramine and phenolphthalein. According to the TGA release, the product is sold over the Internet.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Celerite Slimming Capsules**: The U.S. FDA informed consumers of a company recall of CeleriteTM Slimming Capsules after it was found to contain undeclared sibutramine. 2. **Herbal Flos Lonicerae** (Herbal Xenicol) Natural Weight Loss Formula: The product was found to contain undeclared

sibutramine at more than twice the dose that was normally prescribed before sibutramine was removed from the UK market in 2010.

Health Canada May/11 is advising consumers not to use: 1. **Dr. Health Series CM Factor** The Hong Kong Department of Health warned consumers not to buy or use this product after found to contain substance similar to sibutramine.

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions:

1. **Slim Xtreme Herbal Slimming Capsules** The U.S. Food and Drug Administration informed consumers of a voluntary recall after Slim Xtreme Herbal Slimming Capsules was found to contain undeclared sibutramine.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions:

1. Celerite Slimming Tea The U.S. FDA informed consumers of a company recall of Celerite Slimming Tea after it was found to contain undeclared sibutramine. **2. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet. **3. Fifteen products promoted for weight loss** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use these 15 products after they were found to contain at least one of the following undeclared substances: phenolphthalein, sibutramine, and/or an unauthorized substance similar to sibutramine.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **Slim Forte Slimming Capsules**, **Slim Forte Double Power Slimming Capsules**, **Slim Forte Slimming Coffee** and **Meizitang Botanical Slimming Soft Gel**-The U.S. Food and Drug Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **OxyELITE Pro capsules and Pure Fat Three Days Reduce Weight capsules**- The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine), or a prescription drug (yohimbine).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. 1. **Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones). 2. **Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al,** and **Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine). 3. **Slimming Kapsul** The Hong Kong Department of Health warned that this weight-loss product contains an unauthorized drug (sibutramine) and a prescription drug (spironolactone). 4. **Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a prescription drug (glyburide).

Health Canada Jan/12 advises: 1)**17 weight loss products (see Alert for a complete list)** A-Slim 100% Natural Slimming Capsule, Acai Berry Soft Gel ABC, Advanced Slim 5 >DaiDaiHuaJiaoNang, Dream Body Slimming Capsule, Fruit Plant Lossing Fat Capsule, Health Slimming Coffee, Ja Dera 100% Natural Weight Loss Supplement, Leisure 18 Slimming Coffee, Lishou, Magic Slim Tea, Magic Slim Weight Reduction Capsule, P57 Hoodia, Pai You Guo Slim Tea, PhentraBurn Slimming Capsules, Slender Slim 11 Tengda. The U.S. Food and Drug Administration warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Slimina weightloss capsules, S-shape slim capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain prescription drugs (propranolol, nifedipine) and/or unauthorized drugs (sibutramine, fenfluramine, phenolphthalein). **3. Cardiotium, Paidusu, SlimEasy Herbs Capsule, Tianran Zuanshi Xianweisu** The Hong Kong Department of Health warned that these health products contain prescription drugs (losartan, atorvastatin, thyroxine) and/or unauthorized drugs (sibutramine, phenolphthalein).

Health Canada May/12 1. **CanSui; Lexscl Fat Rapid Loss Capsule; The Extreme-thin Fat Burning Bomb; Xiu Zhi Su L-Carnitine Slimming Capsule** The Hong Kong Department of Health warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). 2. **Lipro Diet Pills; Xiyouji Qingzhi** weight loss capsules The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine).

Health Canada June/12 **1. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil). **2. Japan Weight Loss Blue, Japan Rapid Weight Loss Diet Pills Green; Japan Rapid Weight Loss Diet Pills Yellow:** The U.S. Food and Drug Administration warned that these weight loss products contain prescription drugs (sibutramine, ephedrine alkaloids) and unauthorized drugs (phenolphthalein, and substances similar to sibutramine).

Health Canada Jun/12 testing has identified that the weight loss product "**ZXT Gold**" bee pollen capsules contain sibutramine and phenolphthlalein.

Health Canada is advising Canadians that three unauthorized products "**Goya Bittermelon", "S-organic Cocoa+L-carnitine", or "KaBaNa L-Carnitine 360 Slimming Coffee**", promoted for weight loss have been seized from "Cube Inc.", a box-store in Richmond, B.C. These products contain hidden drug ingredients (sibutramine and phenolphthalein) that may pose serious health risks. Caffeine was also found in two products and was not listed on the product label.

Health Canada Aug/13 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Brazilian Slimming Coffee, Leisure 18 Slimming Coffee, 7 Days Slimming Coffee, Brazilian 7 Days Slimming Coffee, Beauty Secret Slimming Coffee, Body Beauty 5 Days Slimming Coffee, Leisure 18 Slimming Mango Juice, Leisure 18 Slimming Orange Juice, Authentic Leisure 18 Slimming Orange Juice, Super Slim Orange Juice, Coffee Fashion Slimming** The Hong Kong Department of Health has advised consumers not to use these products after they were found to contain the undeclared drug ingredients sibutramine and/or phenolphthalein. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34859a-eng.php **5. Best Slim capsules, Meizi Evolution Botanical Slimming soft gel capsules** The Australian Therapeutic Goods Administration warned consumers not to use these products after they were found to contain the undeclared drug sibutramine.

Health Canada Nov/13 is advising Canadians not to use these foreign health products as they may pose a health risk. These products have been found by regulators in other countries to contain drug ingredients or soy milk allergens that are not declared on the product labels, or a high level of microbial contamination. Prescription drugs should only be taken under the supervision of a healthcare professional. These products are not authorized for sale in Canada and have not been found on the Canadian market, but they may have been brought into the country by travellers or purchased over the Internet:

1. **Aisiyuan V26 Slimming Granules, AcaiBerry Living-XS, and 4C Cosmoslim** , http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36269a-eng.php ;
2. **MAXILOSS Weight Advanced** http://healthycanadians.gc.ca/recall-alert- rappel-avis/hc-sc/2013/36197a-eng.php;
3. **ESV Extra Strong Version, MSV Strong Version, RL Rapid Loss, My Slimmer Me (MSM) soft gel capsules, Natural Miaotiaoyishen capsules, and Paiyouji Natural Slimming Capsules** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36521a-eng.php.

Health Canada Feb/14: 1. **Lightning 10.0+, LV Shou Reduces Fat, and STB Summit of the Thin Body S Woman Degreasing Burning Pill** The Hong Kong Department of Health warned consumers not to use this product after it was found to contain sibutramine, phenolphthalein, and indomethacin.

Health Canada Apr/14 has seized the unauthorized drug, "**L-Showm Weight Loss Pills**", being sold at the U-Box store, located at 2809-4500 Kingsway, Burnaby, BC. Health Canada testing found that it contained an undisclosed ingredient, phenolphthalein.

Health Canada Apr/14: Four unauthorized drugs being sold at two SVN FUEL stores - one in Burnaby and one in Coquitlam, B.C. - were seized by Health Canada as they contain ingredients that are potentially dangerous to the health of consumers. The products, and the unapproved ingredients they contain, include **Jack3d** (DMAA (1, 3-dimethylamylamine), **Red Rockets** (ephedrine and caffeine), **West Pharm Therma Lean** (ephedrine and caffeine), and **OxyElite Pro** (1, 3-dimethylamylamine HCl and Yohimbe Bark extract). They were being promoted for weight management.

Health Canada May/14 **Esbelin siloutte te, Esbelin Siloutte Herbal blend with L-Carnitine, Esbelder man, Esbelder fem, Esbelder siloutte** contains Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine; **Instant Slim** contains sibutramine and phenolphthalein.

Health Canada May/14 One lot of **Lite Fit USA** (Lot Number 13165, Exp. 05/17) is being voluntarily recalled in the U.S. after analysis by the U.S. Food and Drug Administration revealed the lot contains the undeclared prescription drug sibutramine.

Health Canada May/14: 1. **Slim Fortune, Lidiy & Slim Expert**: FDA found sibutramine; 2. **Dr. Mao Slimming capsules, Perfect Body Solutions, Burn 7**: FDA found sibutramine; **Bella Vi Insane Amp'd Up, Be Inspired, Goodliness Fat Reducing capsules, Jimpness Beauty Fat Loss capsules**: FDA found sibutramine and phenolphthalein.

Health Canada June/14: **Asset Extreme, Asset Extreme Plus, Meizitang Citrus, Slimming Diet Berry Plus, Citrus Fit Gold, Hot Detox, Thinogenics c**ontains sibutramine. **Tonic Life BP & Slimfast capsules** contains phenolphthalein . **Dr**. **Ming's Chinese Capsule**, **Magic Slim and Apple's Quic**k **Impact Weight Loss** contains sibutramine and phenolphthalein.

Health Canada July/14: **Bella Vi Insane Bee Pollen Capsules, Bella Vi BTrim Ultimate Boost, Bella Vi BTrim Max, Bella Vi Extreme Accelerator**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and/or phenolphthalein. **Super Fat Burner capsules, Maxi Gold capsules, and Esmeralda softgels**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and phenolphthalein. **Powerful leg-slimming capsules, Pink grain herbal slimming capsules, and Night fat-burning capsules**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain undeclared phenolphthalein and diclofenac. The product, Night fat-burning slimming capsules, was also found to contain undeclaredtheophylline. **Zi Xiu Tang Pollen capsule and Zi Xiu Tang Beauty Face and Figure capsule**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain undeclared sibutramine, phenolphthalein, diclofenac, and ibuprofen. The product, Zi Xiu Tang Beauty Face and Figure capsule, was also found to contain undeclared glibenclamide, and indomethacin.

Heath Canada Aug/14: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use the product **Sanovera Starter** capsules, the Hong Kong Department of Health warned consumers not to use the product **Yanhee Slim** and the United States Food and Drug Administration (FDA) warned consumers not to use the products **Infinity, Asset Bee Pollen, Asset Bold, Slim Trim U, and Natural Body Solution** after they were found to contain undeclared sibutramine. The Australian Therapeutic Goods Administration (FDA) warned consumers not to use **3x Slimming Powder Capsules** after it was found to contain undeclared sibutramine and phenolphthalein.

Health Canada Dec/14 is following up with Rapha Biotech Inc. **RAPHA Vitamin B1** (NPN: 80036493) -- undeclared ingredients: sibutramine, desmethyl sibutramine. **Rapha Diet** (700 mg, 270 Capsules) -- undeclared ingredient: caffeine.

Health Canada Dec/14: The United States Food and Drug Administration (FDA) warned consumers not to use the products **Lingzhi Cleansed Slim Tea, Trim-Fast Slimming Softgel, Sliming Diet By Pretty White, Lipo 8 Burn Slim, and Best Line Suplemento Alimenticio Capsules**. Tthe Hong Kong Department of Health warned consumers not to use the products **Slim Perfect Arm and Slim Perfect Legs** and the Australian Therapeutics Goods Administration (TGA) warned consumers not to use the product **Slyn Both Green capsules** after they were found to contain undeclaredsibutramine. The United States Food and Drug Administration (FDA) also warned consumers not to use the product **Mezo** after it was found to contain benzylsibutramine. **Mix Fruit Slimming**: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain undeclaredsibutramine and phenolphthalein.

Health Canada Dec/14: **Hydro-Lean** was seized from two Calgary stores because the label indicates it contains a combination of ingredients that can cause serious health risks (ephedrine and caffeine).

Health Canada Jan/15: **Star Majestic Slimming**- Undeclared sibutramine & phenolphthalein via Australian Therapeutic Goods Administration. **Sit and Slim II**-Undeclared sibutramine & phenolphthalein via FDA.

Health Canada Mar/15 advises- FDA Mar/15 **Bee Slim & Bee Thin** has undeclaried silbutramine. Singapore Health Sciences Authority Mar/15 **Nutri Drops Grapefruit Diet**: Undeclared sibutramine, benzyl sibutramine & phenolphthalein.

Health Canada Mar/15 advisory regarding "**Altimate Fat Burner Maximum Burn**" being sold by Nature's Source in Vaughan, Ont., the Department received a complaint about the product also being sold at Nature's Source, 2391 Trafalgar Rd., Unit #6 in Oakville, Ont. Altimate Fat Burner Maximum Burn is an unauthorized health product labelled to contain DHEA, yohimbe, caffeine and ephedrine.

Health Canada Jun/15 requests quarantine of drugs linked to **Zhejiang Hisun Pharma** due to data integrity concerns.

Health Canada Aug/15-FDA has **Akttive Capsules & Zero Xtreme Capsules** with undeclared silbutramine.

Health Canada Oct/16: **Adelganzantes R-II, Mang Luk Power Slim, Xcelerated Weight Loss Charged Up, & Xcelerated Weight Loss Turbo Charge**- Undeclared sibutramine by United States Food and Drug Administration.

Health Canada Oct/16: **B-finn**- Undeclared orlistat and 2-(diphenylmethyl)pyrrolidine (desoxy-D2PM)by Hong Kong Department of Health.

Health Canada Oct/16: **Citrus' Fit, Mang Luk Power Slim Detox, Slim Fit X, & Ultimate Lean** -Undeclared sibutramine and desmethylsibutramine by United States Food and Drug Administration.

Health Canada Oct/16: **Double S-** Undeclared sibutramine by Hong Kong Department of Health.

Health Canada Oct/16: **Maxx Easy**-Undeclared sibutramine and lorcaserin, and orlistat by United States Food and Drug Administration.

Health Canada Oct/16: **Mi Show Slimming capsules**- Undeclared sibutramine by Australian Therapeutic Goods Administration.

Health Canada Oct/16: **Xcelerated Weight Loss Ultra Max**- Undeclared phenolphthalein and sildenafil by United States Food and Drug Administration.

Health Canada Oct/16: **Zi Xiu Tang Beauty Face and Figure Capsule**- Undeclared phenolphthalein and fluoxetine by United States FDA.

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MHRA Feb/12 Herbal sliming products found to contain potentially dangerous undeclared pharmaceuticals: **Expelling Grease Slimming Abdomen, V12 Fruit Slimming, 100% Natural Weight Loss Coffee, Leisure 18 Slimming Orange Juice, Fashion Slimming Milk Shake, Langli, Ya Buk & Fruit and vegetables lose weight**. MHRA has received advice from the Danish Medicines Agency that these unlicensed products have been tested and

found to contain the Prescription Only Medicine Sibutramine.

MHRA Feb/12 Following a safety alert issued in October 2010 about slimming products containing Paiyouji the Agency has received a further complaint about a product called '**Paiyouji Plus - Fast Acting Slimming Tea**'. This product has been tested by the Agency and, as in the case of other Paiyouji products, found to contain sibutramine.

MHRA Nov/12 has received advice from the Danish Medicines Agency that this unlicensed product, **Ultra Slim** has been tested and found to contain the Prescription Only Medicine Sibutramine.

MHRA Feb/13 is advising consumers not to use the products specified below due to sibutramine content. Product names: **Fashion Slimming Coffee, L-Carnitine + P57, L-CarnitinL 360 Slimming Coffee, Brazil Potent Slimming Coffee sachets, Coffee 26 Original sachets, Coffee Nature Fashion Slimming sachets, Slender Capsule, Slim-1.**

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Thyroid: Online Extras

1. Other hypothyroid tests: Thyroid peroxidase (TPO) is a key enzyme in thyroid hormonogenesis. Nearly all patients with Hashimoto's thyroiditis will have antibodies to TPO. An **Anti-TPO test** can help identify an autoimmune cause of hypothyroidism. A **bone mineral density test** (BMD) may also be indicated in some patients with long-standing hypothyroidism (esp. in the elderly) to rule out osteoporosis caused by hypothyroidism.

2. Other hyperthyroid tests: A **differential I-131** can be valuable for diagnosis once TSH test shows hyperthyroidism (e.g. thyroiditis has ↓ I-131U, Graves' has diffuse I-131U). **TSH receptor antibodies** (TRAbs) can be used when I-131 testing is contraindicated (e.g. in pregnancy). Graves' disease typically has the presence of both blocking and stimulating TRAbs. An **ECG** may also be clinically indicated in hyperthyroidism in patients with cardiac disease (hyperthyroidism is one risk factor for the development of atrial fibrillation and other arrhythmias).

3. Management of thyroid nodules: Do TSH & ultrasound. If TSH low then do I-131 or technetium scan. If nodule is <1cm or unchanged & no family risk→likely not cancer. Greater likelihood of cancer if: microcalcifications, size greater than 2 cm, & a completely solid make-up. **FNAB** if: nodule growing; >1cm & history unknown; if ultrasound suggests cancer; family/pt history of thyroid cancer; if neck radiation, or vocal/swallowing problems.

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FDA Propylthiouracil-Induced Liver Failure June/09 FDA has identified 32 AERS cases (22 adult and 10 pediatric) of serious liver injury associated with propylthiouracil use. Of the adult cases, 12 deaths and 5 liver transplants occurred. Among the pediatric patients, 1 case resulted in death and 6 in liver transplants. In contrast, for methimazole 5 AERS cases of serious liver injury were identified. All five cases were in adult patients and 3 resulted in death. (**April 21, 2010**: Propylthiouracil: FDA has added a Boxed Warning to the label for propylthiouracil, to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and pediatric patients using this medication. A boxed warning has been added to the hyperthyroidism drug propylthiouracil (PTU) to alert clinicians about the drug's risk for severe liver injury, the FDA announced on Wednesday. The new labeling is based in part on postmarketing safety reports of severe liver injury — including 15 deaths — in 23 adult and 11 pediatric patients taking PTU. A warning about the potential dangers of the drug was issued by the agency last June. The FDA recommends that PTU only be used in patients who cannot tolerate methimazole or other treatments for hyperthyroidism and in women just before and during their first trimester of pregnancy. Patients will now receive a medication guide upon filling a prescription for PTU. FDA drug safety communication)

FDA Nov/15: advising that rare cases of **underactive thyroid have been reported in infants following the use of contrast media containing iodine**, also called "contrast dye," for X-rays and other medical imaging procedures. In all of the reported cases, the infants were either premature or had other serious underlying medical conditions. Available evidence leads FDA to believe that this rare occurrence is usually temporary and resolves without treatment or any lasting effects. See the Drug Safety Communication for a data summary and a list of approved Approved Iodinated Contrast Media Products.

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Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones).

Health Canada May/14 has requested a stop sale and recall of the product "**Thyroid Gland**" (NPN 80044198). The action has been taken because the product contains the prescription drug ingredient thyroid.

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Given these potential adverse effects, the FDA issued an alert on June 4, 2009 that noted the risk of serious liver injury, including liver failure and death, with the use of PTU in adult (1:10,000) and pediatric (1:2,000) patients. These conferences focused on the relative safety of methimazole compared with PTU.[11-14,16] Approximately 30% of patients treated with PTU will have 1- to 2-fold elevations of serum aminotransferase levels. The liver disease associated with PTU can be severe. In the Adverse Event Reporting System (AERS), approximately 22 adult (12 deaths, 5 hepatic transplants) and 10 pediatric (1 death, 6 hepatic transplants) cases of serious hepatic injury associated with PTU treatment were reported. Methimazole, by contrast, was associated with 5 adult cases of serious hepatic injury with 3 deaths. In a system that may overlap with AERS, the United Network for Organ Sharing reported 23 hepatic transplants from 1990 to 2007 (16 adult, 7 children) related to PTU-associated hepatic failure.[11-13,16] Concurrently, no liver transplants related to the use of methimazole were reported. The average PTU dose in children and adults requiring liver transplant was 300 mg daily. Liver failure occurred between 6 and 450 days after starting treatment (median 120 days). Furthermore, there were 2 reports of serious maternal liver disease during pregnancy and 2 reports of liver injury in fetuses of mothers who ingested PTU during pregnancy.[11-14,16]

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Other Agents	Prednisone (Glucocorticoid) 1, 5ᶜ, 50ᶜmg tab; 1mg/ml soln	-Suppresses adrenal function	Classic & Nonclassic congenital adrenal hyperplasia (NCCAH)	-Less effective compared to OCs or anti-androgens[1]	Uncontrolled diabetes, Obesity	Changes typical of Cushing syndrome (weight gain, bone loss), adrenal atrophy	5-7.5mg po daily $8 (5mg tab)
	Ketoconazole NIZORAL 200ᶜmg tab ☎▼	-Adrenal enzyme inhibitor	For patients with Cushing's syndrome while waiting definite therapy	-Similar efficacy to CPA 2-50mg[20]	Hepatic dysfunction Pregnancy, BF	Gynecomastia, dry skin, **hepatotoxicity**, adrenocortical suppression	200mg po daily $38 (200mg tab)
	Leuprolide acetate depot (GnRH analog) LUPRON & DEPOT ☎▼ 5mg/ml vial ✗⊗; Depot: 3.75,7.5,11.25,22.5✗ &30✗ mg	-Potent inhibitor of ovarian steroidogenesis by suppressing LH & FSH	Severe hyperandrogenism of ovarian origin that does not respond to other drugs	-Similar efficacy to CPA 2-50mg, but more adverse effects[20]	Pregnancy, BF Osteoporosis	Osteoporosis Reversable induced menopause	3.75-7.5mg monthly IM, with 25-50ug transdermal estradiol 445_{$415 + $24-30}$
	Metformin GLUCOPHAGE 500ᶜ, 850mg tab	-improves insulin sensitivity	Used in polycystic ovary syndrome (PCOS). Not effective for idiopathic hirsutism	-Small benefit compared to placebo[23] -Inferior to OC or anti-androgen therapy for idiopathic hirsutism[23]	Renal failure	Gastrointestinal upset (minimize by starting low dose $_{250mg\ daily}$, then titrate)	500-2000mg/day (given 250-1000mg BID) $18-28 (500mg tab)

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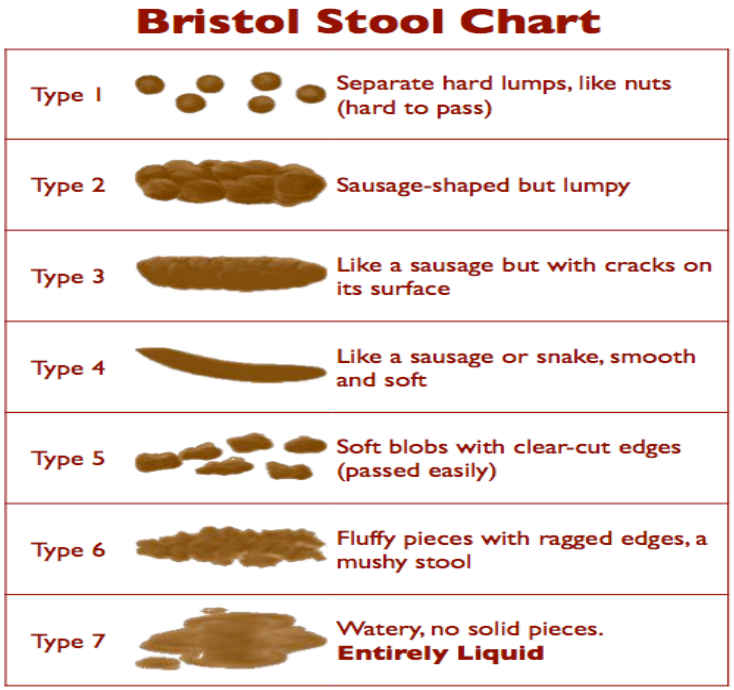

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methodological quality and subject to bias. Further well-designed randomised controlled trials with adequate sample sizes, validated outcome measures (especially patient reported outcome measures) and long-term follow-up are required to allow definitive conclusions to be drawn.

Cochrane reviews CD:

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

Cochrane reviews UC:

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

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Complete List of Abbreviations

2^{o}=secondary ☎=Exception Drug Status SK ✘ =non-formulary SK ✆=prior approval required for NIHB ⊗=not covered by NIHB ▼=covered by NIHB 💻=On-line Extras =reduce dose in kidney dysfunction =reduce dose in liver dysfunction **ac**=before meals **AE**=adverse events **ASA**=acetylsalicyclic acid **BID**=twice daily **CA**=cancer **Ca^{++}**=calcium **CAD**=coronary artery disease **C.difficile**=Clostridum difficile **COXIB**=selective cyclooxygenase 2 inhibitor **CV**=cardiovascular **CYP**=cytochrome P450 enzymes **DAPT**=dual antiplatelet therapy **DI**=drug interaction **DU**=duodenal ulcer **dysfxn**=dysfunction **ENRD**=endoscopy negative reflux disease **Fe^{++}**=iron **g**=generic **GERD**=gastroesophageal reflux disease **GI**=gastrointestinal **GU**=gastric ulcer **H_2RA**=H_2-receptor antagonist **H.pylori**=Helicobacter pylori **HS**=bedtime **hx**=history **IV**=intravenous **LFT**=liver function tests **Mg^{++}**=magnesium **min**=minute **mos**=month **Na^{+}**=sodium **NG**=nasogastric **NSAID**=non-steroidal anti-inflammatory drugs **NNT**=number needed to treat pt=patient(s) **OD**=daily **OR**=odds ratio **OTC**=over the counter **PRN**=as needed **PPI**=proton pump inhibitor **po**=oral **PUD**=peptic ulcer disease **QID**=four times daily **SCr**=serum creatinine soln=solution **SSRI**=selective serotonin reuptake inhibitors **sx**=symptom(s) **tx**=treatment **UBT**=urea breath test **UGIB**=upper gastrointestinal bleed **VBAD**=vomiting, bleeding, abdominal mass, dysphagia **wks**=week(s) **yrs**=years **ZES**=Zollinger-Ellison Syndrome

Alternative PPI Formulations & Routes of Administration		
Dexlansoprazole DEXILANT	30mg, 60mg dual release* capsule ✘ ⊗	**Route of Administration: Oral** Open capsule, sprinkle intact granules onto 1 tablespoon of cold, soft food (e.g. applesauce, yogurt, jam). Swallow immediately. Granules should not be chewed. **Suspension from solid dosage form for po or NG tube:** Open capsule. Mix intact granules with 20mL of water. Swirl. Administer via po or via NG tube. Refill syringe with 10mL of water to flush and administer po or via NG tube; repeat with another 10mL.
Esomeprazole NEXIUM, g NEXIUM is MUPS (multiple unit pellet formulation), & some g will disperse in water – e.g. Mylan will, Apotex will not	20, 40mg delayed release tablet ☎ ⊗	**Route of Administration: Oral** Disperse tablet in half a glass of non-carbonated water. Stir until the tablet disintegrates & drink the liquid with the pellets within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed. **Route of Administration: Gastric tube (8-20 French)** Prepare & give immediately. Pre-flush tube with 20mL sterile water (SW). Place tablet in a 60mL catheter tip syringe. Draw up 50mL of SW for 8-13 French, use 25mL if ≥14 French. Shake to disperse tablet. Hold syringe tip up & check tip for clogging. Attach syringe keeping tip up. Point tip down & give 5-10mL. Remove, shake again & give remaining suspension. Refill syringe with 25mL SW, shake to suspend any remaining sediment & give. Post-flush with 40mL SW for ND, NJ, PGJ and PG tubes and 20-30mL for all other tube types.
	10mg granules (sachet) for oral soln ✘ ⊗	**Route of Administration: Oral** Dissolve granules in 15mL of water. Stir & leave to thicken for a few minutes. Stir again, and drink within 30 minutes. If need be, rinse container by adding more water, stir & drink immediately. **Route of Administration: NG tube** Dissolve granules in 15mL of water. Shake syringe & leave to thicken for a few minutes. Shake the syringe & administer via NG tube within 30 minutes. Refill the syringe with another 15mL, shake & flush the line.
Lansoprazole PREVACID, g	15, 30mg delayed release capsule ☎ ▼	**Route of Administration: Oral** Open capsule, sprinkle intact granules onto 1 tablespoon of cold, soft food (e.g. applesauce, yogurt, jam). Swallow immediately. Granules should not be chewed. **Route of Administration: NG tube (≥16 French)** Open capsule. Mix intact granules into 40mL of apple juice of water. Administer via NG tube. Flush tube with additional apple juice or water.
	15, 30mg oral disintegrating tab **PREVACID FASTAB** ☎✆	**Route of Administration: Oral** Dissolve **FasTab** on tongue with or without water until particles can be swallowed (dissolves in less than 1 minute). Do not chew granules. **Route of Administration: Oral Syringe (≥8 French)** Dissolve 15mg **FasTab** (4mL) or 30mg **FasTab** (10mL) in an oral syringe. Shake. Drink within 15 minutes. Add another 2-5mL to the syringe, shake & drink any remaining contents. **Route of Administration: NG tube** Dissolve 15mg **FasTab** (4mL) or 30mg **FasTab** (10mL) in a syringe. Shake. Administer via NG tube within 15 minutes. Add another 5mL of water to the syringe, shake & flush the tube.
Omeprazole LOSEC, g	10mg☎▼, 20mg delayed release tablet	**Oral suspension:** compound from tablets
	20mg delayed release capsule	**Route of Administration: Oral** Open capsule, sprinkle intact granules onto 1 tablespoon of cold, soft food (e.g. applesauce, yogurt, jam). Swallow immediately. Granules should not be chewed. **Route of Administration: NG tube** Open capsule. Mix intact granules with 10-20mL of 8.4% sodium bicarbonate in a 20mL syringe. Shake & administer via NG tube within 30 minutes. Flush the line with 10mL of water.
Pantoprazole PANTOLOC, g **TECTA**	**Pantoprazole Na^{+} PANTOLOC, g** 20mg⊗, 40mg enteric coated tablet 40mg/10mL injectable ✘ ⊗ (IV ≈ po) **Pantoprazole Mg^{++} TECTA** 40mg enteric coated tablet ☎ ▼	**Suspension from solid dosage form for po or NG tube:** oral suspension available in the U.S. or compounded from tablets **Route of Administration: Intravenous** (only PPI available as an injectable)
Rabeprazole PARIET, g	10, 20mg enteric coated tablet	-

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FDA Feb/12 notified the public that the use of stomach acid drugs known as **proton pump inhibitors** (PPIs) may be associated with an increased risk of **Clostridium difficile**–associated diarrhea (CDAD).
FDA Mar/12 **LINX Reflux Management System** is a surgically-placed string of magnetic titanium beads that is placed at the lower esophageal sphincter. When a person swallows, the device expands to accommodate the liquid or food. Once the food passes, the device keeps a weak lower esophageal sphincter closed, thus preventing material from flowing back into the esophagus.
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Health Canada **Aug/07** is advising consumers that it is currently reviewing new preliminary safety information regarding **serious cardiac events** in patients using Losec (omeprazole) and Nexium (esomeprazole), two prescription drugs used to treat acid-related stomach disorders. (**Feb 27, 2008** Health Canada Completes Safety Review of Losec (omeprazole) and Nexium (esomeprazole) OTTAWA - Further to its Information Update dated August 9, 2007, Health Canada is informing Canadians of the results of its review of safety information for Losec (omeprazole) and Nexium (esomeprazole), two prescription drugs used to

treat conditions where a reduction of gastric acid secretion is required, such as ulcers and reflux. In Canada, omeprazole is also sold in generic form as Apo-omeprazole, Ratio-omeprazole and Sandoz-omeprazole. Esomeprazole is only sold under the trade name Nexium. Nexium (esomeprazole) Based on its review of the data available at this time, Health Canada has concluded that there is no evidence supporting an increased cardiovascular risk associated with the long-term use of esomeprazole. The Department will continue to monitor safety issues related to esomeprazole by conducting further analysis of ongoing long-term studies as this data becomes available. Losec (omeprazole) After a thorough analysis, based on the data available to us at this time, we are unable to definitively conclude if there is a potential for increased cardiovascular risk associated with the long-term use of omeprazole. We will continue to evaluate should more conclusive data become available, and will advise Canadians if any further regulatory actions are required.)

Health Canada Aug/09 **Plavix & PPI Interaction** http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2009/plavix_hpc-cps-eng.pdf

Health Canada Feb/12 is informing Canadians of a possible association between the use of prescription stomach antacids known as proton pump inhibitors (PPIs) and an increased risk of **Clostridium difficile**-associated diarrhea (CDAD).

Health Canada Oct/12 is informing Canadians that the labelling for **methotrexate and Proton Pump Inhibitors** is being updated to include information on a potential interaction between these products.

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Complete Abbreviation List

☎=Exception Drug Status SK ✘ =non-formulary SK ✆=prior approval required for NIHB ⊗=not covered by NIHB ▼=covered by NIHB **ABX**=antibiotic(s) **ac**=before meals **AE**=adverse events **ASA**=acetylsalicyclic acid **BID**=twice daily **CA**=cancer **Ca^{++}**=calcium **cc**=with meals **CDN**=Canadian **CI**=contraindication **CrCl**=creatinine clearance **d**=day(s) **DI**=drug interaction **EtOH**=ethanol/alcohol **g**=generic **g**=gram **GERD**=gastroesophageal reflux disease **H_2RA**=H_2-receptor antagonist **H.pylori**=Helicobacter pylori **hx**=history **ITT**=intention to treat **MALT**=mucosa associated lymphoid tissue **mins**=minutes **NSAID**=non-steroidal anti-inflammatory drugs **OBMT**=omeprazole, bismuth, metronidazole, tetracycline **OTC**=over the counter **PRN**=as needed **po**=oral **PPI**=proton pump inhibitor **PUD**=peptic ulcer disease **QID**=four times daily **sx**=symptom(s) **tx**=treatment **UBT**=urea breath test **VBAD**=vomiting, bleeding, abdominal mass, dysphagia **wks**=week(s) **yrs**=years

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Data suggest that this infection is easily managed in these patients, being cured in nearly all cases.

Extras: **IRRITABLE BOWEL SYNDROME (IBS)**

Discontinued Drugs: **Alosetron** LOTRONEX (2000 -severe constipation & ischemic colitis) 0.5-1mg bid, avail. in USA ♀ special access 5HT3 antagonist. Not avail. in Canada. Avialable in USA.

Tegaserod **ZELNORM**: Mar07- suspended due to CV ischemic events; but Apr08-FDA for Emergency IND situations only use in IBS-constipation & chronic idiopathic constipation in ♀<55yr with no hx of heart problems. 6 mg po bid $160 (NNT=14) 5HT4 agonist Not avail in Canada.

Acupuncture: no difference in IBS symptom severity or IBS-related quality of life when compared to shame-acupuncture.[81]

Patient Handout http://www.nice.org.uk/nicemedia/live/11927/40608/40608.pdf

FODMAPs: fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) may be effective in reducing some IBS symptoms. FODMAPs are poorly absorbed, rapidly fermented short-chain carbohydrates that can increase gas production and induce osmosis in the intestinal lumen, causing bloating and abdominal pain. Some common sources of FODMAPs are apples, cherries, onions, garlic, milk, yogurt, wheat, and high fructose corn syrup. Medical Letter 2016

Notes:

- Children with IBS or functional abdominal pain: probiotic Lactobacillus rhamnosus GG 3 billion colony forming units twice daily reduced # of pain episodes & pain intensity by ≥50% more in tx vs Pl group (8wks; ave age 6).[53]
- A high-fibre diet and increased frequency of bowel movements may not protect against diverticulosis.[72]

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N/V EXTRAS:

Alarm signs - "Red Flags" for more severe GI disease:

- age >55, unintended ↓ weight, progressive dysphasia, persistent vomiting, evidence for GI bleed, family hx of GI cancer, altered mental status, abdom pain, feculent vomiting, hematochezia, melena, focal neurologic deficit.

Links:

NHS – CKS: Nausea and Vomiting in Pregnancy - management: http://www.cks.library.nhs.uk/nausea_vomiting_in_pregnancy ; NGC: ACCC Netherlands: http://www.guideline.gov/summary/summary.aspx?doc_id=11793
CINV Guidelines: 1) MASCC: http://www.mascc.org/content/1.html ; 2) ASCO: http://www.asco.org/portal/site/ASCO/
BWH-Overtreatment of PONV: 1) low doses of ondansetron, 1mg iv q6h, adequate ; 2) allow for onset, 30 minutes http://www.brighamandwomens.org/pharmacoepid/Research/EduMaterials/antiemetics3.05.04-web.pdf

Other:

- Fosapreitant: Injectible form of EMEND, 150mg vial in Canada.

Hyperemesis gravidarum

- N/V in pregnancy common, but hperemesis gravidarum likely affects <1%
- Tx: fluids & electrolytes, thiamine (or IV if prolonged & unable to take po), antiemetics.

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

Deleted product (historical record only).

Droperidol INAPSINE 5mg/2ml amp	0.625-2.5mg IM/IV slow; ?ECG prior $8/amp ✗ ⊗	As above (esp. akathisia); ↑QT? interval & sudden death (controversial) [35]

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FDA Dec/09 The Texas Department of State Health Services and FDA notified healthcare professionals and consumers, especially pregnant or breastfeeding women, to avoid consuming a product called "**Nzu**", taken as a traditional remedy for morning sickness,because of the potential health risks from high levels of lead and arsenic, noted on laboratory analysis by Texas DSHS. Nzu, which is sold at African specialty stores is also called Calabash clay, Calabar stone, Mabele, Argile and La Craie. It generally resembles balls of clay or mud and is usually sold in small plastic bags with a handwritten label identifying it as "Nzu" or "Salted Nzu."

FDA Dec/10 The injectable form of **dolasetron** mesylate (Anzemet) should not be used to prevent nausea or vomiting related to chemotherapy because the drug increases the risk for torsade de pointes. The FDA recommends against using Anzemet injections in patients with congenital long-QT syndrome. The warning does not apply to Anzemet tablets because the risks for developing an abnormal heart rhythm are not as high as with the injections. FDA MedWatch alert (Free)

FDA Sep/11 The U.S. Food and Drug Administration (FDA) is informing the public of an ongoing safety review of the anti-nausea drug Zofran (**ondansetron**, ondansetron hydrochloride and their generics). Ondansetron may increase the risk of developing abnormal changes(QT prolongation & torsades) in the electrical activity of the heart

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Health Canada May/11 ANZEMET (**dolasetron** mesylate) - Withdrawal of **20 mg/mL Intravenous** Injection Due to Potential Risk of Arrhythmias. New data suggest that intravenous administration of the injectable form of ANZEMET (dolasetron mesylate) may result in serious arrhythmias.

Health Canada July/11 is informing health professionals and consumers that the labelling information for the drug **metoclopramide** is being updated to include stronger warnings on the risk of a movement disorder known as "**tardive dyskinesia**."

Health Canada Mar/12: **Domperidone** should be used at the lowest possible dose. The risk of serious ventricular arrhythmias (QT) and sudden cardiac death may be higher in patients taking daily doses greater than 30 mg, and in patients over 60 years old.

Health Canada Oct/12: Ondansetron can cause a dose-dependent prolongation of the electrocardiographic-corrected QT interval (QTc), which can lead to Torsade de Pointes, a potentially life-threatening heart rhythm abnormality. The new maximum recommended single intravenous (IV) dose of ZOFRAN®is 16 mg infused over 15 minutes.

Health Canada May/14 has completed a safety review of the serotonin blocking drugs **dolasetron** (ANZEMET), **granisetron** (KYTRIL and generics), **ondansetron** (ZOFRAN and generics) and palonosetron (ALOXI), which are used for treating nausea and vomiting. This review identified a potential risk of **serotonin syndrome**.

Health Canada Jan/15 **Metoclopramide** - Abnormal Involuntary Movements (**Extrapyramidal** Symptoms) in **Children** - Sandoz Canada Inc., Apotex Inc., Omega Laboratories Limited and Pendopharm Division of Pharmascience Inc.

Health Canada Jan/15 **Domperidone** Maleate - Association with Serious **Abnormal Heart Rhythms and Sudden Death** (Cardiac Arrest). Domperidone may be associated with a small increased risk of serious abnormal heart rhythms and sudden death. Prescribing information changes include a new recommended maximum daily dose, new restrictions of use and stronger warnings.

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See also: Sexual Dysfunction Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Sexual-Dysfx-Drugs-Overview.pdf

Erectile Dysfunction Comparison Chart (ED) Treatment Chart

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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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Australian Therapeutic Goods May/15: **Top Gun for Men** tablets contain undeclared tadalafil; **Power 1 tablets, Dr. Ming's Chinese capsule & Maxman Domina Tu Pareja** tablets contains undeclared sildenafil.

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

FDA: Sept 21, 2007 -- TWC Global LLC, Inc., issued nationwide recall of **Axcil** and **Desirin**, both marketed as dietary supplements, because they contain potentially harmful, undeclared ingredients. FDA laboratory analysis of **Axcil and Desirin** found that the lot of 02B07 contained 3mg/g of sildenafil, the active ingredient of a FDA approved drug used for erectile dysfunction (ED).

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

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

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

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

FDA July/08 Jack Distribution, LLC issued a voluntary nationwide recall of selected lots of **Rize 2 The Occasion Capsules** and **Rose 4 Her Capsules**, marketed as dietary supplements. The products were recalled because certain lots contained

thiomethisosildenafil, an undeclared analog of sildenafil, a FDA-approved drug used for Erectile Dysfunction.

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

FDA Aug/08 chemical analysis of **Xiadafil VIP** tablet lots 6K029 and 6K029-SEI found that the product contained an undeclared ingredient, hydroxyhomosildenafil

FDA Mar/09- Bodee LLC and FDA notified consumers and healthcare professionals of a nationwide recall of all the company's supplement product sold under the name **Zencore Plus**. FDA lab analysis of Zencore Plus samples found the product contains benzamidenafil, an undeclared drug product and a PDE5 inhibitor.

FDA Apr/09 Nature & Health Co. and FDA notified healthcare professionals of a recall of a supplement product, **Libimax**. FDA analysis found the product contains tadalafil.

FDA July/09 and Haloteco notified healthcare professionals and consumers of a nationwide voluntary recall of Libipower Plus. Lab analysis of **Libipower Plus** samples were found to contain undeclared Tadalalafil.

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

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

FDA Nov/09 & RockHard Laboratories notified consumers that **RockHard Weekend**, a product sold as a dietary supplement, contains sulfoaildenafil, an analogue of sildenafil.

FDA Dec/09 warned that **Atlas Operations, Inc**. notified consumers of a nationwide recall of the company's dietary supplements for sexual enhancement. These products are sold as dietary supplements throughout the USA. FDA lab analyses found that the products tested from certain batches contain Sulfoaildenafil.

FDA Mar/10 & Natural Wellness notified consumers that **MasXtreme**, a product sold as a dietary supplement contains aildenafil close in structure to sildenafil and is expected to possess a similar pharmacological and adverse event profile as well as the drug phentolamine which is an alpha-adrenergic blocker.

FDA Apr/10 & Kanec USA notified healthcare professionals of a nationwide recall of **Stud Capsule For Men** [Lot #060607-01/060108-01, Exp 6-2013], after being informed by FDA that laboratory analysis of a sample found the product to be adulterated with sildenafil, an FDA approved drug.

FDA June/10 **Magic Power Coffee**: Product marketed as a dietary supplement for sexual enhancement contains the drug ingredient hydroxythiohomosildenafil.

FDA Aug/10 lab analysis of **Revivexxx Extra Strength** was found to contain undeclared tadalafil.

FDA Aug/10 notified Novacare LLC that certain products appear to contain sulfoaildenafil: **Stiff Nights, Aziffa, Size Matters, Erex, Mojo, Hard Drive, Eyeful, Red Magic, Straight Up, Zotrex, Monster Excyte, WOW, Xaitrex, Verect, Prolatis, Xytamax, Maxyte, Libidinal, OMG, OMG45, and Zilex (with Golden Spear) summers.**

FDA July/10 & Good Health, Inc. is conducting a voluntary recall after FDA lab analyses found that the product tested from certain batches of **Vialipro** contain Sulfoaildenafil.

FDA July/10 notified consumers that lab analysis of lots of ejaculoid **XXTREME** and **stimuloid II** found that the products, sold as dietary supplements, contain sulfoaildenafil

FDA Aug/10 had Lab analysis of **Mr. Magic** to contain hydroxythiohomosildenafil and sulfoaildenafil.

FDA Aug/10 analyzed **TimeOut** and determined that it contains hydroxythiohomosildenafil.

FDA Nov/10 ISSUE: Lab analysis has found **Duro Extend Capsules for Men** to contain Sulfoaidenafil, an analogue of Sildenafil

FDA Dec/10 warned consumers not to use **Man Up Now** capsules, marketed as a dietary supplement for sexual enhancement, because FDA analysis determined that the product contains sulfoaildenafil

FDA Dec/10 notified the public that testing determined that **RockHard Weekend** Lot Numbers 100159 and 100260 sold as blister packs, 3ct bottles and 8ct bottles & **Pandora** Lot Numbers 100378 sold as blister packs & **Passion Coffee** contain an analogue of sildenafil.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analysis confirmed that **Black Ant** contains sildenafil.

FDA Mar/11 ISSUE: FDA lab analysis of **X-Hero** found the product contains sulfosildenafil, the analogue of the active ingredient of an FDA-approved drug. In addition, FDA analysis of **Male Enhancer** sample found the product contains tadalafil.

FDA Apr/11 Lab analyses of **Best Enhancer** found that the products to contain Sulfoaildenafil.

FDA May/11 **Regenerect**: Recall - Undeclared Drug Ingredient of lab confirmed the presence of Sulfoaildenafil.

FDA June/11 lab analyses found Via **Xtreme Ultimate Sexual Enhancer Dietary** Supplement for Men to contain sulfoaildenafil methanesulfonate.

FDA Nov/11 lab analysis for Lot 10090571 found **Virility Max** to contain sulfoaildenafil.

FDA Feb/12 Healthy People Co. notified the public of a recall of the company's dietary supplements sold under the brand names Healthy People Co. FDA lab confirmed presence of Sibutramine & Tadalafil, making these products unapproved new drugs. (Mince Belle Dietary Supplement, PERFECT Men Dietary Supplement , EVERLAX Dietary Supplement, EVER Slim Dietary Supplement, Herbal Drink Acai-man Mangosteen Dietary Supplement, EVER SLIM Shake Mix Dietary Supplement)

FDA Feb/12 Regeneca, Inc. notifed the public of a nationwide recall of **RegenArouse**, Lot Number 130100. FDA lab analysis confirmed the presence of Tadalafil.

FDA Feb/12 is advising consumers not to purchase or use "**Hard Ten Days**," & "**Man King**" a product for sexual enhancement sold on various websites. FDA laboratory analysis confirmed that "Hard Ten Days" contains sildenafil

FDA Apr/12 laboratory analysis confirmed that "**France T253**" contains sildenafil.

FDA Apr/12 is advising consumers not to purchase or use "**X-Rock**," a product for sexual enhancement manufactured by CRM Laboratories and sold on various websites, including www.xrockme.com. FDA laboratory analysis confirmed that "X-Rock" contains sildenafil and hydroxythiohomosildenafil.

FDA Apr/12 laboratory analysis confirmed that "**Instant Hard Rod**" contains aminotadalafil. FDA laboratory analysis confirmed that "**ZenMaxx**" contains aminotadalafil. FDA laboratory analysis confirmed that "**RigiRx Plus**" contains aminotadalafil.

FDA May/12 is advising consumers not to purchase or use "**VMaxx Rx**," a product for sexual enhancement sold on various websites, including www.vmaxxrx.com. FDA laboratory analysis confirmed that "VMaxx Rx" contains the undeclared ingredient sulfoaildenafil. FDA is also advising consumers not to purchase or use "**Boost — Ultra Sexual Enhancement Formula**." This product is promoted and sold on various websites, includingwww.boostultra.biz. FDA laboratory analysis confirmed that "Boost—Ultra Sexual Enhancement Formula" contains sildenafil. FDA is also advising consumers not to purchase or use "**Firminite**," a product for sexual enhancement sold on various websites, including **www.firminite.com.** FDA laboratory analysis confirmed that "Firminite" contains tadalafil.

FDA May/12 West Coast Nutritionals, Ltd. is conducting a recall of all lots of their dietary supplements **Firminite, Extra Strength Instant Hot Rod, & Libidron** to the consumer. FDA lab analysis of Firminite was found to contain undeclared Tadalafil.

FDA May/12 is advising consumers not to purchase or use "**EreXite**," a product for sexual enhancement sold on various websites, including www.amazon.com. FDA laboratory analysis confirmed that "EreXite" contains tadalafil.

FDA Aug/12 CRM Laboratories is conducting a consumer/user level recall of all **X-ROCK 3 Day Pill For Men and Z-ROCK** products sold between October, 2011 and April, 2012. Finished product of X-ROCK 3 Day Pill for Men and Z-ROCK was tested and found to contain an analogue of an ingredient in an FDA-approved drug. Analytical tests conducted by the FDA concluded that the products contained sildenafil and hydroxythiohomosildenafil.

FDA Aug/12 Revatio (**sildenafil**) should **not be prescribed to children and adolescents** with pulmonary arterial hypertension, according to an FDA MedWatch alert. The warning is based on the results of a trial published in Circulation that showed increased mortality at medium and high doses of Revatio, compared with low-*dose treatment, among patients aged 1 to 17 years. Low-dose Revatio did not improve exercise capacity.*

FDA Sep/12: Body Basics Inc. announced that it is conducting a voluntary nationwide recall of **ACTRA-Sx 500 Dietary Supplement** Capsules, Lot 008-A, Expiration December 2013. The Company, through independent lab analysis, has confirmed the presence of Sildenafil Citrate.

FDA Sep/12 Evol Nutrition Associates, Inc./Red Dawn ("Evol Nutrition") notified the public of a nationwide recall of all lots of two dietary supplement products distributed by the company under the names **Mojo Nights and Mojo Nights for Her** to the consumer level. Testing by the FDA revealed the presence of undeclared tadalafil and sildenafil in Mojo Nights (Evol Nutrition is also recalling Mojo Nights for Her).

FDA Dec/12: **Libigrow, Libigrow XXXtreme, Blue Diamond, Blue Diamond Platinum, Mojo Nights, Mojo Nights Supreme, And Casanova**: Recall - Undeclared Ingredients Sulfoaildenafil and Thioaildenafil.

FDA Jan/13 Freedom Trading is conducting a voluntary consumer recall of a product sold as a dietary supplement under the brand name of **Super Power**. This product was sold between August 2012 and January 2013 nationwide & the products contained trace amounts of sildenafil.

FDA Mar/13 Green Planet, Inc. notified the public of a recall of its dietary supplement product **Night Bullet**. Analytical tests conducted by the FDA found that the product contains trace amounts of Sulfohydroxyhomosildenafil and Aminotadalafil, which are analogues of sildenafil.

FDA Apr/13 laboratory analysis confirmed that "**Ninja Mojo"& "Love Rider**" contains tadalafil. FDA also confirmed that "**AFFIRM XL**" contains the undeclared ingredient sulfoaildenafil.

FDA Apr/13 Consumer Concepts, Inc. notified the public of a consumer/user level recall of all **ROCK-It MAN** Male Enhancement Capsules sold between October, 2012 and April, 2013. Analytical tests conducted by the FDA concluded that the product contained hydroxythiohomosildenafil.

FDA Apr/13 **Affirm XL**, Inc. is conducting a voluntary recall to the consumer level after FDA lab analysis testing found the product to contain an analogue of sildenafil.

FDA Apr/13 laboratory analysis confirmed that "**Sex Plus**" contains undeclared sildenafil, tadalafil, sulfosildenafil and dimethylacetildenafil. FDA laboratory analysis confirmed that "**Zoom-Zooma-Zoom**" contains sildenafil, the active ingredient in the

FDA-approved prescription drug Viagra.

FDA May/13 American Lifestyle is announcing that it is conducting a voluntary recall of all lots of **Vicerex** UPC 893490820087 and **Black Ant** UPC 4026666142546. Laboratory analysis conducted by the FDA has determined the Vicerex product contains undeclared tadalafil and the Black Ant product contains undeclared sildenafil.

FDA May/13 is advising consumers not to purchase or use "**Bullet Proof**," a product promoted and sold for sexual enhancement on various websites and in some retail stores. FDA laboratory analysis confirmed that "Bullet Proof" contains tadalafil. Plus Chang Kwung announced today that it is conducting a voluntary nationwide recall of the company's dietary supplements sold under the brand name **Lightning Rod** (500 mg per capsule packaged in 3-count, UPC 6 89076 20257 2 and 12-count bottles, UPC 6 89076 20297 8), because FDA testing found the Lightning Rod Capsules to contain an analogue of Sildenafil.

FDA May/13: BeaMonstar Products notified the public that it is recalling its **SexVoltz, Velextra, and Amerect** capsules. Laboratory analysis conducted by the FDA on SexVoltz and Velextra has determined these products contain undeclared tadalafil.

FDA Jun/13 laboratory analysis confirmed that "**Reload**" , "**Cave Diver**" , "**Super Cheetah**", "**Nights to Remember**" , & "**X Zen Platinum**", contains sildenafil.

FDA Jun/13 A sample of **Royal Dragon Herbal Tonic Balls** contains vardenafil.

FDA July/13 **Clalis, Exten 1300 & MaxTreme Zen** contains sildenafil, while **MVP Mega** contains talalafil.

FDA July/13 **Silver Sword** & **Clalis** contains sildenafil.

FDA Aug/13 Volcano Company is recalling all lots of **Volcano Male Enhancement Liquid and Volcano Male Enhancement Capsules** to the consumer level. FDA test results revealed the Volcano Male Enhancement Liquid has been found to contain undeclared Desmethyl Carbodenafil, Dimethylsildenafil, and Dapoxetine.

FDA Aug/13: Jack Rabbit Inc. announced that it is conducting a voluntary nationwide recall of one lot of the company's dietary supplement product sold under the name **Jack Rabbit**. FDA lab analysis of the product was found to contain Sildenafil and Tadalafil.

FDA Aug/13 Hardmenstore.com is voluntarily recalling 1000 lots of **72HP, Evil Root and Pro Power Max** at the consumer level. According to representatives of the FDA, 72HP, Evil Root and Pro Power Max have reportedly been found to contain amounts of the PDE-5 Inhibitor, sildenafil.

FDA Sep/13 is advising consumers not to purchase or use **XZone Premium**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that XZone Premium contains sildenafil, tadalafil, and dapoxetine.

FDA Sep/13 is advising consumers not to purchase or use **Wood-E**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that Wood-E contains sildenafil.

FDA Sep/13 is advising consumers not to purchase or use **Xzen 1200, Xzen Gold or Xzen XPress,** products promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that it contains either sildenafil & tadalafil.

FDA Sep/13 Haute Health, LLC is voluntarily recalling all lots of **Virilis Pro, PHUK and Prolifta** at the retail and consumer level. Virilis Pro, PHUK and Prolifta have been found to contain amounts of the PDE-5 Inhibitor sildenafil.

FDA Nov/13: Fossil Fuel Products, LLC, is recalling lots QL110714A102 and QL110408B046 of "**RezzRX**." Laboratory analysis conducted by the FDA determined the RezzRX lot QL110714A102 contains undeclared hydroxylthiohomosildenafil and aminotadalafil and RezzRX lot QL110408B046 contains undeclared hydroxylthiohomosildenafil.

FDA Nov/13: Jobbers Wholesale is recalling Lot No. KWAKPMC030505175957019 of **Rhino 5 Plus**, Lot No. JBP-L-1270-70 of **Maxtremezen** and Lot No. KWAKPMC03050517 of **Extenzone**. FDA analysis found these products to contain undeclared desmethylcarbondenafil and dapoxetine, making these products unapproved new drugs.

FDA Nov/13 Vitality Research Labs is recalling lots K58Q and F50Q of **VitaliKOR Fast Acting**. FDA laboratory analysis on VitaliKOR has determined that this product contains undeclared Vardenafil and Tadalafil.

FDA Nov/13: Tendex is voluntarily recalling Lot# F51Q of P-Boost and Lot # F51Q of NatuRECT to the consumer level. FDA laboratory analysis on Lot# F51Q of **P-Boost**, which the firm also labels as **NatuRECT**, has determined that this product contains undeclared tadalafil.

FDA Nov/13 **Alpha Male** contains sildenafil & other analogs.

FDA Jan/14 Midwest Wholesale is voluntarily recalling the following products Boost**: Ultra, XZone Gold, Sexy Monkey, Triple MiracleZen Platinum, Magic for Men, "New" Extenze, and New XZen Platinum**. FDA analysis found these products to contain undeclared Sildenafil and/or Tadalafil.

FDA Jan/14: **JINQIANGBUDOR Red Dragon** & **Tiger King** contains sildenafil; **Bali Mojo** & **Vimax** contains tadalafil; SexRx Contains both sildenafil and tadalafil.

FDA Mar/14 is clarifying its previous recommendation related to prescribing Revatio (**sildenafil**) for children with pulmonary arterial hypertension (PAH). Revatio is FDA-approved only to treat PAH in adults, not in children; however, health care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient.

FDA Mar/14: Nova Products, Inc. issued a voluntary recall of the following products: **African Black Ant (Lot# 2006-000926), Black Ant (Lot# 2006-3627878), XZen Gold (Lot# 130310GL), ZXen Platinum (Lot# 130520PL), XZen 1200 (Lot# 13051012), XZone Gold (Lot# 131110GL), and XZone 1200 (Lot# 13071012)** at the retail level. FDA laboratory analysis on these products has determined that they contain undeclared amounts of sildenafil and tadalafil.

FDA apr/14 is advising consumers not to purchase or use **S.W.A.G**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that S.W.A.G contains sildenafil.

FDA May/14: Eugene Oregon, Inc. is voluntarily conducting this recall because FDA analysis of **African Black Ant, Black Ant, and Mojo Risen** distributed to a third party revealed that the distributed products contained undeclared amounts of the active pharmaceutical ingredients sildenafil and tadalafil.

FDA May/14 is advising consumers not to purchase or use **MV5 Days**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that MV5 Days contains sildenafil,

FDA Jun/14: advising consumers not to purchase or use **Eyeful** contains hydroxythiohomosildenafil; **Liu Bian Li** contains sildenafil; **Dick's Hard Up** contains tadalafil; **3 Hard Knights** contains sildenafil and thiosildenafil; **Full Throttle On Demand** contains propoxyphenyl sildenafil; GoldReallas contains sildenafil and thiosildenafil.

FDA June/14 laboratory analysis confirmed that **Zhen Gong Fu** contains sildenafil.

FDA Jun/14 laboratory analysis confirmed that **Gold Vigra & Miraculous Evil Root** contains sildenafil.

FDA July/14: **Lian Zhan Qi Tian capsules & Weekend Warrior** contains thiosildenafil.

FDA Aug/14 is advising consumers not to purchase or use **Arize**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that Arize contains sulfoaildenafil; and **Herbal Vigor Quick Fix** contains tadalafil.

FDA Nov/14 is advising consumers not to purchase or use **Black Storm**. FDA laboratory analysis confirmed that Black Storm contains sildenafil.

FDA Jan/15 is alerting consumers and health care professionals that **counterfeit versions of Cialis 20 mg tablets** were found in the mail on its way to a U.S. consumer.

FDA Jan/15 laboratory analysis confirmed that **Happy Passengers** contains sildenafil.

FDA Feb/15 laboratory analysis confirmed that **Black King Kong, Germany Niubian, Tibet Babao, 72HP, Night Man, & Libigrow XXX Treme** contains sildenafil.

FDA Mar/15 laboratory analysis confirmed that **Santi Scalper, Vigra, Vigour 300, Sex Men, Super Hard, Plant Vigra, MME MAXMAN, Hard Wang & FX3000** contains sildenafil.

FDA Mar/15 laboratory analysis confirmed that **Bigger Longer More Time More Sperms (sic), Black Ant King, African Superman & Black Mamba Premium** contains sildenafil.

FDA May/15 laboratory analysis confirmed that **Black Panther** contains sildenafil.

FDA May/15 laboratory analysis confirmed that **Viagra 007**contains sildenafil.

FDA May/15 laboratory analysis confirmed that **King of Romance** contains sildenafil.

FDA Apr/15 laboratory analysis confirmed that **Fatloss Slimming Beauty** contains sildenafil.

FDA Apr/15 laboratory analysis confirmed that **Extreme Diamond 3000** contains desmethyl carbodenafil and dapoxetine.

FDA May/15 **Samurai-X, Happy Passengers, & AMPD Gold Bee Pollen** contains undeclared sildenafil.

FDA May/15: **Black King Kong, Tibet Babao, Vigour 300, Hard Wang**, **FX3000, Sex Men, Vigra, Plant Vigra, Santi Scalper, Baolong, Rhino Blitz Gold 3000, Vim-25, Black Mamba Premium, Bigger Longer More Time More Sperms (sic), Herb Viagra, & La Pepa Negra** contains undeclared sildenafil.

FDA May/15: **Male Silkworm Moth Nourishing Oral Liquid** contains undeclared vardenafil.

FDA May/15: **Lean Body Extreme** contains undeclared sibutramine, desmethyl sibutramine, phenolphthalein & sildenafil.

FDA May/15: **Diablos Eca Fire Caps** contains undeclared sildenafil, phenolphthalein, sibutramine & deisobutylbenzylsibutramine.

FDA July 15: **Extreme Diamond 3000** contains Undeclared desmethyl carbodenafil and dapoxetine.

FDA July 15:**Natural Max Slimming** contains Undeclared sildenafil, fluoxetine, andsibutramine.

FDA Aug/15 R Thomas Marketing, through its websites www.herbviagra.com and www.herbsviagra.com, sold the supplements under the names **Black Ant, Herb Viagra, Real Skill and Stree Overlord**. All four items contain undeclared sildenafil.

FDA Oct/15 **Kaboom Action Strips** 12 Pack contains undeclared sulfoaildenafil.

FDA Sep/15: **Miracle Rock 48** has been found to contain undeclared thiosildenafil.

FDA Oct/15 laboratory analysis confirmed that **Wild Sexx Capsules** contains sildenafil and tadalafil.

FDA Oct/15 laboratory analysis confirmed **Ultra SX Capsules, Super Dragon 6000 Capsules, Sex-Love Secret Code Capsules, Paradise Suplemento Natural Ultra Plus Capsules, APEXXX, & S.W.A.G.G.E.R Extreme Capsules** contains sildenafil.
FDA Oct/15 laboratory analysis confirmed that **Fuel Up High Octane, & Fuel Up Plus** contains hydroxythiohomosildenafil.
FDA Nov/15 laboratory analysis confirmed that **Rhino X, Effective Viagra, Sex Drive Capsules, XForMan Plus & Australia Kangaroo Essence** contains sildenafil.
FDA Dec/15 laboratory analysis confirmed that **Rhino Big Horn 3000** contains desmethyl carbodenafil and sildenafil.
FDA Dec/15 laboratory analysis confirmed that **OrgaZen 3000, OrgaZen 3500, & Rhino 7 Blue 9000** contains tadalafil.
FDA Dec/15 laboratory analysis confirmed that **Triple Power Zen Gold 2000, Triple Power Zen Plus 2000, Xtra Zone 2200, Xtra Zone 2400, Xtra Zone 2600, & Diamond 3500** contains sildenafil and tadalafil.
FDA Dec/15 laboratory analysis confirmed that **Triple MiracleZen Extreme 1750 mg, MiracleZen Gold 1750 mg & Triple MiracleZen Plus 1500 mg** contains sildenafil, tadalafil and dapoxetine.
FDA Dec/15 laboratory analysis confirmed that **Eros Power Zone 1900** contains desmethyl carbodenafil and dapoxetine.
FDA Dec/15 laboratory analysis confirmed that **X Again Platinum** contains sildenafil, tadalafil and dapoxetine.
FDA Dec/15: Nuway Distributors llc is voluntarily recalling all lots of **Apexxx** tablets to the consumer level. FDA analysis found Apexxx to contain amounts of the PDE-5 Inhibitor, sildenafil.
FDA Dec/15 laboratory analysis confirmed that **Power Tiger-X c**ontains sulfoaildenafil.
FDA laboratory analysis confirmed that Ginseng Power-X contains sildenafil and sulfoaildenafil.
FDA Feb/16 laboratory analysis confirmed that **Ninja-X** contains sildenafil and thiosildenafil.
FDA Feb/16 aboratory analysis confirmed that **Golden Night** contains sildenafil and hydroxythiohomosildenafil.
FDA laboratory analysis confirmed that **Boss Number #Six** contains tadalafil.
FDA Feb/16 laboratory analysis confirmed that **Mamba is Hero** contains sildenafil, desmethyl carbodenafil, and dapoxetine
FDA Jan/16 laboratory analysis confirmed that **Wonder-Erect Male Gum & Wonder-Erect Male Pills** contains vardenafil.
FDA Feb/16 laboratory analysis confirmed that **Zhong Hua Niu Bian, Weekend Prince, Bull & Bull's Genital** contains sildenafil.
FDA Mar/16 laboratory analysis confirmed that **Sextra** contains sildenafil.
FDA May/16 laboratory analysis confirmed that **Black Label X** contains sildenafil.
FDA May/16: SOS Telecom, Inc. is voluntarily recalling all lots of the following products (**Tiger-X, Ninja-X, Ginseng Power-X, & Super Samurai-X**) to the consumer level because these products were tested by the FDA and found to contain sildenafil.
FDA July/16 laboratory analysis confirmed that **Xcelerated Weight Loss Ultra Max** contains phenolphthalein and sildenafil.
FDA July 16 laboratory analysis confirmed **Super Shangai, Shangai Ultra X & Power Spring (XXX) Oral Liquid** contains sildenafil.
FDA July/16: FDA laboratory analysis confirmed that **Dream Body Advanced + Acai Weight Loss & Cleanse** contains sibutramine, fluoxetine and sildenafil.
FDA July/16: FDA laboratory analysis confirmed that **Dream Body Extreme Gold** contains sibutramine, fluoxetine and sildenafil.
FDA Jul/16 laboratory analysis confirmed that **Ziyinzhuangyang** contains sildenafil.
FDA Jul/16 Laboratory analysis confirmed that **Weili (一炮到天亮or Yi Pao Dao Tian Liang)** contains sildenafil.
FDA Aug/16 laboratory analysis confirmed that **One More Knight 1750** contains tadalfil and dapoxetine.
FDA Aug/16 laboratory analysis confirmed that **Master Zone 1500** contains sildenafil and tadalfil.
FDA Aug/16 laboratory analysis confirmed that L**ove4Long** contains sildenafil.
FDA Aug/16 laboratory analysis confirmed that **De Guo Hei Bei (德国黑倍), Boss-Rhino Gold X-tra Strength, & Anaconda Strong Formula** contains sildenafil.
FDA Aug/16 laboratory analysis confirmed that **Kopi Jantan Tradisional Natural Herbs Coffee** contains desmethyl carbodenafil.

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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.

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

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

Health Canada Apr/07 is warning consumers from the United States FDA found **V.MAX and Rhino Max (Rhino V Max) to contain undeclared amounts of aminotadalafil**, an analogue of tadalafil, used to treat erectile dysfunction.

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

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

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

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

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

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

Health Canada Aug/07 via Medsafe, the New Zealand health regulatory authority, advised the public not to use the products **Darling Capsules, Dali Capsules, Spanish Fly** Capsules, and an unnamed product, because they were found to contain sildenafil.

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

Health Canada Sept/07 is advising consumers not to use **Satis 60 Hours Ever Lasting Formula** is used for the treatment of erectile dysfunction/sexual enhancement. It was found to contain piperidenafil an analogue of vardenafil.. **True Man** and **Energy Max** are used as sexual enhancement/ erectile dysfunction products and were found to contain an analogue of sildenafil or vardenafil.

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

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

Health Canada Mar/08 is warning consumers not to use **ADAM**, an unauthorized product that contains an undeclared pharmaceutical ingredient similar to the prescription drug sildenafil.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Health Canada Sep/08 is advising consumers not to use 3 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lover Liquid Nutriment Herbal Supplement and Onyo** because they were found to contain undeclared pharmaceutical ingredients. Lover Liquid Nutriment Herbal Supplement was found to contain sildenafil while Onyo was found to contain sildenafil, as well as unapproved substances with structures similar to sildenafil and vardenafil. The U.S. Food and Drug Administration warned consumers not to use the product **Rose 4 Her** because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil.

Health Canada Sep/08 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Dr. Life or Chong Cao Ju Wang** because they were found to contain undeclared pharmaceutical ingredients. Dr. Life contains an unauthorised substance similar in structure to tadalafil while Chong Cao Ju Wang contains sildenafil.

Health Canada Oct/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: Swissmedic warned consumers not to buy or use the product **Powertabs** because it contains an unauthorised substance similar in structure to sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Sweet Energizer Vitality** Candy because it was found to contain an unauthorised substance similar in structure to tadalafil.

Health Canada Oct/08 is warning consumers not to use **Eros Fire**, a product promoted to enhance sexual performance, as this product may pose serious health risks. The product was found to contain xanthoanthrafil (also known as benzamidenafil), which is not indicated on the label.

Health Canada Nov/08 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lu Quan** because it contains undeclared glibenclamide and sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine, and **Zhuang Yao Gu Shen** Capsule because it contains sildenafil.

Health Canada Nov/08 is warning consumers not to use **Firm Dose** and **Granite Rooster**, two products promoted to enhance male sexual performance, as these products may pose serious health risks. Firm Dose was found to contain an undeclared pharmaceutical ingredient similar to sildenafil, while the product Granite Rooster was found to contain an undeclared pharmaceutical ingredient similar to tadalafil.

Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital

Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains the undeclared prescription drug sibutramine.

Health Canada Mar/09 Foreign Product Alerts: 68 Weight Loss Products; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien; Relacore
http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php

Health Canada June/09 Foreign Product Alerts: **Jia Yi Jian** (undeclared sibutramine & tadalafil); **Zencore Plus** (undeclared benzamidenafil) & **Zhong Guo Shen Fang** (undeclared med like sildenafil).

Health Canada July/09 is warning that the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **XP Tongkat Ali Supreme** after it was found to contain undeclared tadalafil.

Health Canada Oct/09: **Dynasty Worldwide Jinglida So Young Formula**- The Singapore Health Sciences Authority (HSA) warned consumers to not buy or use since contained undeclared aminotadalafil.
STEAM lot#80214, 90260 -The U.S. FDA informed consumers of a voluntary manufacturer recall of two lots of STEAM after FDA testing found these lots to contain undeclared sulfoaildenafil (lot# 80214) & undeclared tadalafil (lot# 90260).
Syntrax Fyre (contained Yohimbine), **Kam Yuen Brand Wan Ying Yang Gan Wan (contained sildenafil)** - The Hong Kong Department of Health warned consumers not to buy or use these products.

Health Canada Nov/09 is warning consumers not to use Herblex "**Once More**"since it was found to contain sildenafil.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products advertised for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is advising consumers not to use the following foreign health products: 1. **Power-Plus P**: The Singapore Health Sciences Authority issued a recall notice for Power-Plus P (expiry date 03/03/2011) after it was found to contain undeclared tadalafil. 2. **Zeng Da Yan Shi Wan**: The Hong Kong Department of Health warned consumers not to buy or use after it was found to contain undeclared sildenafil.

Health Canada Jan/10 informs that Finish Food Safety Authority: **Full Contact Max Potency** contains thio-sildenafil and thio-homosildenafil; Singapore Health Sciences Authority: **M-Action** contains desmethylacetildenafil and acetilacid. U.S. FDA: **RockHard Weekend** contains sulfoaildenafil.

Health Canada Jan/10 is advising consumers not to use the unauthorized product "**Stiff Nights**" after the U.S Food and Drug Administration (FDA) found that this product contains an undeclared substance similar to the prescription drug sildenafil.

Health Canada Feb/10: **2H & 2D**- Hong Kong Department of Health (HKDH) warned consumers not to buy or use 2H & 2Dafter it was found to contain undeclared tadalafil. Products distributed by **Atlas Operations Inc**. The FDA informed consumers of a voluntary recall by Atlas Operations Inc. of certain lots of some products that were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil. **STRO Emperor** Capsules The Irish Medicines Board warned consumers not to buy or use STRO Emperor Capsules after it was found to contain undeclared tadalafil.

Health Canada Mar/10 is warning Canadians that an unapproved health product, **POWER-MAX** that contains sildenafil.

Health Canada May/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Man Power** The Hong Kong Department of Health warned consumers not to buy or use Man Power product after it was found to contain undeclared tadalafil.

Health Canada June/10 is warning Canadians that the unauthorized health products "**Vigofit**" and "**Once More**," which are promoted to enhance male sexual performance, have been seized by Health Canada inspectors from retail stores in Abbotsford and Surrey, British Columbia. These two products contain sildenafil.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) due to concerns about possible adverse reactions: 1. **Stud Capsule For Men** The U.S. FDA informed consumers of a voluntary recall of one lot (Lot #060607-01/060108-01 Exp 6-2013) after it was found to contain undeclared Sildenafil.

Health Canada July/10 is advising Canadians about "**UP Ultimate Performance for Men**", an unauthorized health product containing undeclared sildenafil.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume 1. **Atlas Operations Inc. expands its U.S. recall of over 30 sexual enhancement supplements** The U.S. FDA informed consumers of an expanded recall of certain lots of products after some were found to contain undeclared sulfoaildenafil. The products are being voluntarily recalled nationwide in the U.S. by the company Atlas Operations Inc. 2. **Stallion, SZM Formula for Men, Tomcat Ali and Volcanic** New Zealand's Medsafe warned consumers not to buy or use these four products after they were found to contain undeclared tadalafil. 3. **Vitalex for men and Vitalex for women** The U.S. FDA informed consumers that the *Vitalex*products were found to contain acetildenafil, which is an unauthorized substance similar to sildenafil.

Health Canada Aug/10 is advising **Magic Power Coffee** The U.S. FDA warned consumers not to buy or use Magic Power Coffee after it was found to contain undeclared hydroxythiohomosildenafil.

Health Canada Aug/10: "**SeXXX DRIVE**", promoted as a herbal supplement to enhance male sexual performance, was tested by Health Canada and found to contain undeclared hydroxyhomosildenafil.

Health Canada Aug/10 has seized the unauthorized sexual enhancement supplements "**Male Enhancement ExtenZe**" and "**Women ExtenZe**" imported and sold by the Happy Paradise Adult Store in Burnaby, British Columbia. The labels of each of these unauthorized products list the prescription ingredient pregnenolone and the controlled drug, DHEA dehydroepiandrosterone). The labels of the unauthorized "Male Enhancement ExtenZe Nutritional Supplements" list the ingredient yohimbe extract (bark).

Health Canada Sep/10 **E.O.D. Erection on Demand**" being promoted as a herbal to enhance male sexual performance, the product was tested by Health Canada and found to contain tadalafil.

Health Canada Sep/10 is advising consumers not to use : 1. **Golden aryuru, Baisheng wei ge, Zhonghua niubian, Ten ka dai 1 bou, Kuai gan bei zeng chao yue zi wo (Happy felling doubly increase [sic]), Ling tou lang, SkyFruit, Chu bi ho ken, Jinbolang, Suika Koso, Lov, I ka ou (2009 nen sin hoso) and/or I ka ou (saisinsui shutsu hoso)** The Japanese Ministry of Health, Labour and Welfare warned consumers not to buy or use the 12 products listed above because they were found to contain undeclared sildenafil and/or other unauthorized substances similar to sildenafil that may pose similar health risks (norhongdenafil, acetil acid, and tioqinapiperifil). 2. **Vialipro** The U.S. FDA informed consumers of a recall of certain lots of Vialipro after FDA tests found product samples to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. MasXtreme** contains undeclared aminotadalafil while the other (#911035) contains undeclared aildenafil and phentolamine **2. Mr. Magic Male Enhancer from Don Wands** contained hydroxythiohomosildenafil and sulfoaildenafil **3. So Hard for Men - Pulse8 for Women - The Rock - Tonic 66** contained the undeclared pharmaceutical substances tadalafil, sildenafil, and/or hydroxyhomosildenafil **4. TimeOut** contained undeclared hydroxythiohomosildenafil.

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 "**Durazest**" and "**Once More**": Certain lots of two male sex enhancement products recalled as they may pose serious health risks. Certain lots (listed below) of two health products promoted for male sexual enhancement, "Durazest for Men" and "Once More," have been voluntarily recalled by Natural Performance Products Ltd. Health Canada laboratory tests identified the presence of a chemical similar to tadalafil (nortadalafil) in one lot of each product.

Health Canada Dec/10 is informing Canadians that NorthRegentRx has begun to voluntarily recall its product, **ResurreXX** from the Canadian market. NorthRegentRx is requesting that wholesalers, distributors and retailers stop sale of this product since contained an undeclared substance "hydroxyhomosildenafil".

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Shaguar, Signature Signergy, VIGRX (green capsule), VIGRX (white capsule), VigRx, VigRX Plus** New Zealand's MedSafe warned consumers to not buy or use these products after they were found to contain undeclared sildenafil, hydroxyhomosildenafil, thiosildenafil, and/or tadalafil. .

Health Canada Feb/11 is advising consumers not to use the following foreign health products promoted for sexual enhancement due to the presence of unauthorized substances (PDE5 derivatives eg. sildenafil): **1. Aziffa, Erex,**

Eyeful, Hard Drive, Libidinal, Maxyte, Mojo, Monster Excyte, OMG, OMG45, Prolatis, Red Magic, Size Matters, Stiff Nights, Straight Up, Verect, WOW, Xaitrex, Xytamax, Zilex (with Golden Spear), Zotrex 2. Prolatis' Duro Extend Capsules For Men 3. Tiger King 4. Vigor-25, Man Up Now

Health Canada Feb/11 is advising consumers not to use the following foreign health product **RockHard Weekend (lots 100159 and 100260 sold as blister packs, 3-count bottles and 8-count bottles)** The U.S. FDA informed consumers of a nationwide voluntary recall of certain lots (see above) of RockHard Weekend and Pandora after lab tests confirmed the products contain an unauthorized substance similar to sildenafil.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Nite Rider Maximum Sexual Enhancer for Men - STUD Capsule for Men:** The U.S. FDA informed consumers of a company recall of these products after they were found to contain undeclared sildenafil.

Health Canada May/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Gold Seagull Long Zhi Wan, Venergy** The Hong Kong Department of Health advised consumers not to buy or use these products after Gold Seagull Long Zhi Wan was found to contain undeclared glibenclamide, while Venergy was found to contain undeclared sildenafil. **2. Rock Hard Extreme, Passion Coffee** The U.S. FDA advised consumers not to buy or use these products after they were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada July/11 "**Man Up Now**" Removed From Sale at Delta and Surrey Stores: May Pose Serious Health Risks to Canadians, was removed from sale at "O! Behave" retail stores in Delta and Surrey, B.C. after Health Canada's testing identified undeclared sildenafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products. These products were also removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. {**Sildenafil: in BAOLONG Switzerland Rolex 168 Prolong Time, BAOLONG Yilishen, Black Gold, Herbal Viagra, "Jin Chong Chao – Golden Cordyceps", Lubiangaowansu, MAGNA-RX, MAXMAN II capsules, Shenrong dabuwan, Traditional Chinese Medicine Viagra, V100, VIGER, VigRX for Men, VINIX capsules, Wolf, "XiongBaTian", Zang Gong Mi Lian Nan Bao} & Zeng Bei Jiu Zhan-Tadalafil.**

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Black Ant** The U.S. Food and Drug Administration warned consumers to immediately stop using *Black Ant* after it was found to contain undeclared sildenafil at an amount three times the starting dosage for the approved prescription drug product. **2. Natural Vigra VIAGRA Tablets and Satibo Capsules** The Australian Therapeutic Goods Administration (TGA) advised consumers to stop using *Natural Vigra VIAGRA Tablets* after it was found to contain undeclared sildenafil, and *Satibo Capsules* after it was found to contain undeclared tadalafil and hydroxyhomosildenafil. **3. X-Hero and Male Enhancer** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *X-Hero* was found to contain undeclared sulfosildenafil while *Male Enhancer* was found to contain undeclared tadalafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products to include a new product, **Tibet Babao**, which was found to contain undeclared sildenafil, a prescription erectile dysfunction drug. This product and several others have been removed from sale at the **Happy Paradise Adult Store in Burnaby, B.C**.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **SXL Sexcellence sachets**- The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains an unauthorized drug (sulfosildenafil).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Maxidus capsules, Chao Jimengnan SuperPowerful Man tablets, Fu Yuan Chun capsules, and Qing Tian Zhu tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain prescription drugs (sildenafil, tadalafil) and/or unauthorized drugs (sulfohydroxyhomosildenafil, sulfosildenafil).

Health Canada Nov/11: An unauthorized health product, "**Stiff One Hard 169**" is being voluntarily recalled from the Canadian market after Health Canada's testing identified an undeclared prescription medication in the product (thiodimethylsildenafil, an undeclared substance similar to the prescription medication sildenafil).

Health Canada Dec/11 is advising "**Yanshiwang**", "**Jin Kong Fu**" and "**Chong Cao She Bian Zhuang Yang Dan**". These products were removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. These contained sildenafil.

Health Canada Jan/12 advises: **1. Get Stiff, Maxi Mize** New Zealand's Medsafe warned that these sexual enhancement products contain prescription drugs (tadalafil, vardenafil, yohimbine) and/or unauthorized drugs (hydroxyhomosildenafil, hydroxythiohomosildenafil). **2. Ying Da Wang tablets** The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains sildenafil.

Health Canada seized a variety of **Stiff4Ever** and **PurePillz** products from The Love Shop retail outlets located in Ontario. These products are unauthorized drugs and are considered potentially dangerous to the health and safety of Canadians. Health Canada tested the Stiff4Ever products, advertised as male sexual stimulants, and identified sildenafil. The labels of the PurePillz products (see below) state that they contain BZP and TFMPP.

Health Canada Mar/12 **Power-X**" has been removed from a Canadian retail location after Health Canada's testing identified undeclared thiodimethylsildenafil which is similar to the prescription medication sildenafil.

Health Canada May/12: Unauthorized health products, **"X-Rock", "Kaboom" and "One For Her"** have been removed from sale from various retail outlets in British Columbia and Saskatchewan. Health Canada's testing identified undeclared prescription drugs sildenafil and tadalafil, and an undeclared substance, hydroxythiohomosildenafil, which is similar to sildenafil.

Health Canada May/12 **1. AdvanceMen capsules; Miraculous Evil Root tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain either a prescription drug (sildenafil) or an unauthorized drug (sulfoaildenafil).

Health Canada June/12 **1. African Black Ant; France T253; Hard Ten Days; Man King; Stree Overlord** : The U.S. Food and Drug Administration warned that these sexual enhancement products contain prescription drugs (sildenafil. One product also contains tadalafil). **2. RegenArouse; RegenErect:** The U.S. Food and Drug Administration informed of a recall because these sexual enhancement products contain a prescription drug (tadalafil). **3. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil).

Health Canada June/12 **Natural Vigor Maximum** (Exemption Number: 138273) has been removed from sale from various retail outlets in Ontario after testing by Health Canada identified a hidden ingredient (dimethylhomosildenafil).

Health Canada July/12 **Lightning Rod**, an unauthorized sexual enhancement product, has been removed from sale from various retail outlets in Ontario, British Columbia and Saskatchewan after testing by Health Canada identified a hidden ingredient (hydroxythiohomosildenafil).

Health Canada Aug/12 These products are not authorized for sale in Canada and have not been found on the Canadian market, but they may have been brought into the country by travellers or purchased over the Internet. **1. Boost – Ultra Sexual Enhancement Formula; EreXite; Mojo Nights:** The U.S. Food and Drug Administration advised consumers not to buy or use these products after they were found to contain one or more of the following undeclared drug ingredients: tadalafil, sildenafil, and unauthorized substances similar to sildenafil that may pose similar health risks. **2. Firminite; Extra Strength Instant Hot Rod; Libidron:** The U.S. Food and Drug Administration informed consumers of a company recall after these products were found to contain undeclared tadalafil. **3. Instant Hard Rod; RigiRx Plus; ZenMaxx**: The U.S. Food and Drug Administration advised consumers not to buy or use these products after they were found to contain undeclared aminotadalafil, which is similar to tadalafil and may pose similar health risks. **4. VMaxx Rx:** The U.S. Food and Drug Administration informed consumers of a company recall of certain lots of *VMaxx Rx* after found to contain undeclared sulfoaildenafil.

Health Canada Dec/12 Three unauthorized health products -- "**Man Up Now", "Black Ant", "Triple Power Zen Gold 1200mg**"-- are being recalled by DVDXPRO after testing by Health Canada identified undeclared ingredients-sildenafil and/or tadalafil.

Health Canada Dec/12 is advising Four unauthorized natural health products have been removed from sale as they may pose serious risks to the health of Canadians. The "**ExtenZe**" products are promoted as sexual enhancement products and contain ingredients that legally require they be sold with a prescription in Canada. ExtenZe Max Strength Gelcaps, ExtenZe Original Tablets, ExtenZe Natural Female Tablets, and ExtenZe Big Cherry Flavour Liquid: Three of these unauthorized products list the prescription ingredient pregnenolone and the controlled drug DHEA (dehydroepiandrosterone) & three of these unauthorized products contain the prescription medication yohimbine (either as yohimbine

HCl or as yohimbe extract).

Health Canada Feb/13: Two unauthorized health products "**18 Again" and "Stiff 4 Hours**" were tested by Health Canada and were found to contain hidden ingredients (sildenafil or tadalafil) that may pose serious risks to the health of Canadians.

Health Canada Feb/13 A Toronto retail outlet (Handy Variety, 591 Sherbourne St.) has voluntarily handed over **counterfeit Viagra and Cialis** to Health Canada following a compliance and enforcement action by the Department. The counterfeit Viagra product is labelled as 100mg tablets (lot number 314833021), and has 11 blister packs of 4 tablets and one incomplete blister of 2 tablets per package. The counterfeit Cialis product is labelled as 20mg tablets (lot number 05668) and contains five blister packs of 2 tablets.

Health Canada Mar/13: An unauthorized natural health product, "**Libigrow**" was tested by Health Canada and found to contain hidden ingredients (sildenafil and tadalafil) that may pose serious risks to the health of Canadians. "Libigrow" was being sold at two retail locations in the province of Québec: Boutique Sexie folie Inc. (Sainte-Catherine) and at Boutique Érotique 5ième avenue Inc. (Valleyfield).

Health Canada Apr/13 **Shan Dian Shou** The Hong Kong Department of Health has advised it contains the undeclared prescription drug sildenafil.

Health Canada May/13 Two unauthorized health products — "**Stiff Nights" and "Stiff 4 Hours**" — were tested by Health Canada & were found to contain hidden ingredients (sildenafil and/or tadalafil) that may pose serious risks to the health of Canadians. The products were being sold at Saints N Sinners Ltd, 1715 Centre Street N.W., Calgary, Alberta.

Health Canada June/13 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Flutulang, Kapsul Gaut (Asam Urat), and True ProLife Vegrow** The Health Science Authority of Singapore advised consumers not to use these products after they were found to contain phenylbutazone, chlorpheniramine, dexamethasone, and a chemical compound similar to the prescription drug sildenafil. **2. Jinmaoshiwang tablets, Naturally Kouxan Best Slim capsules, and Majestic Slimming capsules** The Australian Therapeutic Goods Administration advised consumers not to use these products after they were found to contain sildenafil, sibutramine and phenolphthalein. **3. WOW, Super Power and SLIMDIA Revolution** The U.S. Food and Drugs Administration (FDA) warned consumers not to use these products after they were found to contain diclofenac sodium, methocarbamol, dexamethasone, sildenafil and sibutramine.
4. Libigrow XXXtreme, Blue Diamond, Blue Diamond Platinum, Mojo Nights Supreme, and Casanova The U.S. Food and Drugs Administration warned consumers not to use these products after they were found to contain sildenafil, sulfoaildenafil and thioaildenafil.

Health Canada Aug/13 **2. Steelman Capsules 2** The Hong Kong Department of Health has advised consumers not to use this product after it was found to contain undeclared aminotadalafil. **6. Libigirl capsules** The Australian Therapeutic Goods Administration warned consumers not to use this product after it was found to contain the undeclared prescription drugs sildenafil and tadalafil

Health Canada Aug/13 **Prema G** (Granules packaged in tea packets, NPN: 80035944) was tested by Canada Border Services Agency and found to contain a hidden ingredient (hydroxyhomosildenafil thione).

Health Canada Oct/13 wishes to inform Canadians that seized natural health products being sold by Lion King Health Enterprises Group Ltd., 1328-8368 Capstan Way, Richmond, BC. were tested and found to contain hidden ingredients and unauthorized substances similar to the prescription drug, sildenafil. (**North America Dami Ana 600mg, South America Maca 600mg, Ashwagandha 600mg, Optimusman 350mg, Superman 350mg, Innerget Instant Erection (NPN#80041194), Innerget Prolonged Performance (NPN#80041194), Innerget Everlasting Strength (NPN#80041194), Megaton 2080**.)

Health Canada Nov/13 is advising Canadians not to use these foreign health products as they may pose a health risk.

1. **14 sexual enhancement products** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36233a-eng.php ; SexVoltz (Regular and Maximum Strength); Velextra (Regular and Maximum Strength); Amerect* (Regular and Maximum Strength); Night Bullet; Bullet Proof; Vicerex; Zoom-Zooma-Zoom; Sex Plus; Affirm XL; Ninja Mojo; Love Rider; Stiff Days; ROCK-IT MAN; Libido Sexual Enhancer.
2. **Ziyinzhuangyang tablets, Maxman III, and Mojo Risen** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36519a-eng.php.

Health Canada Dec/13 has updated the list of natural health products seized from **Lion King Health Enterprises Group** Ltd., 1328 - 8638 Capstan Way, Richmond, B.C. that have been tested and found to contain hidden ingredients and unauthorized substances similar to the prescription drug tadalafil.

Health Canada Dec/13 testing of an unauthorized natural health product, **MaxHIMize**, found it to contain bacteria (Enterococcus durans and Bacillus spp) and undeclared caffeine that could present a risk to health. MaxHIMize is being promoted as a dietary supplement and for erectile dysfunction.

Health Canada Feb/14: 1. **Li Long Mei Guo Mo Bang, and Ginseng Tu chong Wan Lin Heong** The Singapore Health Sciences Authority warned consumers not to use this product after it was found to contain sildenafil.

Health Canada Mar/14 is advising Canadians not to use these foreign health products as they may pose a health risk. 1. **Xiang Gang Tian Long Sheng Wu Ke Ji Di Qi Dai Chi Jiu Zhan Shen** http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/38599a-eng.php was found to contain sildenafil. 2. **Various Sexual Enhancement Products** http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/38577a-eng.php was found to have sildenafil andtadalafil. 3. **Majestic Slim Perfect and Yixiu L-Carnitine Slimming Capsules** http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/38609a-eng.php was found to contain sildenafil andphenolphthalein.

Health Canada Apr/14: **Volcano Male Enhancement** liquid & caps: The U.S. Food and Drug Administration warned consumers not to use these products after they were found to contain desmethyl carbodenafil, dimethylsildenafil and dapoxetine**.**

Health Canada May/14 **Blue Stinger** contains sulfoaildenafil**; 72 HP, Evil root and Pro Power Max** contains sildenafil**; Jack Rabbit** contains sildenafil and tadalafil.

Health Canada May/14: 1. **VitaliKOR**: FDA found vardenafil and tadalafil**;** 2. **Vigor Tea sachets:** Australian Therapeutic Goods Administration found sulfoaildenafil**;**
3. **Prolifta capsules, PHUK and Virilis Pro:** FDA found **sildenafil;** 4. **Wood-E, Xzen Gold, Xzen XPress, XZen 1200, and XZone Premium**: FDA found Wood-E contains sildenafil, Xzen Gold and Xzen XPress contain sildenafil and tadalafil, & XZen 1200 contains tadalafil.

Health Canada June/14: **Bali Mojo & Vimax** contains tadalafil., **LOVher capsule**s contains tadalafil, sildenafil and diclofenac. **Erec-Bull,** contains yohimbine. **Best Whips & JINQIANGBUDOR Red Dragon** contains sildenafil. **Super Hard t**ablets contains sildenafil. **CONTROL All Natural Sexual Enhancement** contains sulfoaildenafil and dimethylsildenafil.

Health Canada July/14: **MME Naturally Maxman capsules, Blue Fantasy capsules, African Superman tablets, and MosKa** – energy for adults: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain sildenafil.

Heath Canada Aug/14: The United States Food and Drug Administration (FDA) warned consumers not to use the products **MV5 Days and S.W.A.G**., and the Australian Therapeutic Goods Administration (TGA) warned consumers not to use the product **Zhansheng Weige Cahoyue Xilishi tablets**, after they were found to contain sildenafil. The Australian Therapeutic Goods Administration (TGA) warned consumers not to use **Robust** tablets contained aminotadalafil.
The Singapore Health Sciences Authority warned consumers not to use **Herbal Health V+** after it was found to contain sildenafil and tadalafil. The Singapore Health Sciences Authority warned consumers not to use **Herbal Health Backplus 500mg** after it was found to contain tadalafil.

Health Canada Sep/14: **Gold Vigra, Liu Bian Li, GoldReallas, Black Ant Strong, My Man His Enhancer 12 Pack, Top Man 3 and Vigour 800**: The United States Food and Drug Administration (FDA) warned consumers not to use the products **Gold Vigra, Liu Bian Li and GoldReallas**, and the Australian Therapeutic Goods Administration (TGA) warned consumers not to use the products **Black Ant Strong, My Man His Enhancer 12 Pack, Top Man 3 and Vigour 800**, after they were found to contain sildenafil.
Dick's Hard Up, P-Boost, and NatuRECT: United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain tadalafil.
3 Hard Knights: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain sildenafil andthiosildenafil.
Germany Niubian: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use the product after it was found to contain sildenafil and zopiclone.
Alpha Male: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain sildenafil,aminotadalafil, sulfosildenafil, sulfoaildenafil, hydroxythiohomosildenafil, and dimethylsildenafil.
REDDES (or REDDIES) and **The Rock**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to containsulfosildenafil and hydroxyhomothiosildenafil.
Full Throttle On Demand: The United States Food and Drug Administration warned consumers not to use this product after it was found to contain propoxyphenyl sildenafil.
RezzRX: The United States Food and Drug Administration warned consumers not to use this product after it was found to containhydroxythiohomosildenafil and/or aminotadalafil.

Play Hard for Men: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use this product after it was found to contain yohimbine andhydroxyhomothiosildenafil.
Rhino 5 Plus, Maxtremezen, and Extenzone: The United States Food and Drug Administration warned consumers not to use these products after they were found to containdesmethylcarbondenafil and dapoxetine.

Health Canada Nov/14: An unauthorized health product, **Gra-MaxX Gold**, was seized by Health Canada as it contains an undeclared drug: N-Ethyl Tadalafil.

Health Canada Dec/14 is following up with Rapha Biotech Inc. **Gra-MaxX Gold** (yellow label) -- undeclared ingredient: N-ethyl tadalafil.

Health Canada Dec/14: "**Herberex**" (NPN 80041180) is being recalled nationwide after Health Canada testing confirmed it contains an undeclared drug: tadalafil.

Health Canada Dec/14: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use the products **Zhansheng Weige Chaoyue Xilishi, Chong Cao Zhag Bian Bao, Night Man, and MMC Sex Men capsules** and the United Stated Food and Drug Administration (FDA) warned consumers not to use the product **O.M.G.** after they were found to contain sildenafil. **Arize**: The United Stated Food and Drug Administration (FDA) warned consumers not to use the product Arize after it was found to containsulfoaildenafil. **Herbal Vigor Quick Fix**: The United Stated Food and Drug Administration (FDA) warned consumers not to use the product **Herbal Vigor Quick Fix** after it was found to contain tadalafil.

Health Canada Dec/14: "**Forta for Men**" (NPN 80045132) is being recalled after Health Canada testing confirmed it contains an undeclared drug: homosildenafil.

Health Canada Dec/14: Samson's Supplements stores in Calgary that pose a risk to health. **Nutrex Research Lipo6 Black, Nutrex Research Lipo6 Black Hers, Nutrex Research Lipo6 Unlimited, Nutrex Research Lipo6 Black Ultra Concentrate, West Pharm Yohimbe** Extract (bottle of 50 and 100 capsules), **West Pharm Yohimbe Extract** (bottle of 50 and 100 capsules), **NutraKey Yohimbine** HCl contains Yohimbine. **West Pharm Xtra Lean, West Pharm ThermaLean, West Pharm ThermoMAXXX** (bottle of 80 and 160 capsules), **Twinlab Ripped Fuel** contains Ephedrine and Caffeine. None of the products are approved for sale. The products are promoted for body building purposes, including for weight loss and increased energy, or for sexual enhancement.

Health Canada Mar/15 advises- FDA Mar/15 **Black Storm**: undeclared sildenafil. Australian Therapeutic Goods Administration **Max Hard**: undeclared sildenafil & aminotadalafil.
Rock Hard: undeclared tadalafil. Singapore Health Sciences Authority Mar/15: **SPARTA X**: undeclared hydroxyhomosildenafil & hydroxythiohomosildenafil. Singapore Health Sciences Authority Mar/15:
MAGIC PENIS undeclared sildenafil. Singapore Health Sciences Authority Mar/15
MR ZACK POWERBRO: undeclared propoxyphenyl hydroxyhomosildenafil, propoxyphenyl aildenafil, propoxyphenyl thiohydroxyhomosildenafil & propoxyphenyl thioaildenafil.

Health Canada Apr/15 testing has found that two unauthorized health products, "**Enhance" and "Natural-Power**," contain undeclared sildenafil.

Health Canada May/15 is warning consumers that an unauthorized drug, "**Stiff Rock**" promoted for male sexual performance enhancement was seized from Boutique Érotique 5ième avenue (also known as Boutique Érotique Liberté), 507 Gande-Île, Valleyfield, QC after Health Canada testing confirmed that the product contained drug ingredients: sildenafil; aminotadalafil; and hydroxythiohomosildenafil.

Health Canada Jun/15 requests quarantine of drugs linked to **Zhejiang Hisun Pharma** due to data integrity concerns.

Health Canada Aug/15-Australian Therapeutic Goods Administration has **Golden Root Complex Capsules & Bushen Famous Men Capsules & Laopiaoke Capsules** with undeclared sildenafil.

Health Canada Nov/15:**Dragon** Power, an unauthorized product sold at The Herb Depot, 407-409 Dundas Street West, Toronto, Ontario, was found to contain an undeclared sildenafil.

Health Canada Dec/15: **Mega Power** contains tadalafil .

Health Canada Feb/16: "**Forta for Men**", is being recalled after testing confirmed one lot contains an undeclared drug: tadalafil.

Health Canada Mar/16: Forta for **Men Daily, Forta Xpload and Durazest For Men Volume-** may contain an undeclared drug: sildenafil.

Health Canada Mar/16 says **S Lion Juice Orange 10 gm by Singapore Health Science Authority** undeclared propoxyphenyl thioaidenafil.

Health Canada Mar/16 says **S Lion Juice 20 gm** by Singapore Health Science Authority undeclared thiodimethylsildenafil.

Health Canada Mar/16 says **S Lion Juice 10 gm** by Singapore Health Science Authority undeclared thiodimethylsildenafil and tadalafil.

Health Canada Mar/16 says **S Lion Juice 1** by Singapore Health Science Authority undeclared aminotadalafil and thiodimethylsildenafil

Health Canada Mar/16 says **Rhino 7 3000 & Rhino 7 Platinum 3000 Capsules** by FDA contains undeclared desmethyl carbondenafil and dapoxetine.

Health Canada Mar/16 says **Power Khan** by FDA contains undeclared sildenafil and thiosildenafil.

Health Canada Mar/16 says Australian Therapeutic Goods Administration: **Hongkong Tianli Biological 'Power' tablets, Longue Jambe Frères (Brother Long Legs) tablets** contains undeclared sildenafil.

Health Canada Apr/16: Australian Therapeutic Goods Administration says **100% healthy food for men tablets, & V-MAX Herbal Tablets** contains undeclared sildenafil.

Health Canada June/16: FDA says **Boss Number #Six** contains undeclared tadalafil; **Bull & Bull's Genital** contains undeclared sildenafil; **Ginseng Power-X** contains undeclared sildenafil and sulfoaildenafil; **Golden Night** contains undeclared sildenafil and hydroxythiohomosildenafil; **Neophase Natural Sex Enhancer** contains undeclared hydroxyacetildenafil; **Weekend Prince** contains undeclared sildenafil; & **Wonder-Erect Male Gum** contains undeclared vardenafil.

Health Canada June/16: Australian Therapeutic Goods Administration- **Half Quite** tablets contains undeclared sildenafil; contains undeclared sildenafil and oxytetracycline; **Maxagra** capsules contains undeclared sildenafil and oxytetracycline; **Ninja-X** contains undeclared sildenafil and thiosildenafil; **Sextra** capsules contains undeclared sildenafil and yohimbine & **Zhong Hua Niu Bian** tablets contains undeclared chloramphenicol and sildenafil.

Health Canada July/16: FDA says **Sextra, & Zlimxter Capsules** contains undeclared sildenafil.

Health Canada July/16: FDA says **Salute Capsules** undeclared sildenafil, thiosildenafil, and sulfoaildenafil.

Health Canada July/16: Australian Therapeutic Goods Administration says **MMC Zang Ba Bao tablets, Super Bull 6000 Herbal capsules, & U.S. Black Gold tablets** undeclared sildenafil.

Health Canada July/16: **Wonderblue & B-Hard on Demand** has undeclared sildenafil as well as thiodimethylsildenafil and/or thiomethisosildenafil.

Health Canada July/16 **DR's Secret Bio Herbs Coffee** undeclared tadalafil

Health Canada Aug/16: Australian Therapeutic Goods Administration-**King-Wolf Tablets** undeclared sildenafil.

Health Canada Aug/16: Australian Therapeutic Goods Administration- **MAGNA-RX Capsules** undeclared sildenafil & acetaminophen.

Health Canada Aug/16: FDA-**My Steel Woody** undeclared sildenafil.

Health Canada Aug/16: Australian Therapeutic Goods Administration- **Black Storm** tablets undeclared sildenafil and vardenafil.

Health Canada Aug/16: FDA- **Dream Body Advanced + Acai Weight Loss & Cleanse, & Dream Body Extreme Gold** undeclared sibutramine, fluoxetine, and sildenafil.

Health Canada Oct/16: **Anaconda Strong Formula, Boss-Rhino Gold X-tra Strength, De Guo Hei Bei (德国黑倍), Libigirl, Power Spring (XXX) Oral Liquid, Shangai Ultra X, Super Shangai, The Golden Root, Weili (一炮到天亮 or Yi Pao Dao Tian Liang) , Ziyinzhuangyang**, -Undeclared sildenafil by United States Food and Drug Administration.

Health Canada Oct/16: **Ant Power tablets, Man King capsules**, -Undeclared sildenafil by Australian Therapeutic Goods Administration.

Health Canada Oct/16: **Golden Ant tablets**-Undeclared sildenafil and chloramphenicol byAustralian Therapeutic Goods Administration.

Health Canada Oct/16: **Xcelerated Weight Loss Ultra Max**- Undeclared phenolphthalein and sildenafil by United States Food and Drug Administration.

Health Canada Nov/16: **One More Knight 1750** has undeclared tadalafil and dapoxetine by the United States Food and Drug Administration.

Health Canada Nov/16: **Love4Long** has undeclared sildenafil by the United States Food and Drug Administration.

Health Canada Nov/16: **Kopi Jantan Tradisional Natural Herbs Coffee** has undeclared desmethyl carbodenafil by the United States Food and Drug Administration.

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MHRA Feb/12 has received advice from AGES PharmMed in Austria and the Danish Medicines Agency, warning that these unlicensed products have been tested and found to contain Tadalafil and/or Sildenafil: **AH Free/Reflexit, Stree Overlord, Man King, VigRX, Maxman, Maxman III, Viriya, & Imbiza for Men.**
MHRA: Austrian Sep/12 authorities have issued a warning for **Ramlostan Forte** manufactured by SC Parapharm, Romania. Ramlostan comes in white and blue packaging, with a picture of a ram at the top. Inside, there are ten blue capsules. The Austrian authority (AGES) has issued a warning for this product after finding it to contain Tadalafil.
MHRA Nov/12 has received advice from the Ministry of Health, Jerusalem warning that this unlicensed product, **Shark Essence** has been tested and found to contain Tadalafil and Sildenafil.
MHRA May/14: Singapore Health Sciences Department **Li Long Mei Guo Mo Bang** because it contains sildenafil.
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Recommendation 1: The American College of Physicians recommends that clinicians initiate therapy with a PDE-5 inhibitor in men who seek treatment for erectile dysfunction and who do not have a contraindication to PDE-5 inhibitor use (Grade: strong recommendation; high-quality evidence).
Recommendation 2: The American College of Physicians recommends that clinicians base the choice of a specific PDE-5 inhibitor on the individual preferences of men with erectile dysfunction, including ease of use, cost of medication, and adverse effects profile (Grade: weak recommendation; low-quality evidence).
Recommendation 3: The American College of Physicians does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction (Grade: insufficient evidence to determine net benefits and harms).
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Web Links:

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

Reviewers: Dr. K. Knox (SHR Rehabilitation), C Bell (UofS-SDIS), A Kuntz (SK Health), M Jin (PharmD, Hamilton), & the RxFiles Advisory Committee.

Extras:
Europe/Australia: dapoxetine *Priligy* (30-60mg po taken 1-3 hours prior to intercourse) has official indication for Premature Ejaculation. {short acting SSRI}
Sex and Chronic Pain: link to Mayo Clinic newsletter: http://www.mayoclinic.org/chronic-pain/art-20044369/?utm_source=newsletter&utm_medium=email&utm_campaign=pain-management&pg=2

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RxFiles Urinary Incontinence On-Line Extras:

Other Medications:

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

Oxybutynin (OXY) vs Tolterodine (TOLT) in OAB

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

Other Urinary Incontinence Patient Resources:

- General information: www.simonfoundation.org, www.womensbladderhealth.com; www.continence-foundation.org.uk; www.mypelvichealth.org
- Bladder Retraining: http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-4.pdf ; or http://www.fmpe.org/en/documents/handouts/handout_ui_retraining.pdf
- Pelvic Muscle Exercises (Kegel Exercises): http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-3.pdf
- Voiding Diary: http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-2.pdf
- Patient Information - Urinary Incontinence: http://www.fmpe.org/en/documents/doc_aids/UI-Patient-Handout-1.pdf
- CFPC: www.cfpc.ca/English/cfpc/programs/patient%20education/urinary%20incontinence
- American (ACOG): www.acog.com/publications/patient_education/bp081.cfm

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does not prove a definite advantage for darifenacin over oxybutynin. Further study is needed (especially with a more rational dose comparator) in elderly with urinary incontinence and at high risk for cognitive impairment. Darifenacin may offer a relative advantage or disadvantage to other anticholinergics depending on dose used and individual patient response. Currently, darifenacin offers a cost advantage over some comparators. {Cost/month[SK]: Enablex 7.5-15mg/day= $59; Ditropan XL 5-10mg/day= $84,15-20mg/day=$159; Uromax10-15mg/day=$50-53; Detrol LA 2-4mg/day= $72.} See http://www.rxfiles.ca/acrobat/UI-Darifenacin-Kay-Trial-Q&A.pdf }

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243. FDA: Apr/12 The labels of the alopecia drug Propecia (**finasteride** 1 mg) and the benign prostatic hyperplasia drug Proscar (finasteride 5 mg) are being updated with an expanded list of adverse **sexual effects**, the FDA has announced. Propecia label will include libido, ejaculation, and orgasm disorders that persist after treatment ends; Proscar label will include decreased libido that persists posttreatment & both labels will note reports of male infertility or poor semen quality that improved after drug discontinuation.
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393.

Saskatchewan Ministry of Health: Publicly Funded Vaccines for Selected Special Populations [1]

[Excerpted from Saskatchewan Immunization Manual (Chapter 7; Appendix 7.1, Revised **May 2016**)]

Condition [2]	H. influenzae b **(Hib)**	Hepatitis A **(HA)***	Hepatitis B **(HBV)***	Meningococcal	Pneumococcal	MMR	Vari-cella **(Var)**
Bleeding disorders		X	X				
Cerebrospinal fluid leak, including hydrocephaly				X[14]	X[12]		
Children under grade 6 whose families immigrated to Canada from regions of intermediate or high HBV prevalence			X				
Chronic heart or lung disease					X[12]		
Chronic kidney disease (hemo or peritoneal) dialysis, pre-dialysis [3, 4]			X		X[12]	C [6]	C [6]
Chronic liver disease including alcoholism, Hep C, Hep B, cirrhosis		X	X		X[12]		
Cochlear implant candidate or [5, 11]	X			X[14]	X[12]		
Congenital immunodeficiency (e.g., complement, properidin, factor D deficiency). Rotavirus CI	X			X[14]	X[12]	C [6]	C [6]
Cystic fibrosis					X[12]		
Diabetes mellitus					X[12]		
Hematopoietic stem cell transplant (HSCT) recipient [5, 7]	X	X	X	X[14]	X	C [6]	C[6]
HIV	X		X[13]	X[15]	X[12]	C [6]	C[6]
Homelessness					X		
Immunosuppression related to disease or medical therapy	X			X[14]	X[12]	C [6]	C[6]
Individuals living in facilities for the developmentally challenged			X		X		
Infants at high risk of HBV infection at birth related to mother's status or risk of infection [8]	X		X	X	X		
Illicit drug users (all methods of use) [9]		X	X		X		
Males and females with multiple sexual partners [9]			X				
Men who have sex with men		X	Not funded in SK				
Meningococcal disease case contacts				X			
Percutaneous or mucosal blood and body fluid exposure [9]			X				
Sexual assault (when presenting within 14 days of incident) [9]			X				
Splenic disorders [5, 10, 11]	X			X[14]	X[12]		
Solid organ transplant, including islet cell candidates or recipients [5]	X	X liver	X liver, kidney	X	X[12]	C [6]	C[6]
Malignancies	X				X[12]	C [6]	C [6]
Sickle Cell disease	X			X[14]	X[12]		

* Pre-immunization serology is strongly recommended if lifestyle and behavioural risks are factors.

C – CONTRAINDICATED

Footnotes **Saskatchewan** Immunization Manual Chapter 7 – **Immunization of Special Populations Jan. 2015 (Parts updated May 2016)** http://www.health.gov.sk.ca/sim-chapter7
The Saskatchewan Immunization Manual (amended 2012 - 2016) **http://www.ehealthsask.ca/services/manuals/pages/sim.aspx**

1 For more information on specific vaccines, refer to SIM, Chapter 10, Biological Products.

2 For more information about specific conditions, refer to the specific condition in SIM, Chapter 7, Immunization of Special Populations.

3 Refer in SIM, Chapter 7, Immunization of Special Populations, Appendix 7.4: Hepatitis B Immunization Algorithm for Clients with Chronic Kidney Disease.

4 Refer to Appendix 7.4: Hepatitis B Immunization Algorithm for Clients with Chronic Kidney Disease for appropriate dosages and products appropriate for client's age.

5 Province of surgery transplant physician/team or specialist and SK MHO to determine immunizations.

6 Medical consultations are required; refer to Appendix 7.2: Varicella Immunization Referral Form and Appendix 7.3 MMR Immunization Referral Form. Refer to the specific immune-suppressing condition in SIM, Chapter 7, Special Populations and specific vaccine in SIM, Chapter 10, Biological Products.

7 HSCT recipients require re-immunization due to the ablation of hematopoietic cells in the bone marrow pre-transplant.

8 Refer to SIM, Chapter 7, Special Populations, Section 4.2, Infants Born to HBsAg Positive Mother or High Risk for HB≥ 2000g.

9 Refer to Saskatchewan Guidelines for the Management of Potential Exposures to Hepatitis B, Hepatitis C, HIV, and Recommendations for Post-Exposure Prophylaxis, available at: http://www.ehealthsask.ca/services/manuals/Pages/default.aspx

10 Vaccination with the age-appropriate primary series should be completed for children less than 5 years who have a splenic disorder. 1 Hib dose is required for those 5 years and older regardless of previous Hib immunization history.

11 Includes sickle cell disease, thalassemia major, essential thrombocytopenia, other hemoglobinopathies, celiac disease, and inflammatory bowel disease.

12 1 dose for Pneu-C-13 naïve children 60 months up to and including 17 years of age

13 40ug for those ≥18 years; double dose for those birth up to and including 17 years of age.

14 a high-risk child 12 months of age or older, or an adult who is cohort eligible for a Men-C-C, does not required Men-C-C vaccine when they are eligible to receive Men-C-ACYW-135 vaccine

15 Children up to and including 17 years of age only.

16 eHealth Saskatchewan Panorama Information Bulletin 0022. Quick Reference*: Publicly Funded Vaccine Eligibility and Panorama Risk Factor Category.* Rev. 2016-04-18.

http://www.ehealthsask.ca/services/panorama/immun/Documents/Bulletin%200022%20Publicly%20Funded%20Vaccine%20Eligibility%20and%20Risk%20Factor%20Category.doc Accessed June 28 2016.

1) Breaking the "cold chain"

Canadian Guidelines: Refrigerated vaccines should be stored between +2°C and +8°C. Frozen vaccines should be stored at -15°C or colder. Store light sensitive vaccines away from light. Follow manufacturer recommendations for storage & transport. Administration requires someone trained to give im/sc injections.

Fridges:

-Fridge used should be dedicated to the storage of vaccines only.

-**Use of bar fridges for vaccine storage is the leading cause of cold chain breaks in Canada. Bar fridges are not recommended for the purpose of storing vaccines.**

- Keeping temperature of fridge stable **(2-8° C)**: Avoid opening refrigerator door unnecessarily, store containers of water in refrigerators, or ice packs in the freezer

NEVER store vaccines in the vegetable bin section of the refrigerator. Ideal storage location for vaccine: In the middle compartment, away from floor, coils, walls, and venting for the freezer or cold air.

-Temperature of the compartments of the refrigerator where the vaccine is stored should be checked and logged at least twice a day. Fridge temperatures outside of the 2 to 8 degree C range must be reported immediately to obtain recommendation on the stability of the affected product.

- Fridge temperature recording logs should be retained for 2 years.

- Min-Max thermometer batteries should be routinely changed twice a year: December 1 and June 1 and the date of changing noted on the device.

Transporting Refrigerated Vaccines: Avoid breaking the cold chain

1) Transport vaccines in insulated containers at all times. Hard sided plastic insulated containers, or Styrofoam containers with walls at least 2 inch thick walls should be used. Icepacks should be placed inside the transport container to maintain the cold chain. To prevent freezing the vaccine should never be placed directly onto an ice pack. Instead an insulating barrier (i.e. bubble wrap, Styrofoam peanuts) should be placed between vaccine and ice pack.
2) Make sure vaccine is never placed in trunk of vehicle, or in direct contact with sunlight. Also the vaccine should not be placed in line with the air from the vehicles heater or air conditioner. Vaccine should never be left in a vehicle unattended.
3) If a break in the cold chain identified prior to administration of the vaccine, contact your local public health authority about the appropriate course of action. While waiting for a decision, ensure that the vaccine is stored in appropriate cold chain conditions. The vaccine should not be administered until a decision has been reached.
4) If a break in the cold chain is identified after administration of the vaccine, contact your local public health authority. The type of vaccine, duration and temperature of the exposure will be taken into account in order to determine the course of action. Serological testing or revaccination may be suggested.

Further information: available from the Public Health Agency of Canada's Website. References:

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2) Anaphylaxis Management with vaccine administration:

1) Patients should be kept under supervision for 15 minutes (JE-VAX: 30 minutes) following administration.
2) In order to treat anaphylaxis perform the following steps (note steps a-d should be performed rapidly or simultaneously, however the priority is to complete step a):
   a) **Promptly administer 0.01 mL/kg (maximum 0.5 mL) of aqueous epinephrine 1:1000 by intramuscular (or subcutaneous) injection in the opposite limb to that in which the vaccination was given (or the vastus lateralis). Prompt administration is essential.**
   b) Call for an ambulance
   c) Place the patient in a recumbent position, and elevate their feet.
   d) If necessary, establish an oral airway.
   e) Patients with severe reactions such as cyanosis, dyspnea, should be given oxygen if it is available. Pulse oximetry can be used to monitor if available.
   f) If the vaccine was administered subcutaneously, an additional dose of 0.005 mL/kg (maximum 0.3 mL) of aqueous epinephrine 1:1000, can be injected into the vaccination site to slow down absorption. This should be done shortly after administration of the first dose of epinephrine in moderate to severe cases, and generally should not be repeated. Local injection of epinephrine into an intramuscular vaccination site is contraindicated, as it speeds up absorption of the vaccine.
   g) A dose of diphenhydramine hydrochloride (Benadryl®) can be given as an adjunct to epinephrine. The oral route of diphenhydramine is preferred for conscious patients who are not seriously ill (as the intramuscular injection is painful). Oral dose: 1-2 mg/kg to a maximum single dose of 50 mg.
   h) An inhaled β-agonist should be considered if there is a bronchospasm resistant to an adequate dose of epinephrine (e.g., nebulized salbutamol 2.5-5.0 mg in 3 mL of saline or 1 puff per 3 kg to a maximum of 10 puffs by metered dose inhalers).
   i) Vital signs should be monitored continuously.
   j) Patient should be transported to emergency department for long term monitoring.

◆Epinephrine dosing can be repeated twice at 5-minute intervals if necessary, for a total of three doses. The limb in which the vaccination was given should be avoided. A different limb is preferred for each dose to maximize drug absorption.

3) **Breastfeeding and Vaccinations:** Immunizations for actively breastfeeding women are considered safe, with the exception of smallpox vaccine and yellow fever, by both the CDC and the American academy of pediatrics. Breastfeeding does not appear to influence the maternal immune response. Vaccines do not appear to affect the safety of breast milk for infants.[10,11]

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1. All women of childbearing age should be evaluated for the possibility of pregnancy before immunization. (III-A) 2. Health care providers should obtain an immunization history from all women accessing prenatal care. (III-A) 3. In general, live and/or live-attenuated virus vaccines should not be administered during pregnancy, as there is a, largely theoretical, risk to the fetus. (II-3B) 4. Women who have inadvertently received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of teratogenic risk. (II-2A) 5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks. (III-B) 6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy. (II-1A) 7. Women who are breastfeeding can still be immunized (passive-active immunization, live or killed vaccines). (II-1A) 8. Pregnant women should be offered the influenza vaccine when pregnant during the influenza season. (II-1). Pregnant women should be offered the influenza vaccine (including H1N1 vaccine, when it is available) when they are pregnant during the influenza season. (II-1A) 9. Pregnant women with suspected or documented H1N1 infection should be treated with oseltamivir (Tamiflu, 75 milligrams twice daily for 5 days) within 48 hours of onset of symptoms. (III-B)
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Health Canada Dec/15: After reviewing Canadian and international information regarding the safety of the HPV vaccine **Gardasil**, Health Canada is informing Canadians that the benefits of using this vaccine continue to outweigh the risks. The overall evidence continues to demonstrate that this vaccine can be safely used and that there are no new safety risks.

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Online Extras for Antifungals: Treatment Chart

Other Fungal Agents

- **Tavaborole** Topical Solution (5%): **KERYDIN** – blocks fungal protein synthesis by inhibiting tRNA synthetase; broad spectrum for yeast, molds, dermatorphytes; useful for onychomycosis as somewhat better nail plate penetration than ciclopirox; AE: ingrown toenails $_{\sim 2.5\%}$, site reactions & dermatitis; applied once daily x 48 weeks (include entire nail surface and under tip of toenail).
- **Luliconazole** 1% cream: not in Canada; effective for tinea pedis/cruris; no evidence that it is more effective than other available topical agents.

Anti-inflammatory properties of topical antifungals

- It is difficult to determine the anti-inflammatory effects of topical antifungals in humans as the majority of studies are completed as *in vitro* studies or in animal models. Some studies compared antifungal drugs alone to a combination of antifungal plus steroid combination and had similar efficacies in treatment. A small study (n=20) assessed and compared *in vivo* anti-inflammatory effects of terbinafine, ciclopirox, ketoconazole and other antifungals (econazole, oxiconazole- not commonly used in Canada) with hydrocortisone 2.5%. This study looked at the ability to decrease erythema due to UVB exposure which is thought to mimic the response in dermatophyte infections. It did not study the effects in an actual dermatophyte–induced inflammatory reaction. Terbinafine, ciclopirox, and ketoconazole all demonstrated anti-inflammatory effects. Terbinafine and ciclopirox exhibited statistically significant difference in erythema when compared to control than ketoconazole, econazole, oxiconazole, and hydrocortisone. Ketoconazole exhibited intermediate anti-inflammatory effects. May consider use of these antifungals if there is an inflammatory component to the fungal infection.

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Official Warnings

- June 2014: **TERAZOL** 7 Vaginal Cream 0.4% (**terconazole**); **TERAZOL** 3 Dual-Pak - Vaginal Cream 0.8%/Vaginal Ovules 80 mg (terconazole) - Risk of Anaphylaxis and Toxic Epidermal Necrolysis - Janssen Inc. Very rare cases of serious adverse reactions of anaphylaxis or Toxic Epidermal Necrolysis have been reported during treatment with TERAZOL. Patients should discontinue use of the product if signs or symptoms of serious allergic reactions occur. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/39911a-eng.php; http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/39915a-eng.php

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Extras for ANTI-INFECTIVES FOR COMMON INFECTIONS: Overview

- Antibiotic Associated Diarrhea (AAD): both Lactobacillus-based & yeast-based (Saccharomyces) interventions ↓ risk for AAD (children & adults ≤65yr). NNT=13 10.3-19.1. Based on meta-analysis (Hemple et al.). Some heterogeneity due to varied products?.
- AOM: Prophylactic tx no longer recommended
- Conjunctivitis: 85% viral in adults. Suggest antibiotics if there's no improvement within 5 days or sooner (if the school or daycare requires treatment to come back). Handwashing important to help prevent spread. Bacterial infections are infectious for 24-48 hours after ABX initiation, viral are infectious until the eye clears. Consider washing contact case and replacing contacts if disposable, replace bottle of eye drops if any are used (eg glaucoma). Bacterial=Purulent discharge, swelling of the eye, and a burning sensation, usually persisting throughout the day, red or pink colour of the eye and pts often complain of waking up with eyes "glued shut". Red flag sx: a great deal of discomfort and pain, changes in vision, nausea, vomiting, or severe headache, eyelid edema, severe, continuous, copious, purulent discharge or whose symptoms have persisted for longer than 72 hours should be examined by a medical practitioner. A mild, watery discharge, with itching associated with a concurrent upper respiratory infection signals viral-if only one eye affected, other eye becomes involved in half of the cases. Corticosteroid eyedrops may quickly relieve symptoms, but should be avoided as they can worsen or mask accompanying conditions such as herpetic keratitis.
- Croup: common in first 5 yrs of life; most mild, ~ 1/170 require hospitalization, ~ 1/4500 require intubation. Almost always viral most Parainfluenza virus types 1& 3 common, also influenza types A & B, adenovirus, & respiratory syncytial virus.
  Tx. A) *General*: reassurance, parental presence, oxygen blow by; *Drug*: 1) corticosteroid single dose (**oral dexamethasone** 0.15 - **0.6 mg/kg,** Max 20mg; ↓ symptoms @ 30min, NNT=5); 2) epinephrine via neb
- Impetigo: [Retapamulin Altargo topical USA: for impetigo if resistance]
- Pharyngitis: *Fusobacterium necrophorum* just as common as GAS (~10%) in ages 15-24 and can cause Lemierre syndrome, a life-threatening condition. ABX tx can shorten symptom duration by ~16 hours.

STI

- EPT or Expedited Partner Treatment : a practice where a second prescription is given for chlamydia or gonorrhea, often to the index patient, for the partner
- External Genital Warts (EGW) - adult: caused by human papilloma virus (HPV) especially types 6 & 11; Tx options : 1) Imiquimod 5% cream Apply HS 3x/week; 2) Podofilox 0.5% soln Apply BID x3 days, then no tx x4 days; repeat cycle up to 3x.; 3) Cryotherapy Physician to apply liquid nitrogen q1-2 weeks for maximum 8 weeks; 4)Podophyline 10-25% resin in tincture of benzoin Apply small amount, allow to dry, repeat weekly if necessary (may wash resin off after 1-4hrs application; 5) Trichloroacetic acid 80-90% in 70% alcohol Apply small amount to warts, allow to dry, repeat weekly if necessary (5% EMLA cream pre-application may be used to ↓ burning; 6) Laser tx; 7) Surgical removal.
- Follow-up testing for Chlamydia & gonorrhea: retesting recommended at 3 months after tx.

Cellulitis: Pathogens for select conditions

- Diabetes: group B strep, anaerobes, enterobacteriacea
- Neutropenia: Pseudomonas aeruginosa
- Cirrhosis: Capnocytophaga canimorsus, Enterobacteriacea, Vibrio vulnificuc, Campylobacter fetus
- IV Drug Use: MRSA, Pseudomonas aeruginosa
- Subcutaneous drug use: Eikenella corrodens, Streptococcus anginosus group
- Fresh water exposure: Aeromonas hydrophila complex
- Salt water exposure: Vibrio spp
- Post-trauma with soil/water exposure, cosmetic prodedures, recreational water sports: Mycobacteriou spp (send for mycobacterial culture)
- Fish tank exposure, fisherman: Mycobacterioum marinum (send for mycobacterial culture)
- Reptile: Salmonella spp

Bites: Reptile (Salmonella, Aeromonas), marine animals (Vibrio spp)

Cold Sores: Other/new agents

- Xerese cream: (5% acyclovir + 1% hydrocortisone) – applied at 1st sign of tingling or burning; limited/moderately effective; may prevent 1 in 6 cold sores &/or shorten duration by 1.5 days. ? if corticosteroid ↑ harm.

Antivrial agents: Comparisons

- All 3 agents are pregnancy category B (no risk of evidence in humans)
- Acyclovir: SE: Malaise[12%], GI disturbances[2-5%] Severe (rare) [(<1%)]: Stevens-Johnson syndrome, coma, hallucinations
- Famciclovir: similar to efficacy & safety to valacyclovir SE: headache[9%-39%], GI disturbances[2-10%], Severe: hallucinations, thrombocytopenia[1%], neutropenia[3%], nephrotoxicity
- Valacyclovir: 3-5 fold increase in bioavailability compared to oral acyclovir. SE: headache[13-38%], GI disturbances [5-15%], neutropenia[18%], nasopharyngitis[16%], ALT/AST increases [15%], rash[8%] acute renal impairment reported Serious: thrombotic thrombocytopenic purpura[3%] (immunocompromised, high dose of 8g/day)

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Extra Refs: **Anti-infectives for Common Infections – Overview**

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FDA May/16 is advising that the **serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh** the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

FDA Jul/16 has updated the labels of systemic **fluoroquinolones** (e.g., ciprofloxacin, levofloxacin) to emphasize that they're associated with numerous serious and potentially irreversible adverse effects that can occur simultaneously. For patients with sinusitis, bronchitis, or uncomplicated urinary tract infections, the agency says, these antibacterials should be used only when there are no alternative options. Disabling side effects may include **tendinitis, tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects** (e.g., depression, psychosis). Adverse reactions may begin within hours or weeks of treatment initiation; data suggest that such reactions last, on average, 14 months after stopping treatment.

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Oral Antibiotics: Online Extras

Compounding of Nitrofurantoin Pediatric Suspension, 10mg/mL, 50mL

Nitrofurantoin 50mg/tablet	10 tablets
ORA-Plus	25mL
ORA-Sweet	qs to 50mL

1. Crush ten 50mg nitrofurantoin tablets in a glass mortar to create a fine powder.
2. Add a small amount of ORA-Plus and triturate to a thick, smooth paste. Add the remainder of ORA-Plus by geometric dilution.
3. Bring the suspension to a final volume using ORA-Sweet. Mix briefly with mortar and pestle until a uniform suspension is formed.
4. Dispense in a light-resistant, sealed amber bottle. Product is stable for 91 days with or without refrigeration. Label "Shake Well Before Using".

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Health Canada February, 2006 advises diabetic patients not to use the antibiotic Tequin http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_09_e.html
(Park-Wyllie LY, et al. Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults. N Engl J Med. 2006 Mar 1; [Epub ahead of print] Conclusions As compared with the use of other broad-spectrum oral antibiotics, including other fluoroquinolones, the use of gatifloxacin among outpatients is associated with an increased risk of in-hospital treatment for both hypoglycemia and hyperglycemia)
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Health Canada Oct/06 http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/ketek_hpc-cps_e.html (see also Pharmacist's Letter: Ketek safety info. Dec/06)
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127. Wilson W, Taubert KA, Gewitz M, et al. **Prevention of infective endocarditis guidelines** from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007. DOI:10.1161/CIRCULATIONAHA.106.183095. Available at: http://circ.ahajournals.org. (see also Pharmacist's Letter. May 2007. Guidelines for infective endocarditis. Recommended if: artificial heart valve, history of infective endocarditis, specific congenital heart conditions, or if a heart transplant that develops a problem in a heart valve) American Academy of Pediatric Dentistry Clinical Affairs Committee, American Academy of Pediatric Dentistry Council on Clinical Affairs. Guideline on antibiotic prophylaxis for **dental** patients at risk for infection. Pediatr Dent 2008-2009;30(7 Suppl):215-8. http://www.aapd.org/media/Policies_Guidelines/G_AntibioticProphylaxis.pdf
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131. Pichichero ME, Casey JR. Emergence of a multiresistant serotype **19A pneumococcal strain** not included in the 7-valent conjugate vaccine as an otopathogen in children. JAMA. 2007 Oct 17;298(15):1772-8. In the years following introduction of PCV7, a strain of S pneumoniae has emerged in the United States as an otopathogen that is **resistant** to all FDA-approved antibiotics for treatment of AOM in children.
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133. Ramakrishnan K, Sparks RA, Berryhill WE. Diagnosis and treatment of **otitis media**. Am Fam Physician. 2007 Dec 1;76(11):1650-8.
134. Slapak I, Skoupá J, et al Efficacy of **isotonic nasal seawater wash** in the treatment & prevention of rhinitis in children. Arch Otolaryngol Head Neck Surg. 2008 Jan;134(1):67-74.
135. Monaghan T, Boswell T, Mahida YR. Recent advances in **Clostridium difficile**-associated disease. Gut. 2008 Feb 5; [Epub ahead of print]
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138. Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, et al. Fluoroquinolones compared with beta-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials. CMAJ. 2008 Mar 25;178(7):845-54. In the treatment of **acute bacterial sinusitis**, newer fluoroquinolones conferred no benefit over beta-lactam antibiotics. The use of fluoroquinolones as first-line therapy cannot be endorsed.
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140. Lennon DR et al. Once-daily Amoxicillin vs Twice-daily Penicillin V in Group A {beta}-Hemolytic **Streprococcus Pharyngitis**. Arch Dis Child. 2008 Mar 12; [Epub ahead of print] This adequately-powered study, **once-daily oral amoxicillin** is not inferior to twice-daily penicillin V for the treatment & eradication of GABHS in children with pharyngitis.
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days. However, 80% of participants treated without antibiotics improve within two weeks. Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level.

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147. Kelly CP, LaMont JT. **Clostridium difficile**--more difficult than ever. N Engl J Med. 2008 Oct 30;359(18):1932-40.
148. Muzi F, Gravante G, Tati E, Tati G. **Fluoroquinolones-induced tendinitis** and tendon rupture in kidney transplant recipients: 2 cases and a review of the literature. Transplant Proc. 2007 Jun;39(5):1673-5.
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150. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United kingdom general practice research database. Pediatrics. 2009 Feb;123(2):424-30.
151. Ota KV, Jamieson F, Fisman DN, et al. Prevalence of and risk factors for quinolone-resistant Neisseria gonorrhoeae infection in Ontario. CMAJ. 2009 Feb 3;180(3):287-90. During 2006 in Ontario, 28% of N. gonorrhoeae isolates were resistant to quinolones. Infections in heterosexual men appear to have contributed significantly to the quinolone resistance rate. Medical practitioners should be aware of the widespread prevalence of quinolone-resistant N. gonorrhoeae and avoid quinolone use for empiric therapy.
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Amoxicillin	Ampicillin	Cefprozil	Cefotaxime	Penicillin G
Cefadroxil	Cephalexin	Aztreonam	Ceftriaxone	Cefoxitin
Cefprozil	Cefaclor	Ceftazidine	Cefepime	

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Online Extras - Hepatitis C

Indications & Regimens (continued): Genotypes 4-6.

	GT4				GT5				GT6			
	noncirrhotic		cirrhotic		noncirrhotic		cirrhotic		noncirrhotic		cirrhotic	
	Naïve	Experienced	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.
HARVONI SOF/LDV	12 wks, $67K				12 wks, $67K				12 wks, $67K			
TECHNIVIE ✗ ⊗ PTV/RTV/OBV	12 wks + RBV, $64K				-				-			
ZEPATIER ✗ ⊗ EBR/GZR	12 wks $60K	16 wks + RBV $85K	12 wks $60K	16 wks + RBV $85K								
EPCLUSA ✗ ⊗ SOF/VEL	12 wks, $64K				12 wks, $64K				12 wks, $64K			
SOF + DCV	-				-				-			
ASV + DCV	DCV + ASV with PEGI + RBV											
SOF + SIM	-				-				-			
SOF + RBV	24 wks, $118K				-				-			
SOF + PEGI + RBV	12 wks $60K	12 wks $60K	12 wks $60K	12 wks $60K	12 wks $60K				12 wks $60K			
SIM + PEGI + RBV	24 wks[a] $90K	24-48 wks[a,b] $90K-180K	24-48 wks[a] $90K-180K	24-48 wks[a,b] $90K-180K	-				-			
PEGI + RBV	**The role of interferon-based therapy in GT4-6 is not guideline-recommended, but lack of coverage for alternate regimens may necessitate use.** In the past, 48 weeks of therapy ($21K) was used to treat GT4, GT5, and GT6 in treatment-naïve patients with or without cirrhosis. Expected response rate is around 60%. See **Dosing of Ribavirin and PEG-INF** below.											

Guideline-preferred regimens highlighted in purple.
Regimens containing telaprevir or boceprevir should be avoided in genotypes 4-6 as they are associated with high resistance.

a. First, 12 weeks of SIM + PEGI (+ RBV). Then, stop SIM and continue PEGI (+ RBV) for 12-36 more weeks (i.e. up to 48 total) depending on previous response.
b. Patients previously failing therapy with a protease inhibitor should avoid SIM (and other protease inhibitors).

Naïve=no previous HCV treatment **Exp**=previous HCV treatment with PEGI + RBV.
ASV=asunaprevir **DCV**=daclatasvir **EBR**=elbasvir **GZR**=grazoprevir **LDV**=ledipasvir **OBV**=ombitasvir **PEGI**=pegylated interferon **PTV**=paritaprevir **RBV**=ribavirin **RTV**=ritonavir
SIM=simeprevir **SOF**=sofosbuvir **VEL**=velpatasvir

Other Direct-Acting Antivirals:

GENERIC/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	DOSING	$/COURSE
TECHNIVIE PTV/RTV/OBV PIL Paritaprevir/Ritonavir/Ombitasvir 75mg/50mg/12.5mg tab χ ⊗	✓ Treatment of GT4 only. • AE: fatigue, insomnia, rash, nausea, ↑ALT. **Serious**: allergic reactions, hepatic failure / decompensation (in patients with underlying liver cirrhosis). • DI: **Many. Watch for DIs with HIV meds.** Inhibits CYP3A4, P-gp, OATP: ↑ levels of alfuzosin, colchicine, CBZ, cyclosporine, DOACs, efavirenz, ergot, ethinyl estradiol, fluticasone, gemfibrozil, omeprazole, phenytoin, rifampin, rilpivirine, salmeterol, sildenafil, SJW, statin, tacrolimus, triazolam. ↓**TECHNIVIE**: CYP3A4-inducers (e.g. anticonvulsants). ↑**TECHNIVIE**: CYP3A4-inhibitors (e.g. azole antifungals, clarithromycin). Many other drug interactions - list is not exhaustive! • M: LFTs at baseline and over first four weeks, then periodically; HCV-RNA.	2 combination tabs (75/50/12.5mg) po once daily. Dose **with a meal** to increase absorption. Ritonavir added to decrease paritaprevir metabolism, allowing once-daily dosing.	$56,000 12wks

More online extras on the following pages! It's a bonanza of online extras!

Dosing of Ribavirin and PEG-INF: (see main HCV chart for dosing of ribavirin with direct-acting antivirals)

GENERIC/TRADE	DOSING	TREATMENT DURATION	DOSE REDUCTION / DISCONTINUATION
Ribavirin RBV **COPEGUS** 200mg capsule ☎ ✆ **Ibavyr** 200, 400 ˢ, 600mg☎✆ tab **Moderiba** 200,400,600mgtab☎⊗	Divide daily dose and give BID with food. Take dose in am & supper to minimize insomnia. with **PEGASYS**: **GT1, 4, 5, or 6**: 1000mg/day if <75kg. 1200mg/day if ≥75kg. **GT2 or 3**: 800mg/day with **PEGETRON**: **GT1**: 800mg/day if ≤65kg. 1000mg/day if 66-80kg. 1200mg/day if 81-105kg. 1400mg/day if >105kg. **GT2, 3, 4, 5, or 6**: 800mg/day if ≤65kg. 1000mg/day if 66-85kg. 1200mg/day if >85kg. 1400mg/day if >105kg AND treatment experienced. with **SOF**, **HARVONI**, **HOLKIRA**, **TECHNIVIE**, etc (± **PEG-I**): **GT1, 2, 3, 4, 5, or 6**: 1000mg/day if <75kg. 1200mg/day if ≥75kg.	RBV combined with PEGASYS or PEGETRON: • **GT1:** standard duration is 48 weeks. RVR: 24 weeks if no predictors of poor response *. DVR: 72 weeks. • **GT2 or 3:** standard duration is 24 weeks. Tx-naïve on weight-based RBV: if RVR achieved→ 12-16 weeks, **unless** predictor of poor response *. If relapse occurs, retreat for 24 weeks. GT3: Consider 36-48 weeks in pts without RVR & predictor of poor response *. GT2 or 3 with failed previous course & at least stage 2 fibrosis: retreat x 48 weeks. • **GT4, 5 or 6:** standard duration is 48 weeks. GT4 with mild fibrosis (F0-F2) & baseline HCV-RNA <800,000 IU/mL: 36 weeks. * **Predictors of poor response**: advanced fibrosis, black race, obesity, metabolic syndrome/insulin resistance. Tx strategy is based on **Response Guided Therapy** – length of regimen is dictated by the viral genotype & the pt's HCV-RNA & ALT at pre-specified time points (baseline, TW4, TW12, TW24). Pts should also be tested 12-24wks after tx completion; **any ethnic or racial group → the earlier & greater the viral response, the more likely to achieve SVR.**	**REDUCE RIBAVIRIN DOSE IF:** • **GT1** Hgb <100g/L, or CVD & ↓ Hgb ≥20g/L within 4 weeks, or bilirubin indirect > 7mcmol/L. Reduce dose by 200mg, or by 400mg if on 1400mg/day. Reduce dose by another 200mg if necessary. • **GT2, 3, 4, 5, or 6**: Hgb <100g/L, or CVD & ↓ Hgb ≥20g/L within 4 weeks, or bilirubin indirect >5mg/dL. Reduce dose to 200mg in am and 400mg in pm. • **Prior tx failure**: Hgb <100g/L, or CVD & ↓ Hgb ≥20g/L within 4 weeks, or bilirubin indirect >5mg/dL. Reduce dose by 200mg if on 800-1000mg/day, by 400mg if on 1200-1400mg/day. Reduce dose by another 200mg if necessary. **DISCONTINUE RIBAVIRIN IF:** • Hgb <70-85g/L, or CVD & Hgb <120g/L after 4 weeks on a ↓ dose • **Futility Rules**: EVR not achieved by TW12 or if HCV-RNA detectable at week 24.
PEG-Interferon α-2a PEGI **PEGASYS** ☎ ✆ Φ **Combination Products:** **PEGASYS RBV** ☎ ✆ (=PEG-interferon α-2a + ribavirin) 180 mcg/1 mL vial 180 mcg/0.5mL prefilled syringe & autoinj ProClick ***Refrigerate Syringes***	**180mcg SC once weekly**		**REDUCE PEG-Interferon α-2a PEGASYS DOSE IF:** • HD-CKD → ↓ 135mcg SC once weekly • ANC <0.75x10^9/L → ↓135mcg SC once weekly • Platelets <50x10^9/L → ↓90mcg SC once weekly • ALT progressively ↑ vs transient flare → ↓90mcg SC once wkly **DISCONTINUE PEGASYS IF:** • ANC<0.5x10^9/L restart when ANC>1x10^9/L with 90ug/wk, platelets <25x10^9/L, ALT progressively ↑ despite dose ↓, or concurrent ↑ bilirubin or hepatic decompensation, severe depression, symptoms of colitis, pancreatitis • **Futility Rules:** EVR not achieved by TW12 or if HCV-RNA detectable at TW24.
PEG-Interferon α-2b PEGI UNITRON PEG D/C 2012 **Combination Products:** **PEGETRON** ☎ ✆ (=PEG-interferon α-2b + ribavirin) ***Refrigerate Syringes*** REDIPEN D/C⇒ new CLEARCLICK 80,100,120,150mcg powder for solution	**1.5mcg/kg SC once weekly** **<40kg:** 50mcg SC weekly **40-50kg:** 80mcg SC weekly **51-65kg:** 100mcg SC weekly **66-80kg:** 120mcg SC weekly **81-105kg:** 150mcg SC weekly **>105kg:** 1.5mcg/kg SC weekly		**REDUCE PEG-Interferon α-2b PEGETRON DOSE IF:** • **Tx naïve GT1 or Prior Tx Failure:** if ANC <0.75x10^9/L, WBC<1.5x10^9/L, or platelets <50x10^9/L:↓ dose to 1mcg/kg/week. If required, ↓ dose again to 0.5mcg/kg/wk. • **Tx naïve non-GT1:** if ANC<0.75x10^9/L, WBC<1.5x10^9/L or platelets<80x10^9/L: ↓ dose to 0.75mcg/kg/week **DISCONTINUE PEGETRON IF:** • ANC<0.5x10^9/L, WBC <1x10^9/L, platelets <25x10^9/L (<50x10^9/L if tx naïve non-GT1), bilirubin direct 2.5xULN, bilirubin indirect >7mcmol/L x>4weeks, SCr >150umol/L, ALT/AST 2x baseline AND >10x ULN, severe depression, symptoms of colitis. • **Futility Rules:** EVR not achieved by TW12 or if HCV-RNA detectable at TW24.

Virological Response (VR) - Definitions

- **Sustained VR SVR:** undetectable HCV-RNA at least 12-24wks after treatment
- **Rapid VR RVR:** undetectable HCV-RNA at TW4 → best predictor of SVR
- **Early VR EVR:** ≥ 2log$_{10}$ ↓ in HCV-RNA at week 12 compared to baseline
- **Delayed VR DVR:** ≥ 2log$_{10}$ ↓ in HCV-RNA but still ≥ 50IU/mL at TW12, then <50IU/mL from TW24 until therapy completed
- **Null Response NR:** < 2log$_{10}$ ↓ in HCV-RNA level at TW12 vs baseline
- **Partial Response PR:** ≥ 2log$_{10}$ ↓ in HCV-RNA but still detectable at week 24
- **Breakthrough:** reappearance of HCV-RNA any time on tx after VR achieved
- **Relapse:** reappearance of HCV-RNA post-treatment after VR achieved
- **End of Treatment Response ETR:** undetectable at completion of therapy

Treatment of PEG-INF adverse effects:

1. Thrombocytopenia. Consider eltrombopag for thrombocytopenia induced by PEGI in hepatitis C GT2 or 3.

2. Depression: most common PEGI AE. Observe for signs & symptoms at regular intervals i.e. every 2wks for the first 12wks. Use antidepressants to manage symptoms; may consider starting prophylactically.[85] Consider a lower dose than for standard depression,[Sulkowski et al.] & continue antidepressants through entire HCV regimen & 2-3mos (up to 12mos) afterward. D/C PEGI + RBV if suicidal ideations or severe depression.[4]

3. Flu-like Symptoms. 25-50% of PEGI+RBV pts → acetaminophen 500mg-1g po 30min before PEGI injection. Regular exercise may help with chronic fatigue. Consider administering PEGI on Fridays to ↓ AEs & to avoid missing work.

4. GI Upset. diarrhea dietary fibre, loperamide, dyspepsia H_2RA, or PPI if required, nausea & emesis dimenhydrinate, metoclopramide (see RxFiles Nausea & Vomiting pg 71-72, & OTC pg 140). **D/C HCV meds** with any signs of **colitis** abdominal pain, bloody diarrhea.

5. PEGI-Induced Hypo/Hyperthyroid: PEGI-induced **hypo**thyroid ~4% more common in ♀ & if family hx of thyroid dx; monitor TSH every 12wks; sx may be mask as **fatigue**; tx as per standard hypothyroid LT4. PEGI-induced **hyper**thyroid less common → **D/C HCV meds.**

6. PEGI-Induced Dermatological Reactions: very common ~1/10 pts; **D/C PEGI immediately** if severe reaction e.g. Stevens-Johnson syndrome, angioedema. Monitor pts with pre-existing dermatology conditions very carefully. Psoriasis flares managed with occlusive lotions, topical steroids. Pts who experience alopecia ~20% if tx duration >3mos, usually reversible should use mild hair products.

7. PEGI-Induced Neutropenia: 30-50% of PEGI pts will see ↓ANC during 1st 2wks of tx requiring ↓ in PEGI dose. Granulocyte colony-stimulating factor (G-CSF, **NEUPOGEN**) may be used to maintain PEGI dosing; suggested G-CSF dose 300µg SC once weekly.[5]

Previously Used Direct-Acting Antivirals (no longer recommended, use alternate treatments):

GENERIC/TRADE (Strength & formulations)	TREATMENT REGIMEN	DOSING CONSIDERATIONS	INDICATION(✓)/CONTRAINDICATIONS(CI)/ ADVERSE EVENTS(AE)/DRUG INTERACTIONS(DI)/MONITORING(M)	$/ COURSE
Telaprevir TVR INCIVEK D/C ☎ ✆ FDA 2011 PL 375mg tablet	TVR 750mg po q8h with food ≥20g fat & PEGI+RBV High fat foods ↑drug absorption. e.g. of foods with ≥20g of fat: 4 egg yolks, 2.5 tbsp of butter, 60g of cream cheese, 2.5 cups of whole milk. Tx Naïve /Relapse: Undetectable HCV-RNA (≤10 IU/mL) at TW4 & TW12: **TW1→TW12: TVR+PEGI+RBV, TW13→TW24: PEGI+RBV, $44,000/course**; Detectable HCV-RNA (≤1000 IU/mL) TW4 &/or TW12: **TW1→TW12: TVR+PEGI+RBV, TW13→TW48: PEGI+RBV, $53,000/course** **Prior Partial & Null Responders, or Patients with Cirrhosis:** TW1→TW12: TVR+PEGI+RBI, TW13→TW48: PEGI+RBV **$53,000/course**	• **Futility Rules:** D/C triple therapy if HCV-RNA >1000 IU/mL at TW4 or TW12. D/C PEGI+RBV if HCV-RNA detectable at TW24. • **Anemia Management:** resolves upon discontinuation. May ↓RBV dose see RBV, transfusion, &/or ESA. • Do NOT ↓ TVR dose to manage AE due to concerns with resistance. • Limited evidence: in liver transplant, cirrhosis decompensated, >65yrs, GT2-4, renal impairment. Phase II study in HCV & HIV co-infected patients.[128]	✓ adult HCV **GT1** with PEGI+RBV in tx naïve or prior non-responders to PEGI+RBV **(no longer recommended, use alternate treatments)** **CI:** monotherapy; concurrent tx with alfuzosin, antiarrhythmics (amiodarone, quinidine, flecainide, propafenone), astemizole, cisapride, cobicistat, eletriptan, eplerenone, ergots, oral midazolam, pimozide, rifampin, sildenafil, silodosin, St. John's Wort, statins (atorvastatin, lovastatin, simvastatin), triazolam, terfenadine, vardenafil. **DI: MANY DI's** → strong **CYP3A4/5** & **P-gp** inhibitor. ↑ maraviroc **↓ TVR:** dexamethasone, PIs, efavirenz, rifabutin. **↑ TVR:** macrolides. **TVR ↓:** ethinyl estradiol, escitalopram, methadone. **TVR ↑:** alprazolam, azoles, bosentan, budesonide, colchinine, desipramine, diazepam, digoxin, fentanyl, fluticasone,immunosuppressants, macrolides, nifedipine, salmeterol, tadalafil, trazodone. **TVR ↑or ↓:** warfarin, carbamazepine, phenytoin, phenobarbital. **M:** HCV-RNA (TW4, 12), CBC (TW2, 4, 8, 12), SCr, uric acid, LFT's, bilirubin, TSH **AE: anemia** 41% triple tx vs 22% dual tx, **pruritis**, **diarrhea**, **rash** 56% triple tx vs 34% dual tx, severe rash 4%, Stevens-Johnson Syndrome <1%, DRESS; QT prolongation.	**750mg** q8h or **1125**mg q12h with food ≥20g fat =$35,000/12wk **CDR'13:** cover TVR if lower cost; ↑ HCV-RNA in last 6months; fibrosis stage F2,F3, F4; & a 12wk treatment.
Boceprevir BOC VICTRELIS FDA 2011 PL 200mg capsule ☎ ✆ Refrigerate until dispensed to patient. Stable at room temperature for 3 months. **Combination Products:** VICTRELIS TRIPLE ☎ ✆ (=boceprevir + PEGETRON)	BOC 800mg po q8h with food starting **TW5** of PEGI+RBV Treatment Naïve: Undetectable HCV-RNA (<10 IU/mL) at TW8 & TW28: **TW1→TW4: PEGI+RBV, TW5→TW28: BOC+PEGI+RBV, $32,000/course**; Detectable HCV-RNA at TW8 but Undetectable at TW24: **TW1→TW4: PEGI+RBV, TW5→TW28: BOC+PEGI+RBV, TW29→TW48: PEGI+RBV, $40,000/course** 🇨🇦 Prior PR Relapser: **TW1→TW4: PEGI+RBV, TW5→TW36: BOC+PEGI+RBV, $43,000/course**; **TW1→TW4: PEGI+RBV, TW5→TW36: BOC+PEGI+RBV, TW37→TW48: PEGI+RBV, $47,000/course** Pts with cirrhosis, null responders to previous PEGI+RBV, or tx naive patients with < 1$\log_{10}$ ↓ in viral load at TW4: TW1→TW4: PEGI+RBV, TW5→TW48: **BOC+PEGI+RBV**	• **Futility Rules:** D/C triple therapy if HCV-RNA ≥ 100IU/mL at TW12 or detectable at TW24. • **Anemia Management:** resolves upon discontinuation. May ↓RBV dose see RBV, transfusion, &/or ESA. {Concern if ↓Plt/Alb:?↑sepsis/mortality} • Do NOT ↓ BOC dose to manage AE due to concerns with resistance. Limited evidence: in liver transplant, cirrhosis decompensated, >65yrs, or if renal impairment. Phase II study in HCV & HIV co-infected patients.[127]	✓adult HCV **GT1** with PEGI+RBV in tx naïve or prior non-responders to PEGI+RBV **(no longer recommended, use alternate treatments)** **CI:** monotherapy; concurrent tx with alfuzosin, antiarrhythmics (amiodarone, quinidine, propafenone), anticonvulsants (carbamazepine, phenobarbital, phenytoin), astemizole, cisapride, cobicistat, doxazosin ,drospirenone, ergots, oral midazolam, pimozide, rifampin, sildenafil, silodosin, St. John's Wort, statins (lovastatin, simvastatin), tadalafil, tamsulosin, terfenadine, triazolam; pregnancy in combination with RBV **DI: MANY DI's**→a **CYP3A4/5** & **P-gp** substrate & inhibitor. ↑ maraviroc. **↓ BOC:** dexamethasone, antiretrovirals (e.g. efavirenz), rifabutin. **↑ BOC:** azoles. **BOC ↓:** ethinyl estradiol. **BOC ↑:** alprazolam, azoles, bosentan, budesonide, clarithromycin, colchinine, desipramine, digoxin, fluticasone, immunosuppressants, nifedipine, salmeterol, statins, tenofovir, trazodone, vardenafil. **BOC ↑ or ↓:** warfarin, buprenorphine, methadone, **ritonavir**, quetiapine. **M:** HCV-RNA (TW4 non-cirrhosis tx naive, 8, 12, 24), CBC (TW2, 4, 8, 12), TSH **AE:** anemia 50% triple tx vs 30% dual tx[SPRINT-2], **dysgeusia** 40% triple tx vs 20% dual tx[SPRINT-2], neutropenia 25% triple tx vs 14% dual tx[SPRINT-2], fatigue, nausea, chills.	**800mg** q8h with light meal or snack. = $25,380/24wk **CDR'13**: cover BOC if lower cost; ↑HCV RNA in last 6months; fibrosis stage F2, F3, F4; & a 44wk treatment.

☎=Exception Drug Status SK ✆=prior approval for NIHB Φ=SAIL SK Program ✓=approved indication =↓ dose for renal dysfx =↓ dose for hepatic dysfx ♂=male ♀=female **ALT/AST**=alanine/aspartate transaminase **ANC**=absolute neutrophil count **BMI**=body mass index **CBC**=complete blood count **CDR**=Common Drug Review **CrCl**=creatinine clearance **CV**=cardiovascular **D/C**=discontinue **DRESS**=drug reaction eosinophilia & systemic symptoms **dx**=disease **dysfx**=dysfunction **ESA**=erythropoiesis stimulating agent **GT**=genotype **HD-CKD**=hemodialysis end-stage renal disease **Hgb**=hemoglobin **HIV**=human immunodeficiency virus **hx**=history **IU**=international units **IDU**=intravenous drug user **IL28B**=interleukin 28B **LFT**=liver function test **mos**=months **MSM**=men who have sex with men **PI**=protease inhibitor **pt**=patient **SC**=subcutaneous injection **SCr**=serum creatinine **sx**=symptom **TG**=triglyceride **TSH**=thyroid-stimulating hormone **TW**=treatment week **tx**=treatment/therapy **ULN**=upper limit of normal **WBC**=white blood cell **wk**=week

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Extras

Combos to Avoid: Early virologic failure: abacavir + lamivudine (or emtricitabine) + tenofovir ; didanosine + lamivudine (or emtricitabine) + tenofovir; didanosine + tenofovir + NNRTI; didanosine + emtricitabine(lamivudine) + atazanavir; Caution: emtricitabine(or lamivudine) + tenofovir + nevirapine [72] (early virologic failure in small clinical trials; ARTEN [73] trial: may be okay)
↑AE: Didanosine + stavudine (peripheral neuropthy, pancreatitis & lactic acidosis); ATV + IDV ↑ bilirubin; 2 NNRTI regimen Antagonism: stavudine + zidovudine

- Oral contraceptives + non-ritonavir boosted atazanavir (may ↑ hormone levels; ⇨use lowest dose OC)[74] or indinavir (will maintain hormone levels)

{Refractory large volume diarrhea, HIV related: octreotide (50-500mcg sc TID)$$$ }[75,76]

Didanosine **ddI** VIDEX EC (4g solution) χ ⊗ (125, 200, 250 & 400mg EC cap) ☎ ▼	*400mg po daily* wt>60kg *250mg po daily* wt<60kg (↓ dose with tenofovir-see comments)	390 250	AE: peripheral neuropathy dose-related, pancreatitis, GI upset, portal hypertension retinal Δ's, optic neuritis, ?↑MI DAD DI: allopurinol ↑DDI, ribavirin, methadone ddI soln	PIL	◆ddI soln must be mixed as a buffered solution with antacid ◆except ddI on empty stomach ◆ddI +TDF not 1st line tx; ↓ dose ddI: 250mg if wt>60kg daily; 200mg if <60kg daily ◆DI: ddI+ribavirin→lactic acidosis, hepatic injury
Indinavir **IDV** **CRIXIVAN** (200,400mg cap) ☎ ▼	*800mg po q8h* *800mg/100-200mg RTV po BID*	510 465	AE: renal toxicity, renal calculi, ↑ bilirubin without ↑ LFT's, alopecia & dry skin, nail changes, gallstones & HTN, ↑MI DAD study (77) Note: take with ≥ 2 glasses H2O/dose. Used infrequently due to ↑ AE.	PIL	
Nelfinavir **NFV** **VIRACEPT** 250,625mg tab☎▼; (50mg/g powder for susp)$^{\chi}$ ▼	*1250mg po q12h* *750mg po q8h*	585 530	AE: diarrhea ~35% ◆Do not boost with RTV; not effective ◆Previously avoided in pregnancy, but is now an option (level of EMS corrected)	PIL	

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Extras:

1) Clinical Decision Rule for Point of Care Testing of Influenza Patients: *fever* (2 points), *myalgia* (2 points), *symptoms <48hrs* (1 point), *chills/sweats* (1 point). **0-2points** = 8%; **3 points** = 30%; **4-6 points** = 59%.

Rx Files – Drugs for Influenza
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Physician's First Watch: Feb/08 A common influenza virus has developed a mutation resistant to oseltamivir (Tamiflu) has been found in U.S., Canada, & 4 European nations, the *New York Times* reports. A small percentage of **influenza A/H1N1** — the predominant flu virus infecting people this season — is affected by the **H274Y mutation**. Norway appears to be hardest hit, with 75% (12 of 16) of the isolated viruses showing **resistance to oseltamivir**. In the U.S., Britain, Denmark, and France, roughly 3% to 5% of tested viruses showed resistance (data on Canada were not provided, but reported in Pharmacy Bulletin Board Feb 4/08 at **10%**). "We don't know right now if this is a trend on the upswing or just a small blip," the CDC's chief of epidemiology and prevention told the Associated Press. Officials from the U.S. and World Health Organization told the *Times* they do not currently advise changes in Tamiflu use. In addition, the flu vaccine is still effective against the mutant virus.

Dec/08: Clinicians should remain alert for changes in recommendations that might occur as the 2008--09 influenza season progresses. Recommendations regarding the use of antiviral medications might be revised if surveillance data indicate a substantial and widespread increase in the prevalence of oseltamivir-resistant influenza viruses in the United States. In fact, the interim CDC guidance provides advice for clinicians on how to treat patients with influenza antiviral medications this season. Clinicians can use influenza test results and information, if available, about which viruses are circulating, to help decide which antiviral(s) should be used. If H1N1 viruses are circulating in the community, or it's not clear which viruses are circulating, health care providers are recommended to use an alternative antiviral, zanamivir (Relenza®), or to use combination therapy of oseltamivir and rimantadine. Use of zanamivir or dual therapy with oseltamivir and rimantadine would provide effective treatment against all circulating influenza viruses. In some instances, oseltamivir alone can still be used, such as when influenza B is diagnosed, or H1N1 viruses are not circulating.

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individuals, depending on their level of risk for an allergic reaction.Footnote 6767 Egg-allergic individuals at lower risk for severe allergic reaction can be vaccinated for influenza using a single vaccine dose. The two-step graded protocol is recommended for individuals who are at higher risk for severe allergic reaction. These protocols are as follows:

Full dose - A single vaccine dose without the use of a graded challenge. Individuals should be observed for 30 minutes following administration for symptom development.

Two-step graded dosing - A two-step graded process, whereby 10% of the dose is administered followed by 30 minutes of observation. If no symptoms develop, or symptoms are self-resolving, administer the remaining 90% with another 30 minute observation period. If sustained or severe reactions arise after the initial dose, the vaccine is withheld and the individual should be re-evaluated for receipt of the influenza vaccine.

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CDC data strengthen the evidence that the risk for **Guillain-Barré syndrome (GBS)** associated with the 2009 H1N1 vaccine is similar to the risk seen with seasonal flu vaccines, according to an *MMWR* report. The CDC's analysis of data from October 2009 through March 2010 found that the incidence of GBS was 1.92 per 100,000 person-years among vaccinated individuals and 1.21 per 100,000 person-years among the unvaccinated. If final data confirm this finding, the CDC says, then this would translate to 0.8 excess GBS cases for every 1 million vaccinations — a rate comparable to that found with seasonal flu vaccination. *MMWR* article (Free)

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

FDA June/10 notified consumers and healthcare professionals about a potentially harmful product represented as "**Generic Tamiflu" sold over the Internet**. FDA tests revealed that the fraudulent product does not contain Tamiflu's active ingredient, oseltamivir, but cloxacillin, an ingredient in the same class of antibiotics as penicillin.

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WEBSITES & Updates:

CDC Flu Update:

http://www.cdc.gov/flu/

http://www.cdc.gov/flu/about/season/index.htm

Public Health Agency of Canada- FluWatch:

http://www.phac-aspc.gc.ca/fluwatch/

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Online Extras for Malaria Overview and Prophylaxis:

Hydroxychloroquine PL **PLAQUENIL, g**: 200mg tab *200mg tab = 155mg base* ✓ Chloroquine-sensitive malaria (2nd line - Chloroquine is preferred).	• **AE**: N/V/D (take with food or milk), pruritus, fatigue, seizures, headache & dizziness. Uncommon: alopecia, hair depigmentation, skin eruptions & seizures. May have lower retinal risk than chloroquine. • **CI**: Visual field changes attributable to 4-aminoquinolines. **Caution**: pts with hepatic failure, G6PD deficiency, pre-existing auditory damage, psoriasis, prophyria. • **M**: Opthalmic exam periodically if used long term (> 5 yrs, or sooner in high risk patients).[BMJ,CDC,ACP] Risk very low in first 5 yrs. • **DI**: antacids, cimetidine, digoxin (increase dig level). Vaccine Interaction:[11] assume same as chloroquine (Cholera, Rabies). • Rarely used. May be useful in patients already taking hydroxychloroquine for a separate indication (e.g. rheumatoid arthritis, Lupus).	Pediatric: 6.5mg/kg **weekly with food** • Do not exceed adult dose Adult:: 400 mg **weekly with food** • Begin 2 wk prior, continue during stay and 4 wks after return.	$19

Other Malaria Prevention in Pregnancy options:

Sulfadoxine–pyrimethamine regimen 500/25mg tabs, take 3 tabs together; then give 3 times during pregnancy.

Dihydroartemisinin–piperaquine 40/320mg, take 3 tabs together once a day for 3 days; then give **monthly** or 3 times during pregnancy.

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

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

Recent Resistance Trends: The following areas are chloroquine-sensitive (as of Jan 2016). Note: geographic risk and resistance trends change over time!
-travelers visiting resort areas are not generally at risk
-travel to Central America (except Panama)
-parts of China / Middle east
-travel to **Caribbean** including Haiti and rural areas of Dominican Republic. Many islands in the Caribbean do not require prophylaxis at all.

Approximate Malaria Risk: (1 month stay without chemoprophylaxis)[CCDR 2000 Malaria Recommendations]

-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.

Insecticide Treatment of Clothing and Nets - Tips and Tricks:

1. **Treatment of netting** differs depending on the insecticide. Human error (in measurement, treating for the right length of time, etc.) can decrease efficacy. When possible, buy pre-treated netting. If treating own netting, some products (availability changes over time) include permethrin EC, deltamethrin SC liquid, deltamethrin tablets, lambda-cyhalothrin CS, cyfluthrin EW, and alpha-cypremethrin SC. Follow packet directions to calculate dose of insecticide needed. Dosing is typically dependent on the area of the net and the amount of water the net is able to absorb.

2. **When treating clothing**:
   -wear gloves
   -do not treat underwear
   -some fabrics (e.g. cotton) receive treatment better than others. Permethrin does not adhere well to some synthetic fibres.

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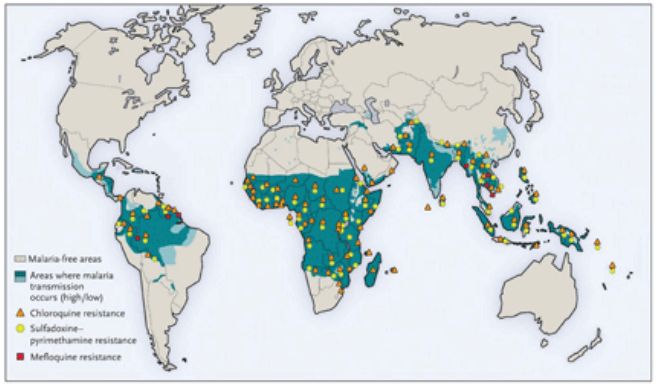

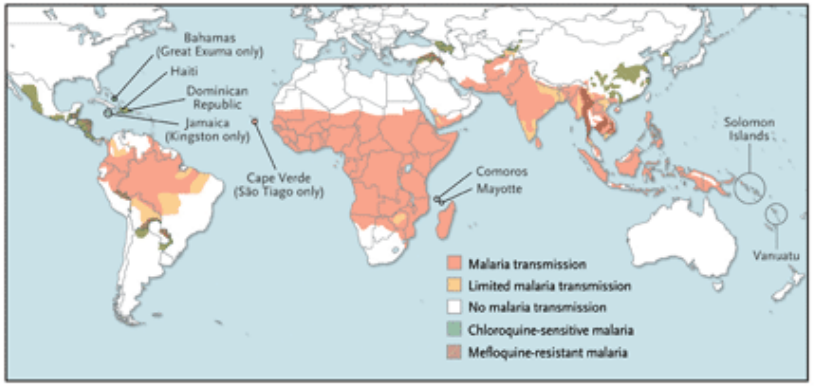

Thumbnails: Areas of Malaria Transmission and Antimalarial Drug Resistance. Data on malaria transmission are for 2007 and are from the World Health Organization. Data on drug resistance are for 2004 and are from the Roll Back Malaria partnership.**NEJM** June 5,2008. 2nd Map Thumbnail: NEJM Aug 7, 2008.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

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Web Sites:

American Lung Association
www.lungusa.org/site/apps/nlnet/content3.aspx?c=dvLUK9O0E&b=2060321&content_id={71CC3CFD-4B3E-49C8-AA88-D76EAE1FB9F5}&notoc=1

National Institute of Allergy and Infectious Diseases
http://www3.niaid.nih.gov/topics/pneumonia/default.htm (English)

Centers for Disease Control and Prevention
www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm (pneumococcal vaccine)
www.cdc.gov/vaccines/vpd-vac/flu/default.htm (influenza vaccine)

National Foundation for Infectious Disease
www.nfid.org/pdf/factsheets/pneuadult.pdf

SEVERE COMMUNITY ACQUIRED PNEUMONIA (SCAP) SCORE OR ESPANA RULE OR PS-CURXO 80

Scoring

Criteria	Points
Major Criteria	
pH <7.3	+13
SBP <90 mmHg	+11
Minor Criteria	
Confusion	+5
B**U**N >10.7 mmol/L	+5
Respiratory rate >30/min	+9
C**X**R multilobar/bilateral infiltrates	+5
Pa**O**$_2$<54 or Pa**O**$_2$/FiO$_2$<250 mmHg	+6
Age ≥ 80 years	+5

Interpretation

Severe CAP: 1 major criterion or 2 minor criteria

Total Points	Risk Class (poor outcome & need for ICU)
<10	Low
10-19	Medium
20-59	High

IDSA/ATS 2007

Scoring

Major Criteria
invasive mechanical ventilation
septic shock with need for vasopressors
Minor Criteria
Respiratory rate ≥ 30 breaths/min PaO_2/FiO_2<250 mmHg
Multilobar infitrates
Confusion/disorientation
BUN ≥ 20 mg/dL
Leukopenia (WBC <4,000 cells/mm^3)
Thrombocytopenia (PLT <100,000 cells/mm^3)
Hypothermia (T <36C)
Hypotension requiring aggressive fluid resuscitation

Interpretation

1 major criterion: direct ICU admission [IDSA 2007 (strong recommendation, LOE II)]

3 minor criteria: direct ICU or high-level monitoring unit [IDSA 2007 (moderate recommendation, LOE II)]

SMART-COP

Scoring

Criteria	Points
Systolic BP <90 mmHg	+2
Multilobar CXR involvement	+1
Albumin <35 g/L	
Respiratory rate (age adjusted) ≤ 50 yr: ≥ 25 breaths/min > 50 yr: ≥ 30 breaths/min	+1
Tachycardia ≥ 125 beats/min	+1
Confusion (new onset)	+1
Oxygenation (age adjusted) ≤ 50 yr: PaO_2 < 60 mmHg or O_2sat ≤90% or PaO_2/FiO_2 < 333 > 50 yr: PaO_2 < 70 mmHg or O_2sat ≤93% or PaO_2/FiO_2 < 250	+2
pH <7.35	+2

Interpretation

Total Points	IVRS risk
0-2	Low risk
3-4	Moderate risk (1 in 8)
5-6	High risk (1 in 3)
7-11	Very risk (2 in 3)

Primary Care Pearl: use SMRT-CO (remove albumin, pH, and PaO2, total out of 8) to inform decisions (does not require lab testing):[13]

- 0 Points — Very low risk of needing IRVS
- 1 Point — Low risk (1 in 20) of needing IRVS
- 2 Points — Moderate risk (1 in 10) of needing IRVS
- 3 Points — High risk (1 in 6) of needing IRVS
- ≥4 Points — High risk (1 in 3) of needing IRVS

References: COMMUNITY-ACQUIRED PNEUMONIA (CAP): SEVERITY ASSESSMENT TOOLS

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DRUGS FOR URINARY TRACT INFECTIONS (UTI)

Prepared by: Loren Regier © *www.RxFiles.ca* Feb/10

1. Highlights

- **Acute uncomplicated cystitis in otherwise healthy ♀**
  - Short course - **3 day** therapy – suitable for cotrimoxazole ($10), trimethoprim & fluoroquinolones (~$20)
  - Nitrofurantoin (e.g. Macrobid) – a minimum of 5-**7 days** treatment is recommended.
- **Fluoroquinolones** have excellent activity against most urinary pathogens; however "overuse" is leading to increasing antimicrobial resistance. *Preserve them for those who really need them!*
- **Asymptomatic bacteriuria** in the institutionalized elderly is common. However, antimicrobial treatment offers no benefit and increases the prevalence of resistant bacteria. *Don't culture asymptomatic residents.*

2. Oral Antimicrobials for Urinary Tract Infections

Trimethoprim/Sulfamethoxazole or Cotrimoxazole (SMX/TMP) {Alternately consider monotherapy with Trimethoprim}

Coverage	*E. coli, P. mirabilis,. K. pneumonia, S. aureus*
Adverse effects	diarrhea, rash, hematologic abnormalities (rare); (May use trimethoprim alone in sulpha allergic patients) (other less common effects: blood dyscrasias, diarrhea, pancreatitis, nephrotoxicity, urolithiasis, hepatotoxicity, hypersensitivity reactions, skin rash, toxic epidermal necrolysis & Stevens-Johnson syndrome. In patients with AIDS, cotrimoxazole produces an increased incidence of toxicity including a syndrome of fever, malaise, nausea and headache. Cotrimoxazole is also associated with disulfiram-like reactions.)
Drug interactions	cyclosporine ↑cyclosp levels & ↑nephrotoxicity, digoxin ↑dig levels, methotrexate ↑MTX toxicity, metronidazole disulfiram reaction, phenytoin ↑phenytoin toxicity, sulfonylureas ↑hypoglycemic effect, warfarin ↑warf effect
Comments	resistance is a problem especially in recurrent UTI; average reported resistance in SK is ~15%, however, higher in some institutional situations. Other antibiotics should be used when resistance ≥20%. maintain hydration

Nitrofurantoin {Macrobid 100mg BID: well tolerated and convenient}

Coverage	*E. coli. K. pneumonia, S. aureus, Enterococcus faecalis*; (not *proteus, pseudomonas*)
Adverse effects	rash, GI upset, increased LFTs; (other less common effects: pneumonitis and other pulmonary reactions, eosinophilia, hemolytic anemia, leukopenia, agranulocytosis, methemoglobinemia, peripheral neuropathy, pseudotumor cerebri, pseudomembranous colitis, nausea, vomiting, pancreatitis, parotitis, hepatitis, systemic lupus erythematosus and cutaneous and allergic reactions)
Drug Interactions	Mg^{++} antacids ↓absorption, norfloxacin ↓norfloxacin effect; Food ↑'s absorption
Comments	maintains excellent activity against *E. coli*, *Enterococci*, & *Staph* avoid in renal dysfunction (CrCl <40-60ml/min); limited tissue penetration; not useful in complicated UTI

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

Coverage	*E. coli, P. mirabilis,. K. pneumonia, P. aeruginosa, +/- S. aureus* (very broad coverage & effective agent)
Adverse effects	headache, GI upset; (Other less common effects: CNS side effects, including seizures; increases in transaminases and in some cases severe and fatal hepatitis have developed. Additionally, hematuria and anaphylactic reactions have been described)
Drug Interactions	antacids ↓absorption; may use a PPI / H2-antagonist; clozapine, glyburide ↑hypoglycemia, iron ↓cipro absorption, metoprolol ↑metop level, phenytoin ↑↓pheny levels, theophylline ↑theoph toxicity, warfarin ↑warf effect, zinc ↓cipro absorption; 1A2 substrates inhibited by ciprofloxacin & levofloxacin ∴ ↑ effect of olanzapine, haloperidol, imipramine, cyclobenzaprine, fluvoxamine, zolmitriptan…
Comments	other fluoroquinolones also effective; pseudomonal coverage with ciprofloxacin & norfloxacin. lower doses suitable for uncomplicated UTI; higher doses for complicated UTI & pyelonephritis

Amoxicillin/Clavulinic Acid (Amox/Clav)

Coverage	*E. coli, P. mirabilis, K. pneumonia, S. aureus, Enterococcus faecalis*
Adverse effects	rash, GI upset (diarrhea, more with q8h dosing ~25% formulations than with q12h formulations ~10%) (Other less common effects: eosinophilia, leukopenia and thrombocytosis; superinfections resulting in candidal vaginitis and pseudomembranous colitis may occur. Caution in patients with a sensitivity to penicillin.)
Drug Interactions	oral contraceptives ↓contraceptive effect, methotrexate ↓MTX clearance & ↑toxicity; Lab: false +'ve Coomb's test
Comments	good coverage for more resistant organisms including enterococcus.

Fosfomycin - single dose

Comments	usually less effective than SMX/TMP , esp for *S. saprophiticus*; however *E. Coli* resistance uncommon

Note: other beta-lactams (amoxicillin, 1st gen cephalosporins) are alternatives although generally less effective clinically than SMX/TMP.

3. Urban Outpatient Susceptibility Patterns (SK) – local susceptibility variation should be considered

- C&S results reflect patients with recurrent/more complicated infections as these patients getting are cultured most frequently
- **Frequency & susceptibility** of pathogens found vary depending on inpatient vs outpatient and complicating factors
- **Probable organisms**: **Acute Cystitis** ⇨ *E. coli, S. saprophyticus*; **Complicated UTI** ⇨ *E. coli, Enterococci, Klebsiella, Proteus, P. aeruginosa*
  Pyelonephritis ⇨ *E. coli, Klebsiella, Enterobacter, Proteus mirabillis*; **Prostatitis** ⇨ E. coli, Gm –ve bacilli, Staph, enterococcus
- ***E. coli*** (most common uropathogen): ~80% S to SMX/TMP; ≥95% S to NTF; ≥87% S to Cipr; ≥86% S to Amox/Clav
- ***Enterococcus***: Resistant to SMX/TMP ≥94% S to NTF; ≥69% S to Cipr; ≥95% S to Amp

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HANDLING LOW BACK PAIN (LBP) - History

Prepared by P. Taillon MD; L. Regier BSP, BA © www.RxFiles.ca May 14

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

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

About 90% of patients with acute low back problems spontaneously recover activity tolerance within 1 month. Most have significant improvement in 6 weeks. A very few may still have some pain at 1 year. Reassure patient regarding excellent prognosis in most cases of LBP.

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Red Flags for potentially serious conditions

Possible fracture	Possible tumor or infection	Possible cauda equina syndrome
Major trauma, such as MVA or fall from height Presence of contusion or abrasion Minor trauma or even strenuous lifting in potentially osteoporotic patient** ↓ **Major risks for osteoporosis: - elderly > 65 - post menopausal - corticosteroid use - alcohol - past OP #	Age over 50 or under 20 History of cancer. Constitutional symptoms such as recent fever or chills or unexplained weight loss. Recent factors for spinal infection; recent bacterial infection (e.g. urinary tract infection,TB); IV drug abuse; or immune suppression (steroids, transplant, or HIV). Pain at rest; pain that is worse when supine; severe nighttime pain.	Saddle anesthesia/numbness *unable to distinguish between passing gas vs stool* Recent onset of bladder dysfunction, such as urinary retention, increased frequency or overflow incontinence Severe or progressive neurological deficit in the lower extremity. (sudden bilateral leg weakness)

Examination

Investigations (if no red flags – not needed in first 4-6 weeks as almost never result in meaningful change in clinical management)

Lumbar-sacral x-ray	CBC, ESR, CRP, U/A	Immediate consultation
Further imaging? (CT, MRI)	Further imaging? (CT, Bone scan)	Imaging

Natural History of acute low back pain:

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

Prevention is Important!

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

Advanced imaging studies - limit to:

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

Associations with chronic pain syndrome (CPS):

- Defined by the coexistence of multiple factors of psychosocial dysfunction e.g.:
  - ↓ activity; kinesiophobia
  - depression
  - somatic focus
  - relationship problems
  - pain behaviors
  - medication abuse
  - low self esteem
  - may be issues of secondary gain in some cases; however, in most cases, pain is real

  List not exhaustive; consider psychosocial indicators

- Consider CPS when pain history of > 6 months.

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

- Treatment:
  - Education on benign nature of non-specific LBP & helpful role of physical activity as tolerated
  - Physical therapy combined with psychological tx
  - Good posture & occupational approaches (eg. lifting)
  - Home or other exercise program
    - ⇨ consider option of a structured 12 wk program, such as a group program
    - ⇨ supervised walking programs
  - Suitable medication

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

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

Treatment of Low Back Pain [21, 22]

Red Flags (assessment considerations):

- pain when recumbent
- saddle anesthesia
- pseudoclaudication
- age >55y or <20
- recent UTI
- trauma (major
- pain persisting >1mo

Tx Guidelines:

- symptomatic relief can be accomplished with OTC medication and/or spinal manipulation
- during acute phase, bed rest >4 days may further debilitate the patient
- low-stress aerobic activity & exercise OK in first 2 weeks; may delay trunk muscle exercises
- recommend return to work/normal activities as soon as possible
- if problems persist, reassessment required
- address nonphysical factors (psych/socioeconomic)

Meds: acetaminophen 1st line; NSAIDs option if necessary & not contraindicated; strong opioids may be necessary for some but consider addiction risk, use treatment agreement and set appropriate boundaries; consider referral.

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randomised study. BMJ 2011;342:d2786.
Henschke N, Ostelo RWJG, van Tulder MW, et al. **Behavioural treatment** for chronic low-back pain. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD002014. For patients with CLBP, there is moderate quality evidence that in the short-term, operant therapy is more effective than waiting list and behavioural therapy is more effective than usual care for pain relief, but no specific type of behavioural therapy is more effective than another. In the intermediate- to long-term, there is little or no difference between behavioural therapy and group exercises for pain or depressive symptoms. Further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates.
Henschke N, Maher CG, Ostelo RWJG, de Vet HCW, Macaskill P, Irwig L. **Red flags** to screen for malignancy in patients with low-back pain. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD008686. DOI:10.1002/14651858.CD008686.pub2. For most "red flags," there is insufficient evidence to provide recommendations regarding their diagnostic accuracy or usefulness for detecting spinal malignancy. The available evidence indicates that in patients with LBP, an indication of spinal malignancy should not be based on the results of one single "red flag" question. Further research to evaluate the performance of different combinations of tests is recommended.
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Lambeek Ludeke C, Bosmans Judith E, Van Royen Barend J, et al. Effect of integrated care for sick listed patients with chronic low back pain: **economic evaluation** alongside a randomised controlled trial. BMJ 341:doi:10.1136/bmj.c6414 (Published 30 Nov 2010)
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MacRae CS, Lewis JS, Shortland AP, et al. Effectiveness of **rocker sole shoes** in the management of chronic low back pain: a randomized clinical trial. Spine (Phila Pa 1976). 2013 Oct 15;38(22):1905-12.
Madsen MV, Gøtzsche PC, Hróbjartsson A. **Acupuncture** treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009 Jan 27;338:a3115. doi: 10.1136/bmj.a3115.
Mafi JN, McCarthy EP, Davis RB, Landon BE. **Worsening Trends in the Management** and Treatment of Back Pain. JAMA Intern Med. 2013 Jul 29.
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Maiers M, Bronfort G, Evans R, et al. **Spinal manipulative therapy and exercise** for seniors with chronic neck pain. Spine J. 2014 Sep 1;14(9):1879-89.
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Martimo K, Verbeek J, et al. **Manual material handling advice and assistive devices** for preventing and treating back pain in workers. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005958. There is limited to moderate evidence that MMH advice and training with or without assistive devices do not prevent back pain, back pain-related disability or reduce sick leave when compared to no intervention or alternative interventions. There is no evidence available for the effectiveness of MMH advice and training or MMH assistive devices for treating back pain.
Maas ET, Ostelo RW, Niemisto L, et al. **Radiofrequency denervation** for chronic low back pain. Cochrane Database Syst Rev. 2015 Oct 23;10:CD008572. The review authors found no high-quality evidence suggesting that RF denervation provides pain relief for patients with CLBP. Similarly, we identified no convincing evidence to show that this treatment improves function. Overall, the current evidence for RF denervation for CLBP is very low to moderate in quality; high-quality evidence is lacking. High-quality RCTs with larger patient samples are needed, as are data on long-term effects.
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McGregor AH, Probyn K, Cro S, Doré CJ, Burton AK, Balagué F, Pincus T, Fairbank J. **Rehabilitation following surgery for lumbar spinal stenosis**. *Cochrane Database of Systematic Reviews* 2013, Issue 12. Art. No.: CD009644. DOI: 10.1002/14651858.CD009644.pub2. Evidence suggests that active rehabilitation is more effective than usual care in improving both short- and long-term (back-related) functional status. Similar findings were noted for secondary outcomes, including short-term improvement in low back pain and longterm improvement in both low back pain and leg pain, although limited impact was observed in relation to improvements in general health status.

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Michaleff Z, Maher CG, Lin C-WC, et al. **Comprehensive physiotherapy** exercise programme or advice for **chronic whiplash** (**PROMISE**): pragmatic randomised controlled trial. Lancet 2014; online April 4.

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Morone NE, Greco CM, Moore CG, et al. A **Mind-Body Program** for Older Adults With Chronic Low Back Pain: A Randomized Clinical Trial. JAMA Intern Med. 2016 Feb 22.

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

Nerland US, Jakola AS, Solheim O, et al. **Minimally invasive decompression versus open laminectomy** for central **stenosis of the lumbar spine**: pragmatic comparative effectiveness study. BMJ 2015;350:h1603.

Ney JP, Difazio et al. Treatment of chronic low back pain with successive injections of **botulinum toxin** a over 6 months: a prospective trial of 60 patients. Clin J Pain. 2006 May;22(4):363-9.

Nice May 2009 Low back guideline summary http://www.nice.org.uk/nicemedia/pdf/CG88QuickRefGuide.pdf (Savigny P, Watson P, Underwood M; Guideline Development Group. Early management of persistent non-specific low back pain: summary of NICE guidance. BMJ. 2009 Jun 4;338:b1805. doi: 10.1136/bmj.b1805. These guidelines from the United Kingdom's National Institute for Health and Clinical Excellence (NICE) give a nod to exercise, manual therapy, analgesics, acupuncture, and combined physical and psychological therapy for patients with low back pain. They advise against many traditional treatments, including lumbar support, traction, and steroid and other injections, citing either a lack of benefit or a lack of evidence. (LOE = 1a))

NICE: National Institute for Health and Care Excellence. **Low back pain and sciatica**: draft guidance. Mar 2016. www.nice.org.uk/guidance/indevelopment/gid-cgwave0681/ documents.

Okmen K, Okmen BM. The efficacy of **interlaminar epidural steroid administration** in multilevel intervertebral disc disease with chronic low back pain: a randomized, blinded, prospective Study. Spine J. 2016 Aug 20.

Oltean H, Robbins C, van Tulder MW, et al. **Herbal medicine for low-back pain**. Cochrane Database Syst Rev. 2014 Dec 23;12:CD004504. C. frutescens (Cayenne) reduces pain more than placebo. Although H. procumbens, S. alba, S. officinale L., S. chilensis, and lavender essential oil also seem to reduce pain more than placebo, evidence for these substances was of moderate quality at best. Additional well-designed large trials are needed to test these herbal medicines against standard treatments. In general, the completeness of reporting in these trials was poor. Trialists should refer to the CONSORT statement extension for reporting trials of herbal medicine interventions.

Overdevest GM, Vleggeert-Lankamp CL, Jacobs WC, et al. **Recovery of motor deficit accompanying sciatica-subgroup** analysis of a randomized controlled trial. Spine J. 2013 Nov 4.

Pengel LH, Refshauge KM, Maher CG, et al. **Physiotherapist**-directed exercise, advice, or both for subacute low back pain: a randomized trial. Ann Intern Med. 2007 Jun 5;146(11):787-96. In participants with subacute low back pain, physiotherapist-directed exercise and advice were each slightly more effective than placebo at 6 weeks. The effect was greatest when the interventions were combined. At 12 months, the only effect that persisted was a small effect on participant-reported function.

Peul WC, Bredenoord AL, Jacobs WC. **Avoid surgery as first line treatment** for non-specific low back pain. BMJ. 2014 Jul 16;349:g4214.

Phillips FM, et al. **Lumbar spine fusion** for chronic low back pain due to degenerative disc disease: a systematic review. Spine (Phila Pa 1976). 2013 Apr 1;38(7):E409-22.

Pillastrini P, et al. Effectiveness of **Global Postural Re-education** in Patients With Chronic Nonspecific Neck Pain: Randomized Controlled Trial. Phys Ther. 2016 Mar 24.

Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, et al. Drugs for relief of pain in patients with **sciatica**: systematic review and meta-analysis. BMJ 2012;344:e497.

Poetscher AW, Gentil AF, Lenza M, et al. **Radiofrequency denervation** for facet joint low back pain: a systematic review. Spine (Phila Pa 1976). 2014 Jun 15;39(14):E842-9.

Ribeiro LH, Furtado RN, Konai MS, et al. Effect of **facet joint injection** versus **systemic steroids** in low back pain: a randomized controlled trial. Spine (Phila Pa 1976). 2013 Nov 1;38(23):1995-2002.

Rodríguez-Oviedo P, Ruano-Ravina A, Pérez-Ríos M, et al. School **children's backpacks**, back pain and back pathologies. Arch Dis Child. 2012 Mar 10.

Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: an updated cochrane review. Spine. 2008 Jul 15;33(16):1766-74. The evidence from the 65 trials included in this review suggests that NSAIDs are effective for short-term symptomatic relief in patients with acute and chronic low back pain without sciatica. However, effect sizes are small. Furthermore, there does not seem to be a specific type of NSAID, which is clearly more effective than others. The selective COX-2 inhibitors showed fewer side effects compared with traditional NSAIDs in the randomized controlled trials included in this review. However, recent studies have shown that COX-2 inhibitors are associated with increased cardiovascular risks in specific patient populations.

Rubinstein SM, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. **Spinal manipulative therapy** for chronic low-back pain. *Cochrane Database of Systematic*

Reviews 2011, Issue 2. Art. No.: CD008112. DOI: 10.1002/14651858.CD008112.pub2. High quality evidence suggests that there is no clinically relevant difference between SMT and other interventions for reducing pain and improving function in patients with chronic low-back pain. Determining cost-effectiveness of care has high priority.

Rubinstein SM, Terwee CB, Assendelft WJJ, de Boer MR, van Tulder MW. **Spinal manipulative therapy** for acute low-back pain. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD008880. DOI: 10.1002/14651858.CD008880.pub2. SMT is no more effective in participants with acute low-back pain than inert interventions, sham SMT, or when added to another intervention. SMT also appears to be no better than other recommended therapies.

Rundell SD, Sherman KJ, Heagerty PJ, et al. The clinical course of **pain and function in older adults** with a new primary care visit for back pain. J Am Geriatr Soc. 2015 Mar;63(3):524-30.

Sands-Lincoln M, Goldmann D. **Acetaminophen** in the Management of Acute and Subacute Low Back and Neck Pain. Am J Med.2016:129(8):806-807

Santilli V, Beghi E, Finucci S. Chiropractic manipulation in the treatment of acute back pain and sciatica with disc protrusion: a randomized double-blind clinical trial of active and simulated spinal manipulations. Spine J. 2006 Mar-Apr;6(2):131-7. Epub 2006 Feb 3.

Saragiotto BT, Maher CG, Yamato TP, et al. **Motor control exercise** for chronic non-specific low-back pain. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD012004. DOI: 10.1002/14651858.CD012004. There is very low to moderate quality evidence that MCE has a clinically important effect compared with a minimal intervention for chronic low back pain. There is very low to low quality evidence that MCE has a clinically important effect compared with exercise plus EPA. There is moderate to high quality evidence that MCE provides similar outcomes to manual therapies and low to moderate quality evidence that it provides similar outcomes to other forms of exercises. Given the evidence that MCE is not superior to other forms of exercise, the choice of exercise for chronic LBP should probably depend on patient or therapist preferences, therapist training, costs and safety.

Saragiotto BT, Machado GC, Ferreira ML, et al. Paracetamol (**acetaminophen**) for low back pain. Cochrane Database Syst Rev. 2016 Jun 7;6:CD012230. We found that paracetamol does not produce better outcomes than placebo for people with acute LBP, and it is uncertain if it has any effect on chronic LBP.

Schneider M, Haas M, Glick R, et al. Comparison of **spinal manipulation methods and usual medical care for acute and subacute low back pain**: a randomized clinical trial. Spine (Phila Pa 1976). 2015 Feb 15;40(4):209-17.

Sears ED, Caverly TJ, et al. Clinicians' Perceptions of **Barriers to Avoiding Inappropriate Imaging** for Low Back Pain-Knowing Is Not Enough. JAMA Intern Med. 2016 Oct 17.

Sheeran L, van Deursen R, Caterson B, et al. **Classification-guided versus generalized postural intervention** in subgroups of nonspecific chronic low back pain: a pragmatic randomized controlled study. Spine (Phila Pa 1976). 2013 Sep 1;38(19):1613-25.

Sherman KJ, et al. Comparing **yoga**, exercise, and a self-care book for chronic low back pain: a randomized, controlled trial. Ann Intern Med. 2005 Dec 20;143(12):849-56. (InfoPOEMs: A yoga program specifically aimed at patients with chronic low back pain is more effective than either exercise treatment or self-care in decreasing functional disability in patients with chronic low back pain. The style of yoga is called viniyoga and was adapted for use in patients with low back pain. (LOE = 1b))

Sherman KJ, Cherkin DC, Wellman RD, et al. A randomized trial comparing **yoga, stretching, and a self-care book** for chronic low back pain [online October 24, 2011]. Arch Intern Med. doi:10.1001/archinternmed.2011.524.

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Spence MM, Shin PJ, Lee EA, Gibbs NE. Risk of injury associated with **skeletal muscle relaxant** use in older adults. Ann Pharmacother. 2013 Jul;47(7-8):993-8.

Srinivas SV, Deyo RA, Berger ZD. Application of "**Less Is More**" to Low Back Pain Low Back Pain. Arch Intern Med. 2012 Jun 4:1-5.

Staal JB, Nelemans PJ, de Bie RA. **Spinal injection therapy** for low back pain. JAMA. 2013 Jun 19;309(23):2439-40.

Steffens D, Maher CG, Li Q, et al. **Weather** does not affect back pain: Results from a case-crossover study. Arthritis Care Res (Hoboken). 2014 Jul 10.

Steffens D, Ferreira ML, Latimer J, et al. **What triggers an episode of acute low back pain**? A case-crossover study. Arthritis Care Res (Hoboken). 2015 Feb 9.

Steffens D, Maher CG, et al. **Prevention of low back pain**: a systematic review and meta-analysis [online Jan 11, 16]. JAMA Intern Med. doi:10.1001/jamainternmed.2015.7431.

Su W, Yegappan C, Carlisle EJF, et al. Reduced level of consciousness from **baclofen** in people with low kidney function. BMJ 2009;339:b4559, doi: 10.1136/bmj.b4559 (31Dec09)

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Web Sites:

American Academy of Family Physicians (information available in English and Spanish) http://familydoctor.org/online/famdoces/home/common/pain/treatment/117.html

MedlinePlus http://www.nlm.nih.gov/medlineplus/backpain.html

National Institutes of Neurological Disorders and Stroke http://www.ninds.nih.gov/disorders/backpain/backpain.htm

The Arthritis Foundation http://ww2.arthritis.org/conditions/DiseaseCenter/back_pain.asp

A) Peri-Operative Pain Management Considerations [24,25,26, 37,38] **(See RxFiles Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Peri-Operative%20Pain%20Management.pdf)**

B) Select Acute Pain Q&As

Sara Blott BSP,SHR Pharmacy Resident ; L Regier - www.rxfiles.ca

1) Should codeine still be considered a first line opioid for mild-to-moderate pain? [39,40]

- **Codeine is an effective opioid for mild-to-moderate pain but caution is required with its use.**
- **Constipation & stomach upset are especially common.**
- Inter-individual variability in the activity of CYP-2D6 enzyme (enzyme that converts codeine to morphine)
- Slow metabolizers: unable to convert enough codeine to morphine for analgesic response; **can still get the side effects without the benefit**
- Ultra-fast metabolizers: more morphine converted from codeine, **at increased risk of opioid toxicity**
- **Have to watch out for 2D6 interactions ie: fluoxetine, paroxetine, haloperidol, amiodarone, quinidine, ritonavir**
- Note: studies[41-43] indicate that NSAIDs are ***equally as effective*** as acetaminophen + codeine for treatment of acute pain, and may be associated with fewer side effects

2) Where does ketorolac fit in? [44,45]

- In general, no significant difference in efficacy among PO NSAIDs, INCLUDING ketorolac (but patients may respond differently to different NSAIDs)
- Current data support that the analgesic effects of IM ketorolac is similar to that of PO NSAIDs at an equipotent dose
- Ketorolac has been shown to have similar analgesic effects as low to moderate doses of opioids
  One RCT compared IV ketorolac and butorphanol for pain in patients with suspected biliary colic in ED. Both tx were effective for management of pain and demonstrated few AE.
- Ketorolac 10 mg PO x 1 equivalent efficacy to single PO doses of ⇨ acetaminophen 500-1000mg, ASA 650mg, naproxen sodium 550 mg, and ibuprofen 400 mg.
- Ketorolac 10 mg PO BID equivalent efficacy to diclofenac 50 mg PO BID
- Ketorolac 30 mg IM x1 equivalent efficacy single doses of ⇨ indomethacin 100 mg PR, naproxen sodium 550 mg po. {Ketorolac 30mg may also be given IV}
- No difference in the rate and extent of absorption between PO and IM ketorolac (onset ~30 min); some reports of quicker onset with ketorolac IM (~10 min);
  - Duration of analgesia lasts 6-8hours.
  - ** IM ketorolac only for patients who cannot tolerate the PO route and for no more than 2 days (Max 120mg/day)
  - IV ketorolac alternative to IM. (Max 120mg/day)
- **No reason to recommend ketorolac over other NSAID**. ↑ risk for GI complications Highest risk of GI bleeding of any NSAID and renal toxicity with prolonged use
- Canadian labelling: max duration for PO ketorolac 5 days for postsurgical pain & 7 days for MSK pain

3) Are topical NSAIDs effective? [47]

- Evidence from a large number of studies – topical NSAIDs, work well. They may be a practical option if pain is localized to one area (especially sprains, strains, and overuse injuries). As pain affects more areas, it becomes more practical to use an oral NSAID.
- Gels have generally provided best effect.
- Onset of pain relief delayed relative to oral admin.
- Evidence for good effect available only for topical diclofenac, ibuprofen, ketoprofen, and piroxicam.
- ~60-70% of patients will have successful pain control over 7 days with topical NSAID, compared to 40% with placebo (NNT 4-5 for 1 week for 50% pain reduction)
- Local AE no worse with topical NSAID vs topical placebo
- Systemic AE are rare, occurring no more frequently with topical NSAID vs placebo; no serious AE reported. (≤ 6% systemic absorption from topical diclofenac.)

4) Is there a concern about short term NSAID use and impaired fracture healing? [48]

- Still a very controversial issue. Animal studies have indicated delayed healing and non-union with NSAIDs.
- Systematic literature search (2012) by *Kurmis et al*. ⇨ majority of included studies were small-scale, retrospective or observational in nature, with limited control of confounders
- Research has focused on non-union following vertebral fusion but it is uncertain if this can be extrapolated to the appendicular skeleton.
- Recent evidence – NSAID use within 90 days of injury in older patients significantly associated with non-union; long duration ↓ local bone formation by 58%
- In contrast: other studies found delayed union and non-union to be as high as 10% in the absence of NSAID use.
- There are no RCTs looking at the effect of short-term & long-term NSAID use on fracture healing. Data from the *Kurmis et al. review* suggest: "**NSAID use probably safe, even in immediate post-injury period** but there is no clear consensus regarding the true safe interval and duration"
- One study demonstrated that short-term administration of celecoxib, rofecoxib, and low-dose ketorolac had no significant effects on non-union

5) What is a rational combination of analgesics?

- **Multimodal analgesia** ⇨ strategy using more than one class of analgesic agent or technique to improve analgesia through either additive or synergistic effects while ↓ opioid-related SE
- Ie: post-op combination of an opioid and non-opioid analgesic, with or without a regional anesthetic block (or epidural local anesthethic)
- Systematic review of gabapentin adjunctive therapy post-op: ↓post-op pain, ↓opioid & opioid-related SE (with the cost of ↑ sedation)
- Gabapentin initiated at same time as antivirals for acute shingles is reasonable to ↓ pain beyond 1 month.
- Post-op ketamine can ↓opioid-induced hyperalgesia; use of ketamine has shown improved pain scores and ↓ morphine consumption
- Combining any or all of the following may be rational in some patients:
  a) acetaminophen, b) an NSAID, c) an opioid
- Combining two NSAIDs is <u>not</u> rational as AEs are increased without additional benefit.

6) What options are there for treatment of pain resulting from acute herpes zoster (shingles)?

- antiviral tx within 72hrs of shingles onset reduces the risk of post-herpetic neuralgia (see common infections chart)[49]
- If ocular/visual symptoms, may refer to ophthalmologist as may require other treatment, e.g. mydriatic eye drops dilate pupil & ↓ risk of scarring
- Acetaminophen, NSAID or opioid as per pain ladder
- Prednisone (60mg/day x7, then ↓ 30mg/d x7, then 15mg/d x7)
- Gabapentin, pregabalin, nortriptyline or lidocaine patch (See chronic pain chart)[50]

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Table 1 (above): Pain Conditions – Specific Drug Therapy Options

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

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

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

Pearls that might change your Practice

- Amitriptyline is one of the best studied TCAs used in various pain conditions, but nortriptyline in a dose of 25-≥50mg HS may often be effective and better tolerated (less sedation, less dry mouth, less weight gain, etc.).
- Gabapentin doses with evidence for effectiveness in neuropathic pain are often in the 900-1800mg/day range (~1800mg commonly required in trials); some patients lack benefit due to subtherapeutic dose. {Lacks official pain indication.}
- If you want a patient to have an adequate trial on a drug that often has side effects, start at a low dose, titrate up gradually, and counsel that side effects often diminish with 1-2 weeks. Initial and usual target doses are noted where applicable in Table 2. A gradual tapering can also reduce withdrawal syndromes.
- Choose a drug that may cover multiple complaints. (e.g. a person with frequent headache/migraine and weight gain concerns may benefit from topiramate; however remember tolerability, cost and evidence lacking in CNCP)
- Topical agents (capsaicin, NSAIDs, lidocaine 5%, morphine $_{\text{if painful open ulcer}}$) may have a role in select conditions.
- Sleep is a frequent concern. If pain is a cause of poor sleep, consider a longer-acting analgesic to cover the nighttime period and/or agents that are helpful in sleep/pain disorders (amitriptyline $_{\text{10-50mg HS,}}$ methotrimemprazine $_{\text{5-25mg HS}}$).
- Other anecdotal pearls: 1) corticosteroid spray topically to decrease fentanyl patch irritation. 2) Haloperidol 0.5mg HS-BID PRN to reduce severe nausea but avoid sedation. 3) Favor gabapentin dosing towards bedtime (e.g. 300mg BID, 600mg HS) to reduce daytime side effects. 4) If fentanyl patch required but too potent, uncover only half of patch (or tape half) to decrease dose. 5) In some locales, generic hydromorphone has lower street value than Dilaudid. 6) 10% of Caucasians are poor metabolizers of CYP2D6 (required to get the active metabolites of codeine & tramadol); thus consider opioid naïve.

Extras:

- **Renal Failure** – Considerations: that need to alter approach to drug selection will depend on degree of renal dysfx (e.g. GFR ≥20ml/min, 10-20ml/min, <10ml/min), pain severity & drug dose required, use of dialysis.
  A) Less problematic options may include: acetaminophen, tramadol, topicals (capsaicin, nitro spray?); hydromorphone, fentanyl, methadone. {Always include non-drug techniques.}
- **Cisplatinin** related neuropathy: prevention with Vitamin E 400mg/day starting before, and going for 3 months after cisplatinin treatment.
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- **Links FYI**: Patient Info - Pain Management: http://www.medschoolforyou.com/Subjects.aspx
  Cognitive Behavioural Therapy for Insomnia: http://www.cbtforinsomnia.com/
  Pain Training – Online: http://www.algo-md.com/en/index.php (fee for course)
  Pain Approaches: Distinctives in the Acute vs Palliative vs CNCP use of Opioids: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Approaches-Acute-Palliative-CNCP.pdf
  Methadone dosing in pain management: http://pain-topics.org/pdf/OralMethadoneDosing.pdf
  Chronic Pain & Sexual Fx (External Link): http://www.mayoclinic.org/chronic-pain/art-20044369/?utm_source=newsletter&utm_medium=email&utm_campaign=pain-management&pg=2

Opioids & SCI: Ref's

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Additonal articles:

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Web Sites:

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Gout and Uric Acid Education Society www.gouteducation.org/

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GENERIC/TRADE (Strengths & formulations)	LOWEST ANTI-INFLAMMATORY, USUAL RANGE & MAXIMUM DOSE	$/30d	Class/Comments
Acetaminophen TYLENOL, g **OTC ✘** (=paracetamol) Chewable tablet: 160mg ✘ ▼ Rapid-dissolving tablet: 80, 160mg ✘ ▼ PL Immediate release caplet/tablet: 160, 325, 500mg ✘ ▼ Extended release caplet: TYLENOL ARTHRITIS 650mg ✘ ⊗ Gelcap: 500mg ✘ ⊗ Drops: 80mg/mL ✘ ▼ Liquid: 16mg/mL, 80mg/mL, 32mg/mL ✘ ▼ Suppository: 120, 160, 325,650mg ✘ ▼ **▼ Max NIHB is 3600mg/day.** **Caution: ingredient of many products! Unintentional duplication of use sometimes with overdose is common!**	**Lowest Anti-inflammatory:** 650mg po QID 1,300mg ER po TID **Usual Range:** 325-1000mg po TID-QID **Maximum:** 4g/day. Consider limiting dose to ≤3250mg/day, especially if elderly or chronic use. Consider limiting to ≤2600mg/day if hepatic/renal disease or chronic alcohol (≥3 drinks/day) use. **Pediatrics:** 10-15mg/kg q4-6hr; **Max**: 75mg/kg/day	$20 $25	**NON-ANTI-INFLAMMATORY ANALGESIC** • Compared to NSAIDs/COXIBs, lowest risk for CV events & GI ulcer/bleed • Option in osteoarthritis • **D**: warfarin ↑ INR with scheduled chronic use of acetaminophen. Concurrent use of isoniazid, zidovudine, or barbiturates may promote hepatotoxicity. • **M**: **LFTs** with chronic use & if ↑ alcohol use [Larson'05] • **Acute Overdose: hepatotoxic** (#1 cause of drug-induced transplant) >140mg/kg or >7.5g - Level within 24 hours predictive [Rumack-Matthew Nomogram 36]

Combination Product to Reduce Dyspepsia: ASPIRIN STOMACH GUARD: ASA 325/500mg & Ca^{++} Carbonate 227.5/350mg **OTC ✘** ⊗

New Drugs/Formulations:

- low-dose **diclofenac submicron** particles (ZORVOLEX) [Not in Canada] – 18, 35mg capsules. ↓ in particle size ↑'s surface area resulting in faster dissolution & absorption. No comparative evidence.
- low-dose **indomethacin submicron** (TIVORBEX) [Not in Canada] – 20, 40mg capsules. ↓ in particle size ↑'s surface area resulting in faster dissolution & absorption. No comparative evidence. Potent NSAID & ↑ AEs.
- low-dose meloxicam (VIVLODEX) [Not in Canada] – 5, 10mg capsules. ↓ in particle size ↑'s surface area resulting in faster dissolution & absorption. No comparative evidence.

Discontinued Products:

NSAIDs: Choline Mg^{++} Trisalicylate TRILISATE, Fenoprofen NALFON, Piroxicam BREXIDOL, Salsalate DISALCID, Tolmentin TOLECTIN.

COX-2 Inhibitors:

- Lumiracoxib PREXIGE 100mg daily. Discontinued October 2007. Rare severe hepatic toxicity at doses ≥200mg/day.
- Rofecoxib VIOXX 12.5mg (OA) to 25mg (OA/RA) daily. Discontinued September 2004. VIGOR: CV events NNH=83, GI NNT=129/8 months.
- Valdecoxib BEXTRA 10-20mg daily (OA, RA). Discontinued April 2005 in Canada, USA. Rare severe skin reactions e.g. exfoliative dermatitis & Stevens Johnson Syndrome.

Trials:

- PRECISION: CV risk of celecoxib vs ibuprofen vs naproxen http://clinicaltrials.gov/ct/show/NCT00346216?order=4 N Engl J Med. 2016 Nov 13. DOI: 10.1056/NEJMoa1611593

NSAIDS, COXIBs & OTHER ANALGESICS: Comparison Chart

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

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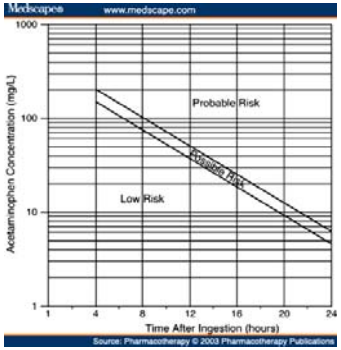
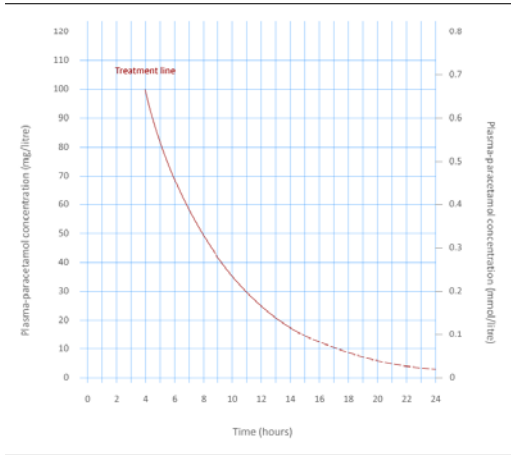


MHRA Sept 2012: Paracetamol (acetaminophen) overdose: Simplification of the use of intravenous acetylcysteine



{There is some evidence for the use of fomepizole as a CYP2E1 inhibitor and for decreased hepatotoxicity in the setting of acetaminophen overdose... To date, the evidence is all animal models but when the patient will otherwise die, the potential benefit outweighs the lack of human evidence.}

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Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007400. DOI: 10.1002/14651858.CD007400.pub2. Topical NSAIDs can provide good levels of pain relief; topical diclofenac solution is equivalent to that of oral NSAIDs in knee and hand osteoarthritis, but there is no evidence for other chronic painful conditions. Formulation can influence efficacy. The incidence of local adverse events is increased with topical NSAIDs, but gastrointestinal adverse events are reduced compared with oral NSAIDs.

Derry S, Derry CJ, Moore RA. Single dose oral **ibuprofen plus oxycodone** for acute postoperative pain in adults. Cochrane Database Syst Rev. 2013 Jun 26;6:CD010289. The combination of ibuprofen 400mg + oxycodone 5mg provided analgesia for longer than oxycodone alone, but not ibuprofen alone (at the same dose). There was also a smaller chance of needing additional analgesia over about eight hours, and with no greater chance of experiencing an adverse event.

Derry S, Moore RA, Gaskell H, et al. **Topical NSAIDs for acute musculoskeletal pain in adults**. Cochrane Database Syst Rev. 2015 Jun 11;6:CD007402. Topical NSAIDs provided good levels of pain relief in acute conditions such as sprains, strains and overuse injuries, probably similar to that provided by oral NSAIDs. Gel formulations of diclofenac (as Emugel(R)), ibuprofen, and ketoprofen, and some diclofenac patches, provided the best effects. Adverse events were usually minimal.Since the last version of this review, the new included studies have provided additional information. In particular, information on topical diclofenac is greatly expanded. The present review supports the previous review in concluding that topical NSAIDs are effective in providing pain relief, and goes further to demonstrate that certain formulations, mainly gel formulations of diclofenac, ibuprofen, and ketoprofen, provide the best results. Large amounts of unpublished data have been identified, and this could influence results in updates of this review.

Derry S, Wiffen PJ, Moore RA. **Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults**. Cochrane Database Syst Rev 2015;7:CD011509. For ibuprofen 200 mg + caffeine 100 mg particularly, the low NNT value is among the lowest (best) values for analgesics in this pain model. The combination is not commonly available, but can be probably be achieved by taking a single 200 mg ibuprofen tablet with a cup of modestly strong coffee or caffeine tablets. In principle, this can deliver good analgesia at lower doses of ibuprofen.

Derry S, Wiffen P, Moore A. **Topical Nonsteroidal** Anti-inflammatory Drugs for Acute Musculoskeletal Pain. JAMA. 2016 Feb 23;315(8):813-814.

Derry S, Conaghan P, Da Silva JA, et al. **Topical NSAIDs for chronic musculoskeletal pain in adults**. Cochrane Database Syst Rev. 2016 Apr 22;4:CD007400. Topical diclofenac and topical ketoprofen can provide good levels of pain relief beyond carrier in osteoarthritis for a minority of people, but there is no evidence for other chronic painful conditions. There is emerging evidence that at least some of the substantial placebo effects seen in longer duration studies derive from effects imparted by the NSAID carrier itself, and that NSAIDs add to that.

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Doherty M, Hawkey C, Goulder M, et al.A randomised controlled trial of **ibuprofen, paracetamol or a combination** tablet of ibuprofen/paracetamol in community-derived people with knee pain. Ann Rheum Dis. 2011 Sep;70(9):1534-41.

Donati M, Conforti A, Lenti MC, et al. Risk of **acute and serious liver injury associated to nimesulide and other NSAIDs**: data from drug-induced liver injury case-control study in Italy. Br J Clin Pharmacol. 2016 Mar 18.

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Dreischulte T, Donnan P, Grant A, et al. Prescribing--A **Trial of Education, Informatics, and Financial Incentives**. (antiplatelets & NSAIDS) N Engl J Med. 2016 Mar 17;374(11):1053-64.

Drendel AL, Lyon R, Bergholte J, et al. Outpatient pediatric **pain** management practices for **fractures**. Pediatr Emerg Care. 2006 Feb;22(2):94-9. Most children with fractures have the "worst" pain in the first 48 hours after injury and used analgesia for 3 days after injury. There are noteworthy functional limitations for both children and their caregivers. Ibuprofen and acetaminophen with codeine are the analgesics most commonly used, with no clear superiority.

Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK. A randomized clinical trial of **ibuprofen** versus acetaminophen with codeine for acute pediatric arm fracture pain. Ann Emerg Med. 2009 Oct;54(4):553-60.

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Drugs in Pregnancy and Lactation. 9th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Philadelphia, PA: 2011.

Eliassen AH, Chen WY, Spiegelman D, Willett WC, Hunter DJ, Hankinson SE. Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and **risk of breast cancer** among premenopausal women in the Nurses' Health Study II. Arch Intern Med. 2009 Jan 26;169(2):115-21; discussion 121. These data **suggest** that the use of aspirin, other NSAIDs, and acetaminophen is not associated with a reduced risk of breast cancer among premenopausal women.

Elmunzer BJ, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the **prevention of post-ERCP pancreatitis**. Gut. 2008 Sep;57(9):1262-7.

Elmunzer BJ, Scheiman JM, Lehman GA, et al. U.S. Cooperative for Outcomes Research in Endoscopy (**USCORE**). A randomized trial of rectal **indomethacin** to **prevent post-ERCP pancreatitis**. N Engl J Med. 2012 Apr 12;366(15):1414-22.

Enthoven WT, Roelofs PD, Deyo RA, et al. Non-steroidal anti-inflammatory drugs for **chronic low back pain**. Cochrane Database Syst Rev. 2016 Feb 10;2:CD012087. Six of the 13 included RCTs showed that NSAIDs are more effective than placebo regarding pain intensity. NSAIDs are slightly more effective than placebo regarding disability. However, the magnitude of the effects is small, and the level of evidence was low. When we only included RCTs at low risk of bias, differences in effect between NSAIDs and placebo were reduced. We identified no difference in efficacy between different NSAID types, including selective versus non-selective NSAIDs. Due to inclusion of RCTs only, the relatively small sample sizes and relatively short follow-up in most included trials, we cannot make firm statements about the occurrence of adverse events or whether NSAIDs are safe for long-term use.

Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. **Acetaminophen** Use and the **Risk of Asthma** in Children and Adults: A Systematic Review and Metaanalysis. Chest. 2009 Aug 20. [Epub ahead of print]

European Medicines Agency (**EMA**), 2012. Agency finalises review of recent published data on **cardiovascular safety of NSAIDs** [online]. Available:http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/10/news_detail_001637.jsp&mid=WC0b01ac058004d5c1

FDA- **Acetaminophen and Liver Injury**: Q & A for Consumers 2009 http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM172664.pdf

FDA Dec/09 , Endo, & Novartis revised the Hepatic Effects section of the Prescribing Information to add new warnings and precautions about the potential for elevation in liver function tests during treatment with all products (**including diclofenac gel**) on **diclofenac** sodium. In postmarketing reports, cases of drug-induced **hepatotoxicity** have been reported in the first month but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

FDA June/12 cautioned late last week against using **Reumofan Plus**, a dietary supplement marketed as a "natural" pain reliever for arthritis, osteoporosis, and other conditions. The drug, which is made in Mexico but available online, contains unlabeled and potentially harmful pharmaceutical ingredients: diclofenac, methocarbamol & sometimes dexamethasone. (Dec/12 FDA: Reumofan Plus is being relabeled and sold under the name "**WOW**.")

FDA Aug/12 is issuing an updated alert that **Reumofan Plus and Reumofan Plus Premium** contain undeclared active ingredients found in prescription drugs that should be used only under the supervision of a health care professional. It contains Diclofenac Sodium and Methocarbamol.

FDA Aug/13 laboratory analysis confirmed that **Ortiga contains the prescription drug ingredient, diclofenac**.

FDA Jan/14 is recommending health care professionals **discontinue prescribing and dispensing prescription combination drug products that contain more than 325 milligrams (mg) of acetaminophen** per tablet, capsule or other dosage unit.

FDA Feb/14 analysis of **Arth-Q supplement** contains hidden ingredient ibuprofen.

FDA Mar/14: Pain Free By Nature is recalling "**Reumofan Plus**" Tablets purchased through their website at www.painfreebynature.com, after FDA discovered that the product was distributed in packaging that did not reveal the presence of the active pharmaceutical ingredients methocarbamol and **diclofenac**, making it an unapproved drug.

FDA Apr/14: Nano Well-being Health Inc. issued a voluntary recall of **Super Arthgold**, 500 mg capsules to the consumer level. FDA laboratory analysis has found the product to contain chlorzoxazone, diclofenac and indomethacin.

FDA Apr/15 is alerting pet owners, veterinarians, health care providers and pharmacists that pets are at risk of illness and death when exposed to topical pain medications containing the nonsteroidal anti-inflammatory drug (NSAID) **flurbiprofen**. People using these medications should use care when applying them in a household with pets, as even very small amounts could be dangerous to these animals.

FDA Jul/15 is strengthening an existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (**NSAIDs**) increase the chance of a **heart attack or stroke**.

FDA Dec/15 Lucy's Weight Loss System is voluntarily recalling all lots of **Pink Bikini White powder Capsules**, 30 white (750MG per capsule) to the consumer level. Pink Bikini has been found positive for diclofenac.

Felson DT. Clinical practice. **Osteoarthritis of the knee**. N Engl J Med. 2006 Feb 23;354(8):841-8.

Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of **aspirin on long-term risk of colorectal cancer**: consistent evidence from randomised and observational studies. Lancet. 2007 May 12;369(9573):1603-13. Use of 300 mg or more of aspirin a day for about 5 years is effective in primary prevention of colorectal cancer in randomised controlled trials, with a latency of about 10 years, which is consistent with findings from observational studies. Long-term follow-up is required from other randomised trials to establish the effects of lower or less frequent doses of aspirin.

Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. Arch Intern Med 2007; 167:394-399. The frequency of **nonnarcotic analgesic** use is independently associated with a moderate increase in the risk of incident **hypertension**. Given the widespread use of these medications and the high prevalence of hypertension, these results may have important public health implications.

Forestier R, Desfour H, Tessier JM, et al. **Spa therapy** in the treatment of knee osteoarthritis: a large randomised multicentre trial. Ann Rheum Dis. 2010 Apr;69(4):660-5. Epub 2009 Sep 3.

Fosbøl EL, Folke F, Jacobsen S, et al. Cause-Specific Cardiovascular Risk Associated With Nonsteroidal Antiinflammatory Drugs Among Healthy Individuals. Circ Cardiovasc Qual Outcomes. 2010 Jun 8. (**Diclofenac & rofecoxib**)

Foster NE, Thomas E, Barlas P, Hill JC, Young J, Mason E, Hay EM. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. BMJ. 2007 Sep 1;335(7617):436. Epub 2007 Aug 15. The addition of **acupuncture** to a course of advice and exercise for osteoarthritis of the knee delivered by physiotherapists provided no additional improvement in pain scores.

Fransen M, et al. HIPAID Collaborative Group. Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial. BMJ. 2006 Sep 9;333(7567):519. Epub 2006 Aug 2. These data do not support the use of routine prophylaxis with NSAIDs in patients undergoing **total hip replacement surgery**.

Friday JH, Kanegaye JT, McCaslin I, Zheng A, Harley JR. **Ibuprofen** provides analgesia equivalent to **acetaminophen-codeine** in the treatment of acute pain in children with extremity injuries: a randomized clinical trial. Acad Emerg Med. 2009 Aug;16(8):711-6. Epub 2009 Jul 14. Acute pain relief from ibuprofen is equivalent to that of acetaminophen-codeine for children presenting to the emergency department with extremity injury. More than half the children in this study were consequently found to have fractures. (LOE = 1b)

Friis S, Riis AH, Erichsen R, et al. Low-Dose **Aspirin or Nonsteroidal Anti-inflammatory Drug** Use and **Colorectal Cancer** Risk: A Population-Based, Case-Control Study. Ann Intern Med. 2015 Aug 25.

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

Gatoulis SC, Voelker M, Fisher M. Assessment of the Efficacy and Safety Profiles of **Aspirin 1gm and Acetaminophen With Codeine**: Results From 2 Randomized, Controlled Trials in Individuals With Tension-Type Headache and Postoperative Dental Pain. Clin Ther. 2011 Dec 12.

Gauer RL, Semidey MJ. Diagnosis and Treatment of **Temporomandibular Disorders**. Am Fam Physician. 2015 Mar 15;91(6):378-386.

Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of **steroid injections** for shoulder and elbow tendonitis: a meta-analysis of randomized controlled trials. Ann Rheum Dis. 2009 Dec;68(12):1843-9. Epub 2008 Dec 3. In the first 3 months of tendinitis of either the elbow or shoulder, injected corticosteroids are more effective than placebo or physical therapy, but no more effective than treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). In the longer term they are no more effective than any treatment. What hasn't been studied is the effectiveness of steroid injections in patients for whom NSAID treatment isn't effective, since this is the usual progression of treatment of these painful conditions. (LOE = 1a-)

Gelber AC**. In the Clinic**: **Osteoarthritis**. Ann Intern Med. July1,2014. ITC1-2.

Gislason GH, et al. **Risk of Death or Reinfarction** Associated With the Use of Selective Cyclooxygenase-2 Inhibitors and Nonselective Nonsteroidal Antiinflammatory Drugs After Acute Myocardial Infarction. Circulation. 2006 Jun 19; [Epub ahead of print] For any use of rofecoxib, celecoxib, ibuprofen, diclofenac, and other NSAIDs, the hazard ratios and 95% confidence intervals for death were 2.80 (2.41 to 3.25; for rofecoxib), 2.57 (2.15 to 3.08; for celecoxib), 1.50 (1.36 to 1.67; for ibuprofen), 2.40 (2.09 to 2.80; for diclofenac), and 1.29 (1.16 to 1.43; for other NSAIDS); there were dose-related increases in risk of death for all of the drugs. There were trends for increased risk of rehospitalization for MI associated with the use of both the selective COX-2 inhibitors and the nonselective NSAIDs. CONCLUSIONS: Selective COX-2 inhibitors in all dosages and nonselective NSAIDs in high dosages increase mortality in patients with previous MI and should therefore be used with particular caution in these patients.

Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs) in chronic **heart failure**. Arch Intern Med. 2009 Jan 26;169(2):141-9.

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

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

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

Health Canada Oct/07 Foreign Product Alerts: ***Zhen Feng Da Brand Xi Tong Wan*** is promoted as a pain reliever. Lot #060908 has been found to contain undeclared indomethacin, a prescription anti-inflammatory drug that should only be taken under the guidance of a health

professional. ***Wellring Brand Yin Qiao Jie Du*** is a health product promoted to treat cold and flu symptoms. Lot#51005 has been found to contain undeclared acetaminophen. ***Gu Ci Dan*** and ***Xu Log Bou*** are promoted as pain relievers and have been found to contain indomethacin.

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

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

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

Health Canada June/09 is informing Canadian health care professionals and consumers of recent restrictions regarding the use of the prescription drug piroxicam. Health Canada has conducted a safety review and concluded that **piroxicam** should no longer be used to treat short-term pain and inflammation due to an increased risk of serious skin reactions and gastrointestinal problems relative to other similar drugs.

Health Canada July/09 is warning consumers not to use the unauthorized health product labelled as **Specific-Formula Arthro-Ace** as it was found to contain undeclared dexamethasone and may cause serious health effects.

Health Canada July/09 is warning that the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **Air Ikan Haruan** after it was found to contain undeclared dexamethasone. The Hong Kong Department of Health warned consumers not to buy or use the product **Neovidan** after it was found to contain undeclared prednisolone and mefenamic acid.

Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine, while **Cao Gen Bai Lin Wan** contains undeclared dexamethasone and chlorpheniramine.

Health Canada Aug/10 **Huo Luo Jing Dan** The Singapore Health Sciences Authority warned consumers not to buy or consume Huo Luo Jing Dan after it was found to contain undeclared indomethacin, dexamethasone and prednisolone.

Health Canada Oct/11 **Huo Li Bao and Ren Sem Tu Chon Chin Kuo Pill** - The Singapore Health Sciences Authority warned that these Chinese pain-relief products contain prescription and/or over-the-counter drugs (furosemide, piroxicam, chlorpheniramine, and/or dexamethasone).

Health Canada Dec/11 is advising Canadians that Vita Health's product, "**Compliments Muscle and Back Pain Relief Regular Strength**" contains a significant labelling error in the French dosing directions that may pose serious risks to children (less than 12 years of age).

Health Canada Apr/13 **1. Diet Garcinia Forte; Shan Dian Shou; Aulura Energy Dietary Supplement** The Hong Kong Department of Health has advised consumers not to use these products after they were found to contain sibutramine and phenolphthalein, drug ingredients that were not declared on their product label. Shan Dian Shou also contains the undeclared prescription drug sildenafil. **2. Snake Powder Capsule for Rheumatism; Jia Rong Zhuang Gu Tong Bi Jiaonang; Long Ren Tang Fu She Gu Rang Jiao Nang** The Hong Kong Department of Health advised consumers not to use these products after they were found to contain multiple prescription and non-prescription drugs that were not declared on their product label. (prednisone, indomethacin, diclofenac, hydrochlorothiazide, cimetidine, prednisone, theophylline, dexamethasone etc). **3. Tinea Schwartz's; Tiao Jing Bu Xue Pills; Yeung Ng Tong Tin Hee Pills** The Hong Kong Department of Health advised consumers not to use these products after they were found to contain prescription drugs that were not declared on their product label (prednisone, indomethacin, diclofenac). **4. Quan Xie Jin Gu Tong; Xinhuang Pian; Jin Gu Feng Shi Kang Jiao Nang** The Hong Kong Department of Health advised consumers not to use these products after they were found to contain multiple prescription and non-prescription drugs that were not declared on their product label. (prednisone, piroxicam, diclofenac, indomethacin, naproxen).

Health Canada Apr/14: Nano Well-being Health Inc. issued a voluntary recall of **Super Arthgold**, 500 mg capsules to the consumer level. FDA laboratory analysis has found the product to contain chlorzoxazone, diclofenac and indomethacin, making it an unapproved new drug.

Health Canada May/14 **Ortiga** contains diclofenac.

Health Canada June/14: **Pro ArthMax** contains diclofenac, ibuprofen, naproxen, indomethacin, chlorzoxazone.

Health Canada June/14: **Zi Xiu Tang Pollen capsule and Zi Xiu Tang Beauty Face and Figure capsule**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain undeclared sibutramine, phenolphthalein, diclofenac, and ibuprofen. The product, Zi Xiu Tang Beauty Face and Figure capsule, was also found to contain undeclared glibenclamide, and indomethacin.

Health Canada Sep/14: **JIN LONG Snakes Bones Rheumatic Capsules**- The Singapore Health Sciences Authority warned consumers not to use this product after it was found to contain betamethasone, piroxicam,oxethazaine, paracetamol (also known as acetaminophen) and furosemide.

Health Canada Oct/14 Diclofenac - Update to Heart and Stroke Related Safety Information and Decrease in the Maximum Recommended Daily Dose for Tablets and Suppositories - Novartis Pharma Canada Inc. and Pfizer Canada Inc. Diclofenac at 150 mg per day, is associated with an increased risk of serious cardiovascular adverse events. The maximum recommended daily dose of systemic **diclofenac** is now **100 mg per day**. Diclofenac is not recommended in patients with pre-existing cardiovascular or cerebrovascular disease.

Health Canada Dec/14: **Joint-Soft**: The Singapore Health Sciences Authority warned consumers not to use the product **JOINT-SOFT** after it was found to contain piroxicam anddexamethasone. The Singapore Health Sciences Authority warned consumers not to use the product **KEBIGUTAIJIAONANG** after it was found to contain piroxicam, hydrochlorothiazide, and prednisone. The Singapore Health Sciences Authority warned consumers not to use the product **Pil Raja Urat Asli** after it was found to contain piroxicam and indomethacin.

Health Canada Mar/15 advises- **Feng Shi Ling**: undeclared diclofenac & indomethacin.

Health Canada Apr/15 is working with the Canadian manufacturers of prescription oral **ibuprofen** products to update the safety information regarding the risk of serious **cardiovascular side effects** (e.g., heart attack and stroke) when these products are used at high doses (**at or above 2400 mg/day**). This risk increases with dose and duration of use.

Health Canada Jul/15 is taking additional steps to minimize the risk of **liver damage** and improve **acetaminophen** safety. This action is in light of a Health Canada review that assessed acetaminophen and liver injury in the Canadian context, a summary of which is available on Health Canada's website.

Health Canada Dec/15: **Naproxen Emo** contains naproxen.

Health Canada Feb/16 is informing Canadians that Pfizer Consumer Healthcare has initiated a voluntary **recall of 124 lots of Advil liquid** products for infants and children because of a potential risk of inconsistences in dosing of the product.

Health Canada Mar/16 says **Asia Black, Black Widow 25, Burn Fat Now, Extreme Stack, Fataway Ultimate Stack, MaxOut Body, Metabolic Accelerator, Methyldrene Original 25 Dietary Supplements, ThermoFX, Thermogenic Fat Burner & Thin and Slim Naturall**y by FDA contains undeclared salicylic acid.

Health Canada June/16: Singapore Health Sciences Authority-**Meizitang Botanical Slimming 100% Natural Soft Gel** contains undeclared diclofenac.

Health Canada Aug/16: Hong Kong Department of **Health-4L Slimness and 4L Slimburn Plus** undeclared diclofenac.

Health Canada Sep/16 is releasing an updated **Labelling Standard for over-the-counter acetaminophen** products to help consumers use these products more safely. Product packages will include clearer instructions and stronger warnings to help reduce the potential for liver damage. Improvements to the Labelling Standard include: clearer instructions on packages that emphasize the importance of using the lowest effective dose; not exceeding the recommended daily maximum (which is 4,000 mg for adults) in a 24-hour period; using these products for no more than five days for pain or three days for fever; and not mixing them with alcohol if drinking three or more drinks in a day; displaying the words "contains acetaminophen" in bold, red text in the top right corner of the front of the package to make it easier for consumers to know if a product contains this drug; a new Drug Facts table for packages to provide product instructions, warnings and other safety information in a consistent, quick-reference format; and a recommendation that all children's liquid products include a calibrated dosing device, so parents and caregivers can be sure that they're giving their child the right amount.

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OPIOID ANALGESIC: COMPARISON CHART

Extras:

- Buprenorphine Transdermal System (BuTrans Patch) Q&A – Aug 2010: http://www.rxfiles.ca/rxfiles/uploads/documents/BuTrans-QandA.pdf
- Fentanyl Nasal Spray (LAZANDA): available in USA, for cancer related breakthrough pain; 100ug/100mcL, 400ug/100mcL; time to onset =11 minutes; always start at 100ug spray, allow 2 hrs between doses, stepwise ↑ in dosage, max 4 doses in 24hrs.
- Fentanyl Sublingual Tablet (PALADIN, ProStrakan in USA): 100, 200, 300, 400, 600, 800 ug.
- Hydrocodone + Ibuprofen (REPREXAIN, VICOPROFEN, others): available in USA. (5/200, 7.5/200, 10/200 mg)
- Hydrocodone ER (HYSINGLA ER): available in USA; when dissolved it forms a viscous gel to ↓ abuse risk.
- Hydrocodone ER (ZOHYDRO ER): available in USA; when dissolved it forms a viscous gel to ↓ abuse risk.
- Methadone injection (IV): available via special access program (SAP) in Canada
- Morphine + naltrexone (EMBEDA): available in USA; naltrexone sequestered core added to ↓ abuse risk.
- Oxycodone: + naloxone (TARGINIQ ER): available in USA; naloxone added to ↓ abuse risk.
- Oxycodone: new products USA: (OXECTA), (ROXYCODONE), (OXYCONTIN: harder to crush/break & when dissolved it forms a viscous gel to ↓ abuse risk)
- Oxycodone XR + acetaminophen – USA: (XARTEMIS XR 7.5mg / 325mg; typical dose, 2 tabs q12h)
- Oxycodone + Ibuprofen (COMBUNOX): available in USA. (5 / 400 mg)
- Oxymorphone (OPANA, OPANA ER): available in USA; IM, rectal, & recently oral; 3x more potent than oral morphine; avoid alcohol as ↑↑↑ peak concentrations. (IR tabs: 5,10mg; e.g 5mg q4-6h prn. ER tabs: 5, 7.5, 10,15,20,30, 40mg; e.g. 10mg q12h).
  - Oxymorphone OPANA ER Abuse Thrombotic thrombocytopenic purpura (TTP) strongly associated with injection drug abuse of OPANA ER.
- See also RxFiles Substance Abuse Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Substance-Abuse.pdf (sections: 4- Addiction screening; 5-Universal Precautions in Pain Medicine; 6-Red Flags for Aberrant Rx Drug Use)
- Oral Morphine for Cancer Pain: Systematic Review (Cochrane): Somewhat effective in 9/10 patients; 6/10 patients, very satisfied; 1/20 stopped due to AEs, Common AE: constipation, N&V.

Fentanyl Patches: "Attempting to give 1/2 patch"

The rate of medication delivery from Duragesic® patches is in proportion to the surface area of drug reservoir in contact with the skin. Prior to the availability of the 12.5 mcg/hr strength, the following procedure was occasionally used to achieve this rate:

1. An occlusive dressing like Opsite was put on the skin.
2. A 25 mcg/hr patch was then applied on top with half on the skin and half on the dressing.

This approach lacks documentation and can not be routinely recommended.

Fentanyl / Opioid Patch Exchange Tool: http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Patch-Exchange-Disposal-Tool.pdf

Opioid Intolerance:

- **Pseudoallergy**
  - **COMMON**! May use non-opioid, lower opioid dose, alternate opioid even from same class; add H1 $_{\text{diphenhydramine}}$ +/- H2 $_{\text{ranitiidine}}$ blocker, moisturizers, cold compresses
    - Flushing, itching, hives, sweating, and/or mild hypotension
    - Itching, flushing or hives at injection site only

These symptoms **may** be due to a *pseudoallergy*. It's a result of histamine release, a pharmacologic side effect of some opioids. Options for this patient include:

1. A nonopioid analgesic (e.g., acetaminophen, an NSAID)
2. Avoidance of codeine, morphine, and meperidine, the opioids most commonly associated with pseudoallergy
3. Use of a more potent opioid less likely to release histamine. Potency, from lower to higher:
   meperidine<codeine<morphine<hydrocodone<oxycodone<hydromorphone<levorphanol<fentanyl
4. If needed, concurrent administration of an antihistamine…an H1 (e.g., diphenhydramine) and perhaps an H2 blocker (e.g., cimetidine)
5. Dose reduction, if tolerated

- **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 Reversal Agent for Overdose: Naloxone (IV, IM, SC; sometimes intranasal off-label, new nasal spray [FDA Nov/15]). Dose, initial 0.4-2mg IV for adults, may repeat q2-3 minutes up to total maximum of 10mg. Will precipitate withdrawal.
- Used to treat life threatening respiratory depression, and sometimes, since short acting, just to temporarily bring patient to consciousness to gather information, then allow back into unconsciousness while drug is eliminated from system.

Opioid Chemical Class

1. **Phenylpiperidines**: meperidine, fentanyl, sufentanil, remifentanil
2. **Diphenylheptanes**: methadone, propoxyphene
3. **Morphine group**: morphine, codeine, hydromorphone, oxycodone, oxymorphone, nalbuphine, butorphanol, levorphanol, pentazocine

New Drugs {Not yet in Canada)

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

Additional References & Links:

- **Canadian Guidelines for Safe and Effective Use of Opioids**: http://nationalpaincentre.mcmaster.ca/index.html
- **Responsible Physician Opioid Prescribing Resources (USA) Links:** http://www.responsibleopioidprescribing.org
- Health Canada – Company – Dosage Conversion Guidelines for Fentanyl; Revised Mar 2010: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2010/fentanyl_2_hpc-cps-eng.pdf
- **Opioid Manager Tool**: Point of care tool summarizing Canadian Guidelines:
  - **From CEP**: http://www.effectivepractice.org/index.cfm?pagePath=CEP_TOOLS/Opioid_Manager&id=23515
  - **From NPC:** http://nationalpaincentre.mcmaster.ca/opioidmanager/
- Tramadol warning (FDA): http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213264.htm
- **AFP article Aug 2012 - on Rational Use of Opioids for Management of Chronic Nonterminal Pain** http://www.aafp.org/afp/2012/0801/p252.html

Treatment Agreements:

Medscape discussion on use in primary care. http://www.medscape.com/viewarticle/711659?src=mp&spon=30&uac=93517FV
Canadian Guideline sample at http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b05.html
RxFiles 1 page version at http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.pdf ; Customizable MS-Word versionhttp://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.doc
RxFiles 2 page version at: ♦customizable MS Word: http://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.docx ♦pdf: http://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.pdf

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FDA July/09 notified healthcare professionals that it is taking several actions to reduce the risk of overdose in patients using pain medications that contain propoxyphene because of data linking propoxyphene and fatal overdoses. The agency will require manufacturers of propoxyphene-containing products to strengthen the label, including the boxed warning, emphasizing the potential for overdose when using these products and to provide a medication guide to patients stressing the importance of using the drugs as directed.
FDA Nov/10 is requesting that manufacturers of the painkiller propoxyphene pull the drug from the market because of concerns over cardiotoxicity. (Propoxyphene is marketed alone as Darvon and combined with acetaminophen as Darvocet.) The agency's request is based on data showing that, even when taken at therapeutic doses, the drug can lead to potentially dangerous changes in the heart's electrical activity, including prolonged PR and QT intervals and widened QRS complex. The FDA advises clinicians to stop prescribing propoxyphene and to ask current users to discontinue the drug. FDA's MedWatch alert (Free)
FDA: July/12 Clinicians who prescribe extended-release and long-acting opioids may receive training as part of an FDA effort to curb misuse. With the risk evaluation and mitigation strategy, pharmaceutical companies must develop programs to train clinicians on how to choose patients for opioid therapy appropriately, how to weigh the risks and benefits for a given patient, how to counsel patients against misuse, and how to spot signs of opioid misuse and addiction. The first training programs are expected to be available by March 2013. Currently, this training is optional, but the Obama administration has endorsed a mandatory training plan.
FDA Aug/12 is reviewing reports of children who developed serious adverse effects or died after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. Recently, three pediatric deaths and one non-fatal but life-threatening case of respiratory depression were documented in the medical literature.
FDA Sep/13 Extended-release and long-acting (ER/LA) opioid pain relievers are no longer indicated for merely moderate pain, the US Food and Drug Administration (FDA) announced today as part of a sweeping move to stem the deadly misuse and abuse of the drugs. Previously, the labels for ER/LA opioid analgesics stated that they were indicated for "moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time." The labels now will state that the drugs are indicated "for the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate."
FDA Sep/15 is investigating the use of the pain medicine tramadol in children aged 17 years and younger, because of the rare but serious risk of slowed or difficult breathing. This risk may be increased in children treated with tramadol for pain after surgery to remove their tonsils and/or adenoids. FDA is evaluating all available information and will communicate final conclusions and recommendations to the public when the review is complete. In the body, tramadol is converted in the liver to the active form of the opioid, called O-desmethyltramadol. Some people have genetic variations that cause tramadol to be converted to the active form of the opioid faster and more completely than usual.
FDA Jan/16 is warning consumers not to use Licorice Coughing Liquid, a cough syrup product sold over-the-counter, because it contains unidentified morphine.
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Health Canada July/10 RELISTOR (methylnaltrexone bromide) Subcutaneous Injection - Association with gastrointestinal perforation - Wyeth Canada Patients with advanced illness being treated with RELISTOR may be at increased risk of gastrointestinal perforation.

Health Canada Nov/10 Darvon-N (dextropropoxyphene) - Recall and Withdrawal in Canada - Paladin Labs Inc. Paladin Labs Inc. in collaboration with Health Canada would like to inform healthcare professionals of the voluntary recall and withdrawal of the opioid analgesic Darvon-N (dextropropoxyphene) in Canada. (widen the QRS complex, prolong the QT interval and therefore increase the risk of serious abnormal heart rhythms.)

Health Canada's Jun/12 review recommends codeine be used in patients aged 12 and over. This recommendation is based on very rare cases of serious side effects and deaths in children that have been attributed to codeine, when given directly to a child, or to babies from breast milk.

Health Canada Oct/13 Reminding Canadians to safely use and dispose of fentanyl patches to prevent accidental exposure. A fentanyl patch is an adhesive patch that is placed on the skin. It delivers the drug fentanyl, continuously through the skin and into the blood stream to control pain. Accidental exposure to fentanyl can be very dangerous and even lead to death.

Health Canada Aug/14 is advising healthcare professionals and Canadians that it has implemented labelling changes for the class of drugs known as controlled-release opioid pain medicines, to enhance their safe and appropriate use. The changes provide standardized wording that more clearly outlines the risks and safety concerns associated with controlled-release opioids. The updated guidance also encourages more appropriate patient selection and monitoring.

Health Canada Dec/15: Herba Pini Syrop contains codeine.

Health Canada Aug/16 is taking new action to improve the safe use of two prescription opioid drugs, codeine and hydrocodone, to help further address the rare but potentially life-threatening risk of breathing problems in children and adolescents. Serious breathing problems known as respiratory depression (slowed breathing) are a known risk with the use of any opioid, particularly when too much is taken. The action is in light of Health Canada safety reviews that identified the need for new warnings and restrictions on prescription codeine and hydrocodone products, to enhance their safe use. Specifically, the reviews determined that: codeine should no longer be used (contraindicated) in patients under 18 years of age to treat pain after surgery to remove tonsils or adenoids, as these patients are more susceptible to the risk of serious breathing problems. Codeine (prescription and non-prescription) is already not recommended for children under the age of 12, for any use. Hydrocodone is no longer recommended in under six years of age. This recommendation is based on rare cases of serious breathing problems including deaths in children in this age group, usually involving higher-than-recommended doses.

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Preventing Rx Forgery & Drug Diversion [v]

Common Methods Used in Forgery

- ***Alter*** a legitimate prescription to ↑ the dose or quantity of a controlled substance (e.g. add a zero)
- ***Add*** to a prescription (e.g. add drug to the bottom of another prescription)
- ***Forge***/duplicate a prescription via scanner/printer
- ***Double-doctoring***

Prevention

- Limit supply on street via careful patient selection & dosing strategies.
- Identify unfamiliar patients: ask for picture I.D.
- Take an independent history and obtain collaborative verification
- **Recognize drug seeking signs**
  - Allergic to weak opioids or NSAIDs
  - Knows clinical terms and street names for prescription drugs
  - Request specific drugs & have perfect story - *It's OK to say "No"*
  - Signs of intoxication or abuse
- **Check electronic prescription drug profile** &/or contact previous or current regular practitioner
  - *"Offer to check it & then watch them run…"*
  - {e.g. PIP in SK = prescription information program}
- Steer away from preferred street drugs (e.g. oxycodone, hydromorphone, morphine, Percocet)
- **Prescribe with safeguards in place**
  - Limit quantities & / or have pharmacist provide "part-fills" (e.g. small amounts given more frequently)
  - Assess for addiction risk {e.g. Tools: 1) ORT [7] ; 2) CAGE-AID[7]}
  - Consider a treatment agreement for all; (don't assume patients know) (concept of "universal precautions" in pain medicine[vi])
- **Tips for prescription writing to prevent forgery**
  - No spaces (e.g. "-----10mg"; not " 10 mg")
  - Use numerical & written form for quantities (e.g. disp: # fifteen [15only])
  - Fill unused prescription space with a pen stroke/scribble
  - Secure prescription pads to prevent theft & number sequentially
- Send prescriptions electronically by FAX or E-Prescribed (e.g. on PIP); do not give copies of faxed or electronic prescriptions to patient.

A Few Related Considerations for Potential New Opioid Rx's:

- History & assessment: Identify patient (e.g. picture ID) if not from local area
- If **psychiatric** component/history, post-traumatic stress (**PTSD**) +/- co-medication esp benzodiazepines, addiction risk, as well as opioid-associated mortality risk, is elevated. Having Mental Health involvement can be extremely useful in managing patients needing concurrent psychiatric care (issues of central dysregulation of pain, impulsiveness, & somatization).
- **Communication** with the primary physician/family physician on the assessment, pain assessment, diagnosis and intent of the prescriber may assist in helping the **"inheriting physician"** to know possible courses of action and/or recognize both legitimate and problematic concerns.
- Role for **short-term regular dosing** of NSAIDs or acetaminophen when pain expected to be constant over a few days (e.g. take regular for 5 days, then prn).
- NSAIDs such as **Ibuprofen 400-600mg QID** or **naproxen 375-500mg BID** often as/more effective than alternative weak/combination opioids such as Tylenol 3s, Percocet, and even low doses of potent opioids.
- **Consider local street value or desirability** of drug/formulation to abusers
  - Short/rapid acting opioids: may be easier to abuse and have higher value
  - Brand name opioids often have higher value
  - Oxycodone and hydromorphone generally considered of more value on the street & in high addiction risk communities (North America)
  - Media attention has heightened concerns regarding OxyContin/oxycodone. May indicate increased risk potential (real or perceived), but this is controversial. Some theoretical potential for the increased kappa agonist effect with oxycodone (associated with euphoria). [2012: **OxyNEO** replaced OxyContin to help ↓ abuse risk.]
- **Pill load**: the more tablets one has, the more potential to *"borrow from tomorrow to feel better today"* or *"use left over for fun"*; this may be problematic in those at risk. Part-fills or bubble packs may be useful to discourage this!
- Have an **exit strategy**/plan (e.g. let patient know that an unsuccessful trial will be followed by a gradual tapering of the drug dosage before stopping.)
- **Consider the usual course/timeline** for physiologic structural healing and pain resolution and titrate/reduce/ D/C pain meds accordingly.
  - For example, what generally happens with this type of acute tissue injury at e.g. 72hours, 1-2weeks, 3-6 weeks, 3 months
- Take a **team approach** whenever dealing with the problem of misuse & diversion of prescription drugs.[vii] ***Don't just abandon the patient!***

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See also:

1) **RxFiles Opioid CNCP Newsletter 2011**: http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-2011-Newsletter.pdf
2) **Opioid Manager Tool**. Accessed at: http://nationalpaincentre.mcmaster.ca/opioidmanager/ [8]
3) **Urine Drug Screening Q&A.** 2011. http://www.rxfiles.ca/rxfiles/uploads/documents/members/Urine-Drug-Screening-UDS-QandA.pdf
4) **Opioid Treatment Agreements**: at www.RxFiles.ca (several templates downloadable; earch for "agreement" or "opioid")
5) **Canadian Guideline** for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain — Part B: Recommendations …Version 5.5 April 30, 2010. [NOUGG] Accessed at: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf
6) **Opioid in CNCP Newsletter 2005** http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-Chronic-NonCa-NEWSLETTER-Header.pdf
7) **Opiod Risk Tool** (ORT): Accessed at: http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b02.html {Alternately: CAGE-AID: http://www.partnersagainstpain.com/printouts/A7012DA4.pdf }

UDS: 1) **Codeine**: ⇨ Opiate +ve; ⇨ morphine (possibly hydrocodone). 2) **Hydrocodone** ⇨ Opiate +ve; ⇨ Hydromorphone. 3) **Hydromorphone**: ⇨Opiate +ve. 4) **Morphine**: ⇨Opiate +ve; ⇨Hydromorphone (very minor). 5) **Oxycodone**: ⇨ Opiate –ve; ⇨Oxymorphone. 6) **Oxymorphone** ⇨Opiate –ve. 7) **Tramadol**: ⇨Opiate –ve. 8) **Fentanyl**: ⇨Opiate –ve. 9) **Buprenorphenol**: ⇨Opiate –ve. 10) **Heroin**: ⇨6-monoacetyl morphine & morphine

⇨ Online Extras

Opioid Treatment Agreements

- Useful for:
  - Identifying drug abuse
  - Reducing doctor shopping
  - Outlining how "requests" will be handled
    - E.g. early refills? Running out due to "borrowing from tomorrow"
  - Educating patients on:
    - What to expect?
    - What not too expect?
      - realistic expectations for 30-50% reduction in pain
    - Importance of non-drug interventions
    - Role or lack thereof for "prns" in therapeutic plan
  - Outline responsibilities and expectations
    - monitoring plans, especially functional goals
    - how opioids will be obtained and taken
    - use of concomitant drugs
    - storage and security requirements
    - consequences for non-adherence or aberrant behaviour
  - option of including informed consent components
  - proactive managing of highly functioning, charming and convincing individuals with borderline personality traits – to pre-empt typical conflict that can arise
- The more routine the clinicians use of an agreement, the easier it is!
  - Removes stigma of "suspicion" and any issues of trust
  - Offers best practice protection to all

Education Programs of Interest

- *Inventory of Pain and Addiction Education Programs for Canadian Prescribers*
  - From the National Pain Centre in collaboration with CCSA
  - Link: http://nationalpaincentre.mcmaster.ca/tools.html

References: **Pain Approaches: Acute/Palliative/CNCP chart**

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Additional information:

CAMH: Video discussion of issues around how to taper. http://knowledgex.camh.net/videos/Pages/tapering_presopioids_selby2013.aspx

Opioid Taper Template & related materials at: www.RxFiles.ca

Opioid Manager tool from Canadian CNCP guideline group: http://nationalpaincentre.mcmaster.ca/opioidmanager/

RxFiles Opioid Taper Template TOOL: http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Taper-Template.pdf

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[7] Chronic Insomnia in Older Adults (RxFiles Q&A) http://www.rxfiles.ca/rxfiles/uploads/documents/Insomnia-Older-Adults-QandA.pdf

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Extras

Table: Ten-year absolute fracture risk for women [2] (CAROC basal risk 2010)

Age (years)	Low Risk < 10%	Moderate Risk 10% - 20%	High Risk > 20%
	LOWEST T-SCORE Femoral neck		
50	> - 2.5	- 2.5 to - 3.8	<- 3.8
55	> - 2.5	- 2.5 to – 3.8	< - 3.8
60	> - 2.5	- 2.5 to – 3.8	< - 3.8
65	> - 2.3	- 2.3 to – 3.7	< - 3.7
70	> - 1.9	- 1.9 to – 3.5	< - 3.5
75	> - 1.7	- 1.7 to – 3.2	< - 3.2
80	> - 1.2	- 1.2 to – 2.9	< - 2.9
85	> - 0.5	- 0.5 to – 2.6	< - 2.6
90	> -0.1	- 0.1 to – 2.2	< - 2.2

Table 3: Ten-year absolute fracture risk for men [2] (CAROC basal risk 2010)

Age (years)	Low Risk < 10%	Moderate Risk 10% - 20%	High Risk > 20%
	LOWEST T-SCORE Femoral neck		
50	>-2.5	-2.5 to -3.8	<-3.8
55	>-2.5	-2.5 to -3.9	<-3.9
60	>-2.5	-2.5 to -3.9	<-3.9
65	>-2.5	-2.5 to -3.7	<-3.7
70	>-2.4	-2.4 to -3.7	<-3.7
75	>-2.3	-2.3 to -3.7	<-3.7
80	>-2.3	-2.3 to -3.8	<-3.8
85	>-2.1	-2.1 to -3.8	<-3.8
90	>-2.0	-2.0 to -3.8	<-3.8

There are two risk assessment tools currently available and recommended in the 2010 Canadian OP Guidelines:

1) **CAROC Charts/Graphs**
   (as per tables at left & graphs on previous page)
   ⇨ requires BMD
   http://osteoporosis.bluerush.ca/www/pdf/caroc_oct_2010.pdf

2) **FRAX Canada – Online Calculator**
   ⇨ can be used with OR without a BMD
   http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19

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References: Osteoporosis Treatment Chart

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FDA Nov/10 has approved **denosumab** (marketed as **Xgeva**) for the prevention of fracture and bone pain in patients with cancer that has metastasized to the bone. FDA news release (Free) Xgeva prescribing information (Free PDF)

FDA July/11 notified healthcare professionals and patients about its ongoing review of data from published studies to evaluate whether use of **oral bisphosphonate** drugs is associated with an **increased risk of cancer of the esophagus**. FDA has not concluded that taking an oral bisphosphonate drug increases the risk of esophageal cancer. There are insufficient data to recommend endoscopic screening of asymptomatic patients.

FDA Sep/11 notified healthcare professionals and patients of an update to the drug label for **Reclast (zoledronic acid)** regarding the risk of kidney failure. Cases of acute renal failure requiring dialysis or having a fatal outcome following Reclast use have been reported to FDA. The revised label states that Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment.

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Health Canada Dec/11 is updating Canadians with respect to its review of bisphosphonate drugs, used to treat osteoporosis, and the risk of a rare but serious type of thigh bone fracture known as an "**atypical femur fracture** <1% ."

Health Canada May/12: Cases of severe, sometimes **fatal, symptomatic hypocalcemia associated with XGEVA (denosumab)** treatment have been reported in cancer patients with bone metastases

Health Canada Nov/12 **PROLIA (denosumab)** - Association with the Risk of **Atypical Femoral Fractures** - Amgen Canada Inc. Cases of atypical femoral fractures associated with PROLIA (denosumab) treatment have been reported in patients participating in an ongoing clinical trial involving postmenopausal women with osteoporosis.

Health Canada Oct /15 **Strontium health products**: New restrictions to address possible heart and circulatory-related risks. At Health Canada's request, companies are strengthening product labels for certain strontium-containing natural health products with new restrictions, to minimize a possible increased risk of cardiovascular-related side effects (e.g., heart attack, stroke, blood clots) in people who are at risk of these types of events.

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MHRA Aug/12 There is an increased risk of **cancer associated with the long-term use of calcitonin**. Because of this risk, calcitonin-containing medicines should no longer be used in the treatment of osteoporosis. All intra-nasal calcitonin sprays, which are the only formulation of calcitonin licensed for osteoporosis, will be withdrawn from the European market.

MHRA Apr/16 **Aflibercept** (Zaltrap▼): minimising the risk of **osteonecrosis of the jaw**. Dental examination and appropriate preventive dentistry should be considered before treatment, especially for patients also treated with an intravenous bisphosphonate. https://www.gov.uk/drug-safety-update/aflibercept-zaltrap-minimising-the-risk-of- osteonecrosis-of-the-jaw

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MHRA – Drug Safety Update July 2015: **Denosumab** (Xgeva▼, Prolia); intravenous bisphosphonates: **osteonecrosis of the jaw**—further measures to minimise risk. Patient reminder cards about the risk of osteonecrosis of the jaw are being introduced; denosumab 120 mg is now contraindicated in patients with unhealed lesions from dental or oral surgery.

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Web Links:

Calculating Bone Mineral Densitometry, BMD fracture risk http://www.halls.md/bone-mineral-densitometry/bmd.htm
National Osteoporosis Foundation (NOF) http://www.nof.org/
Osteoporosis Canada – www.osteoporosis.ca
QFractureScore http://www.qfracture.org/
Simple Calculated Osteoporosis Risk Estimation (SCORE) tool http://osteoed.org/tools.php (sensitivity 91%, specificity 40%)[BMD]

Extras, Links & References:

- **AMETOP**: **tetracaine** (amethocaine) **4% Gel** : Adults (including geriatrics) & children over 1 month of age: **Apply** contents of the tube to the skin starting from the centre of the area to be anesthetized & cover with an occlusive dressing. The contents expellable from 1 tube (approximately 1 g) will cover & anesthetize an area of up to 30cm^2 (6×5 cm {~ 3/4 area of a credit card}). Smaller areas of anesthetized skin may be adequate in infants & small children. Adequate anesthesia can usually be achieved for venepuncture following a 30-minute application time, & for venous cannulation following a 45-minute application time; after which the gel should be removed with a gauze swab & the site prepared with an antiseptic wipe in the normal manner. It is not necessary to apply tetracaine gel for longer than the above times & anesthesia is maintained for 4 to 6 hrs in most patients after a single application. [Clinical Trial in progress: Ametop vs Maxilene: http://www.druglib.com/trial/02/NCT00353002.html]

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

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

- **acetaminophen use with vaccination:** may ↓ immunogenicity ∴ avoid if possible.
- **Benzocaine** –in NG tube placement controversial[10] Causes methemoglobinemia!!! AVOID!
- **Lidocaine iontophoresis** {Numby Stuff}: mild electric current penetrates skin more quickly; effective in 10-20min.[43] EMLA similar or slightly better.[44,45] (Tingle may be bothersome.)
- **TAC** tetracaine 0.5% / epinephrine 0.05% / cocaine ≤ 11.8%; AE: seizures, arrhythmias, fatal; requires narcotic storage (LET preferred)
- **Cancer Pain:** Reference [46]
- **Urethral Catheterization**: lidocaine gel 2 min prior to insertion while setting up then use as the lubricant as well (video: http://www.uihealthcare.com/topics/medicaldepartments/urology/catheterization/index.html)
- **Acetaminophen vs ibuprofen**: http://www.cps.ca/English/statements/DT/dt98-01.htm For fever:[47]
- **SHR Peds Pain Links**: http://www.usask.ca/pediatrics/services/pain/
- CADTH. Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emerg.: A Review of Clinical Outcomes and Economic Evaluation http://cadth.ca/media/pdf/O0428_Short-Acting-Procedural-Sedation_to_e.pdf

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

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Pain Intensity Scoring:

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

FLACC SCALE – for assessing pain in very young children non-verbal; suitable for cognitively impaired

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

- Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.
- From ***The FLACC****: A behavioral scale for scoring postoperative pain in young children*, by S Merkel and others, 1997, Pediatr Nurse 23(3), p. 293-297. Copyright 1997 by Jannetti Co. University of Michigan Medical Center.

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

This is a thumbnail image. The full-size FPS-R with instructions is available on page 3 at http://www.iasp-pain.org/FPSR Numbers are not shown to children.

0 2 4 6 8 10

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

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FDA Jan/09 An public health advisory reminds patients and physicians of potentially serious side effects from the improper use of topical anesthetics, including lidocaine, tetracaine, benzocaine, and prilocaine. The latest advisory was prompted by a small study that tested whether lidocaine reduced discomfort during breast mammography. No serious adverse events were noted. However, the FDA remains concerned about the potential for seizures, irregular heartbeat, and breathing problems when topical anesthetics are applied over a large area or are covered by plastic wrap or a heating pad. Two deaths were previously reported in women using the anesthetics before laser hair removal.

FDA Aug/12 is reviewing reports of children who developed serious adverse effects or died after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. Recently, three pediatric deaths and one non-fatal but life-threatening case of respiratory depression were documented in the medical literature.

FDA Jun/14 warns that prescription oral viscous lidocaine 2 percent solution should not be used to treat infants and children with teething pain. We are requiring a new Boxed Warning, FDA's strongest warning, to be added to the drug label to highlight this information. Oral viscous lidocaine solution is not approved to treat teething pain, and use in infants and young children can cause serious harm, including death

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Health Canada Apr/12 is informing Canadians that it has requested companies to add new risk statements to the packaging and labelling of licensed benzocaine products. In April 2011, Health Canada reminded Canadians of certain health risks associated with benzocaine products, including a very rare but serious blood condition known as methemoglobinemia that can affect sensitive individuals.

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RA – EXTRAS

Approach & Considerations for Drug Tx in RA

- Initial: DMARD + NSAID +/- Corticosteroid for symptoms. MTX often the DMARD of choice, however, HCQ is safer but suitable only for mild cases.
  -NSAIDs now used primarily for bridging and pain management.
  -Oral corticosteroids associated with complications, so use controversial. Short courses &/or low doses for ≤2yrs sometimes used (↓ joint pain & systemic symptoms). Intra-articular injections useful & few AEs.
  -Earlier combo DMARD or biologic tx warranted for those with high disease activity & poor prognostic factors.
  {Features of poor prognosis include: functional limitation, extraarticular disease rheumatoid nodules, RA vasculitis, Felty's syndrome, +'ve rheumatoid factor, anti-cyclic citrullinated peptide antibodies, bony erosions radiographic.}
- TNF inhibitors - 1st line biologics after an inadequate response to a DMARD. They are given +/- MTX (synergistic). Note, infliximab given with MTX (not recommended for monotherapy).
  - ◆Initial TNF inhibitor choice: varies with clinician (often etanercept rapid onset, short t ½ or infliximab)
  - ◆Relative to other agents, TNF-inhibitors may be more effective in relieving symptoms & limiting joint destruction. They often also act more rapidly.
  - ◆AEs: 1) Injection site reactions (back pain, fever, urticaria, dyspnea, ↓BP): common with etanercept, golimumab, certolizumab, & adalimumab.
    2) Cytopenia: uncommon, but can occur with any anti-TNF tx. Monitor CBC.
    3) The potential for Serious Infections: (eg. bacterial sepsis, TB reactivated & disseminated, fungal, viral & opportunistic unusual eg. *p. jiroveci*) are important; screen for active infection, latent TB, etc.
    4) Malignancies (esp. lymphomas): reported but causality not established. The condition of RA ↑ lymphoma risk on its own. Avoid anti-TNF tx in patients with recent ca.
    5) Other AEs: (rare) – CHF, reversible lupus-like syndrome, demyelinating conditions eg. M.S. (avoid if hx), hepatoxicity (caution with infliximab).
  - ◆If 1st TNF inhibitor is not effective, switching to a 2nd TNF inhibitor may be effective; however, many specialists will opt for a non-TNF biologic for a different mechanism of action.
- Non-TNF Biologics – include rituximab co-admin with a DMARD; pre-treat to prevent infusion reaction, abatacept +/- a DMARD, tocilizumab may work in ≥2wks, AEs (many; severe complications reported), anakinra less effective.
- Aggressive early therapy with MTX &/or a biologic ⇨ longer remissions, less joint destruction & improved quality of life.
- Combination Tx with 2-3 DMARDs (or a DMARD + biologic): often more effective than monotherapy without more toxicity.
  - ◆Triple DMARD Tx: MTX +SSZ + HCQ (+/- prednisone low-dose ≤7.5-10mg/day) effective. ◆MTX + Biologic more efficatious than either alone. ◆Combination of 2+ Biologics NOT recommended as ↑ toxicity!
- Comorbidity & biologics ACR RA 2012:
  - 1) Hepatitis
    a) Hep C ⇨ potentially recommend etanercept;
    b) Hep B: untreated chronic or treated chronic with Child-Pugh class B or higher: avoid any biologic!
  - 2) Malignancy
    a) treated solid malignancy >5yrs or non-melanoma skin ca >5ys ago – recommend any biologic;
    b) treated solid malignancy <5yr or treated non-melanoma skin ca within 5yr – recommend rituximab;
    c) treated skin melanoma, & treated lymphoproliferative malignancy – recommend rituximab;
  - 3) CHF
    a) NYHA class III-IV with ejection fraction ≤50%: avoid anti-TNF biologics!

Vaccinations: before DMARD or biologic, immunize for influenza, pneumococcal, hep-B & HZV. Live vaccines should not be given to patients on biologics (should be given ≥1 month prior to starting tx).

Pain Management in RA:

- Neuromodulators: Cochrane Review RCT, placebo controlled - few trials, all short term (~2-5 weeks) with high risk of bias (ie. Weak evidence)
  1) Nefopam (ACUPAN): not in Canada; 5HT, NE & DA receptor blocking; NNT=2 for pain relief, offset by significant SE's
  2) Topical capsaicin: reasonable add-onn option; NNT=2-3 for pain relief, offset by some burning at application site
  3) Oromucosal cannabis: small reduction in pain, highly offset by SE's leading to withdrawal (NNH=3) including dizziness 26%, dry mouth 13% & lightheadedness (10%)
  4) Lack of data for other agents included: anticonvulsants, ketamine, bupropion, methylphenidate

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FDA Sep/11 notified healthcare professionals that the Boxed Warning for the entire class of **Tumor Necrosis Factor-alpha (TNFα) blockers** has been updated to include the risk of infection from two bacterial pathogens, **Legionella and Listeria**. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNFα blockers have been revised so that they contain consistent information about the risk for serious infections and the associated disease-causing pathogens.

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Health Canada Aug/09 TNF blockers & risk of **cancer** in children and young adults http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_137-eng.php
Health Canada June/11 **RITUXAN (rituximab) - Fatal Infusion Related Reactions** in Patients with Rheumatoid Arthritis
Health Canada Oct/12 is informing Canadians and Canadian health care practitioners that the labelling for **methotrexate and Proton Pump Inhibitors** (eg. Omeprazole) will include information on a potential interaction between these products.
Health Canada Feb/13 Severe skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (**SJS**) have been reported very rarely in patients who were given **RITUXAN** for the treatment of cancer or disorders of the immune system such as rheumatoid arthritis (RA). Some cases resulted in death.
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June 9;352:2379-88. (Conclusions: Vitamin E had no benefit in patients with mild cognitive impairment. Although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment, the rate of progression to Alzheimer's disease after three years was not lower among patients treated with donepezil than among those given placebo.) (InfoPOEMs: Vitamin E does not slow progression of mild cognitive impairment to full-fledged Alzheimer's disease. Donepezil provides an early benefit that is gone by 3yr. A secondary analysis found that donepezil appeared more beneficial for pts with the apolipoprotein E4 (APOE) gene. This finding requires prospective confirmation before we begin to test all pts with mild cognitive impairment for APOE & use it to guide therapy.(LOE = 1b)) Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL; Alzheimer's Disease Cooperative Study Group. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology. 2009 Jun 16;72(24):2115-21.

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Health Canada May/10: Novartis, in consultation with Health Canada, is informing healthcare providers and consumers that serious adverse events including **death** were associated with errors/misuse of the **Exelon Patch**.
Health Canada Nov/13 **Risperidone- and paliperidone**-containing products are primarily prescribed for the treatment of schizophrenia; however, the risk of Intraoperative floppy iris syndrome (**IFIS**) applies to all patients undergoing cataract surgery, who have been exposed to these products, irrespective of indication.
Health Canada Nov/14 REMINYL ER (**galantamine** hydrobromide) - New Safety Information Regarding the Risk of **Serious Skin Reactions** - Janssen Inc. Very rare cases of serious skin reactions have been reported in patients taking REMINYL ER.
Health Canada Jan 2015 Alzheimer's drug Aricept (donepezil) - New warnings on the serious risks of muscle breakdown and of a neurological disorder. (Rhabdomyolysis, NMS). http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43469a-eng.php
Health Canada Jan/15 Alzheimer's drug **Aricept** (**donepezil**) - New warnings have been added to the prescribing information for the Alzheimer's drug Aricept (donepezil) advising of the risk of two rare but potentially serious conditions: muscle breakdown (**rhabdomyolysis**) and a neurological disorder called **neuroleptic malignant syndrome** (**NMS**).
Health Canada Feb/15 **Risperidone** - Restriction of the Dementia Indication - Janssen Inc. The indication for risperidone in dementia has been restricted to the **short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type**. The indication no longer includes the treatment of other types of dementia.
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Useful Web sites:
Alzheimer Society Canada www.alzheimer.ca
Alzheimer Association USA www.alz.org
Alzheimer Society UK www.alzheimers.org.uk

Drugs with Anticholinergic Effects [4,5,6,7]

Diseases associated with an essential cholinergic deficit include Alzheimer's dementia, Lewy body dementia & to some extent other dementias (not frontal). Anticholinergic drugs worsen the deficit & are therefore highly problematic. **Donepezil** ARICEPT, **rivastigmine** EXELON, and **galantamine** REMINYL are reversible inhibitors of the enzyme acetylcholinesterase. Because of the mechanism of action, medications with anticholinergic effects can interfere with the activity of donepezil, rivastigmine and galantamine. The reverse page of this document contains a list of drugs with anticholinergic effects, with an emphasis on those with moderate to high activity. Drug coverage (in Sask.) may be affected if a patient is using a drug on this list concurrently with donepezil, rivastigmine or galantamine.

Not only is drug coverage of concern, the use of drugs with anticholinergic activity can increase the risk of adverse effects (e.g., cognitive dysfunction, delirium) in the elderly. Drugs with low anticholinergic activity may be good alternatives to drugs with more anticholinergic activity. For example, SSRIs with lower anticholinergic activity are preferred over tricyclics for treatment of depression in the elderly. However, it's not just the use of single drugs with significant anticholinergic activity that can cause trouble. Individuals who take multiple medications with low anticholinergic activity may also have increased risk of adverse effects. In fact, even small increases in so-called anticholinergic burden or load increases the risk of morbidity & mortality in older individuals.[8]

Total Anticholinergic Load: both highly anticholinergic drugs plus others (eg. digoxin, paroxetine, ranitidine) contribute to the anticholinergic load & cognitive impairment. Review each medication the patient is taking.

Spectrum of Anticholinergic Side-Effects

Mild	Moderate	Severe
• Dryness of mouth (modest)	• Moderately disturbing dry mouth/thirst • Speech problems • Reduced appetite	• Difficulty chewing, swallowing, speaking • Impaired perception of taste & texture of food • Dental decay, periodontal disease, denture misfit • Mucosal damage • Malnutrition • Respiratory infection
• Mild dilatation of pupils	• Inability to accommodate • Vision disturbances • Dizziness	• Increased risk of accidents & falls leading to decreased function • Exacerbation/precipitation of acute angle closure glaucoma
	• Esophagitis • Reduced gastric secretions, gastric emptying (atony) • Reduced peristalsis, constipation	• Fecal impaction (in patients with constipation) • Altered absorption of concomitant medications • Paralytic ileus, pseudo-obstruction
• Urinary hesitancy		• Urinary retention, urinary tract infection (in patients with urinary hesitancy)
	• Increased heart rate	• Conduction disturbances supraventricular tachyarrhythmias • Exacerbation of angina • Congestive heart failure
• Decreased sweating		• Thermoregulatory impairment leading to hyperthermia (heat stroke). {Additional risk if also on diuretic.}
• Drowsiness • Fatigue • Mild amnesia • Inability to concentrate	• Excitement • Restlessness • Confusion • Memory impairment	• Profound restlessness & disorientation, agitation • Hallucinations, delirium • Ataxia, muscle twitching, hyperreflexia, seizures • Exacerbation of cognitive impairment (in patients with dementia)

Tips to Deal with Anticholinergic Side-Effects

General approach:

- Identify the cause
- Discontinue unnecessary offending medications
- Reduce the dose
- Look for effective alternatives that are less likely to cause the side-effect

Dry Mouth:

- 80% of the most commonly prescribed medications cause dry mouth (eg. Incontinence meds, Parkinson's meds, antidepressants, antipsychotics, NSAIDs, opioids, muscle relaxants, antihistamines, benzodiazepines, antihypertensives [clonidine, alpha-blockers, beta-blockers, calcium channel blockers, diuretics, ACE inhibitors]).
- When appropriate, instruct patients to take meds associated with dry mouth early in the day since salivary production is lowest at night
- Divided doses may also be less likely to cause dry mouth than a single large dose
- Consider therapeutic alternatives that are less likely to cause dry mouth
- Avoid: alcohol-containing mouthwashes, alcoholic beverages, caffeine, tobacco
- Swish with water every 2 hours
- Drink plenty of fluids while eating to make swallowing easier; avoid foods that are hard to chew
- Chewing sugar-free gum or sucking on sugar-free candy mechanically stimulates salivation and can be recommended to promote salivation in patients with functioning salivary glands
- Nondrug options: bedroom humidifier; artificial saliva or oral moisturizers/lubricants (*Mouth Kote, Biotene Gel, Moi-Stir Spray*)
- Pharmacologic options: pilocarpine (muscarinic agonist) 5 to 10mg of pilocarpine 3 or 4 times daily to a max of 30mg daily– will cause salivation in patients with functioning salivary glands. Duration of action is 3 to 5 hours. Common side effects (dose-dependent): sweating, nausea, rhinitis, flushing, urinary frequency. CI: uncontrolled asthma, narrow-angle glaucoma, acute iritis. **Pilocarpine eye drops** cost significantly less than pilocarpine tablets and can be used orally for treatment of dry mouth. **4 drops of the 2% solution, directly on tongue or add to small amount of water & swish and swallow, 3 times daily** (can swish and spit to reduce systemic side effects).

GERI-RXFILES ANTICHOLINERGIC REFERENCES

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EXTRAS for The Frail Elderly & Long-term Care Drug Tx and Select Considerations:

Antiplatelets / Antithrombotics

DUAL THERAPY RECOMMENDED CHEST'12

ASA + Clopidogrel: Consider PPI. Omeprazole &esomeprazole ↓ clopidogrel's conversion to active drug, ? clinical significance. Consider using pantoprazole, or lansoprazole. (?rabeprazole)

- Atrial Fibrillation: 2nd line for $CHADS_2$=1 or 2° stroke prevention: indefinite; $CHADS_2$ ≤1 + coronary stent x 1yr; $CHADS_2$ = 0 + ACS (without stent) x 1yr • Post-ACS ± PCI x 1-**12** mons ACC'11
- CABG for NSTE ACS: indefinitely •Transcatheter aortic bioprosthetic valve: 3 mons
- PCI with **BMS**: ASA 75-325mg DAILY + clopidogrel x 1 month, then ASA 75-100mg DAILY + clopidogrel x 11 months, then single antiplatelet tx thereafter.
- PCI with **DES**: ASA 75-325mg DAILY + clopidogrel x 3months (limus type) to 6months (taxel type), then ASA 75-100mg DAILY + clopidogrel until 12 mons post-stent, then ASA or clopidogrel thereafter.
- PCI without stent: clopidogrel + ASA 75-325mg DAILY x 1 mon, then ASA or clopidogrel thereafter.
- Below-knee peripheral artery bypass graft with prosthetic grafts: 1 year
- Ischemic stroke/TIA secondary prevention: 24,25,26monotherpay for most, if DAPT initiated, duration should be limited (21 CHANCE to 90 MATCH days) as bleeding risk increases without added benefit. AHA'14 Awaiting POINT27 trial for more efficacy data.

DUAL THERAPY RECOMMENDED CHEST'12

ASA + Dipyridamole: Recurrent stroke; ? hemodialysis draft patency DAC 5.8 vs 43 mons 376

ASA 75-100mg + Prasugrel: Post-ACS + PCI

ASA 75-100mg + Ticagrelor: Post-ACS ± PCI

ASA 81mg + Warfarin: PAD – **NOT** recommended Wave

- AF ($CHADS_2$≥1) + ACS (without stent): 12 mons
- Mechanical valves & low bleed risk: indefinite
- Post MI x 3 mons in high risk patients45, then dual antiplatelet tx for up to 12 mons, then single antiplatet
- Recurrent embolism in mitral valve stenosis or regurgitation

TRIPLE THERAPY RECOMMENDED

ASA + Clopidogrel + OAC AF ($CHADS_2$≥2) +ACS/PCI CCS'12

ASA + Clopidogrel + Warfarin (INR 2-3) CHEST'12

- Atrial Fibrillation ($CHADS_2$ ≥2) + Coronary Stent
  - Triple therapy x 1 month for BMS, 3-6 months for DES, then warfarin + 1 antiplatelet until 1 year post-stent. Warfarin to continue as single agent thereafter.
- Post-MI in high-risk patients & **BMS** x 1 month, then warfarin & ASA for 2nd & 3rd month, then dual antiplatelets for months 4-12, then ASA or clopidogrel.
- Post-MI in high-risk pts & **DES** x 3-6 mons, then dual antiplatelet up to 12 mons, then ASA or clopidogrel.

Sleep/Insomnia

↓ in the efficiency of sleep (amount of time spent in bed sleeping) 28

- Take same amount of time to fall asleep, but spend more time in Stage 1 & 2 non-REM and less time in Stage 3 & 4 and REM sleep More awakenings contribute to the reduction in sleep efficiency (→ complaints of non-restorative sleep problems); leads to daytime napping & earlier bedtime
- Assess possible causative factors (e.g. obstructive sleep apnea nocturnia, often no report of snoring,)

$NNT_{=13}$ >$NNH_{=6\ in\ elderly}$22

- Of note, this meta-analysis evaluated the benefits of sedative use, as determined by *subjective* reported changes in sleep variables, and the risks as determined by adverse events and morning-after psychomotor impairment of short-term treatment (>5days) with sedative hypnotics in older people (>60yrs) with insomnia (free of psychiatric or psychological disorders)
- The NNT vs NNH, although twice as large, should be used as a rough indicator only as more than double the number of participants contributed to the "harm" data than to the "effectiveness" data (2220 vs 1072)

Benzodiazepine tapering:

- Decrease dose slowly over several weeks to months to avoid withdrawal symptoms
- Long-acting benzos do NOT require tapering: chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, nitrazepam
- Remember: any form of caffeine (even small amounts) can be stimulating eg. tea, coffee, pop to the elderly when taken in the evening & should always be stopped before consideration is given to using a "sleeping pill"

- ◆Avoid antihistamines (1st generation): highly anticholinergic, tolerance develops2
- ◆Avoid dimenhydrinate: anticholinergic2
- ◆Avoid TCAs: highly anticholinergic, orthostatic hypotension2
- ◆Avoid barbituates: physical dependence; tolerance to sleep benefits; ↑ risk of overdose at low doses2
- ◆Avoid benzos: risk of cognitive impairment, delirium, falls, fractures *may be appropriate for seizures, REM sleep disorder, benzo or ethanol withdrawal, severe GAD, periprocedural anesthesia, end-of-life care2
- ◆Avoid chloral hydrate: tolerance occurs within 10 days; risk of overdose2
- ◆Avoid chronic use (>90days) of nonbenzodiazepines: similar AE to benzos; minimal improvement in sleep latency & duration2
- ◆Avoid oral decongestants eg. pseudoephedrine: CNS stimulant effects2

Link to Insomnia in RxFiles Older Adults Q&A:
http://www.rxfiles.ca/rxfiles/uploads/documents/Insomnia-Older-Adults-QandA.pdf

Dependent *Pedal* Edema (without heart failure)

- *Some ankle swelling during the day is normal! Reassure patient, family &/or caregiver!*
- Can use compression stockings/hosiery; Instruct pt to sit with feet raised or lie down in the evening followed by going to the bathroom before bedtime to help ↓ ankle swelling & need for diuretic

- ◆ Review drugs that may cause, especially CCBs nifedipine felodipine, amlodipine, to assess if indicated. Remember for many older adults, a SBP of 150 or even 160 may be suitable, especially if further treatment results in ↑ risk of falls, dizziness, orthostatic hypotention, etc.
- ◆ No evidence of efficacy in treating
- ◆ Unnecessary or excessive use of furosemide may cause hypokalemia, electrolyte imbalance & dehydration.

Overall Geriatric Goals

Maintain & improve:

- Physical functioning (eg. activities of daily living)
- Psychological functioning (eg. cognition, depression)
- Social functioning (eg. social activities, support systems)
- Overall health (eg. general health perception)

Additional abbreviations: ♂=male ♀=female ↑=increase ↓=decrease ≠=does not equal **A1C**=glycated hemoglobin **ac**=before meals **ACCORD-BP**=Action to Control Cardiovascular Risk in Diabetes – Blood pressure trial **ACEI**=angiotensin converting enzyme inhibitor **admin**=administration **AF**=atrial fibrillation **AGS**=American Geriatrics Society **AHA**=American Heart Association **ARB**=angiotensin receptor blocker **B12**=vitamin B12 or cobalamin **Benzos**=benzodiazepines **BID**=twice a day **BMD**=bone mineral density **BP**=blood pressure **BPH**=benign prostatic hypertrophy **BPSD**=behavioural & psychological symptoms of dementia **Ca++**=calcium **CHADS2**= tool for predicting risk of stroke (CHF, HTN, Age ≥75, DM, Prior stroke) **CHEP**=Canadian Hypertension Education Program **COPD**=chronic obstructive pulmonary disease **COX-2**=cyclooxygenase-2 **dig**=digoxin **e.g.**=for example **FRAX**=fracture risk assessment tool **GAD**=generalized anxiety disorder **h**=hour **HAS-BLED**=score for bleeding risk on oral anticoagulation in atrial fibrillation **HF**=heart failure **Hg**=mercury **HTN**=hypertension **HYVET**=Hypertension in the Very Elderly Trial **i.e.**=that is; in other words **ISH**=isolated systolic hypertension **IU**=international unit **JATOS**=Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients **K+**=potassium **kg**=kilogram **LTC**=long-term care **Mg++**= Magnesium **mmHg**=millimetres of mercury **NNH**=number needed to harm **NNT**=number needed to treat **NSAID**=nonsteroidal antiinflammatory drug **OA**=osteoarthritis **pc**=after meals **prn**=as needed **po**=by mouth **PROSPER**=Prospective Study of Pravastatin in the Elderly at Risk trial **q**=every **QID**=four times a day **QOL**=quality of life **REM**=rapid eye movement **SBP**=systolic blood pressure **STOPP**=screening tool of older people's potentially inappropriate prescriptions **T2B**=time to benefit **T2DM**=type 2 diabetes mellitus **TID**=three times a day **ug**=microgram **UI**=urinary incontinence **UKPDS**=United Kingdom Prospective Diabetes Study **UTI**=urinary tract infection **Va/DoD**=Veterans Affairs and Department of Defense **vs**=versus **w/out**=without

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LTC-Elderly-Pearls Chart: References

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Recommendations for determining the level of concern when considering treatment modification based on **relapse**:

Criteria	Level of Concern		
	Low	Medium	High
Rate	1 relapse in 2nd year of tx	1 relapse in 1st yr of tx	>1 relapse in the 1st yr of tx
Severity	**Mild**	**Moderate**	**Severe**
	-steroids not required	-steroids required	-steroids/ hospitalization required
	-minimal effect on ADL	-moderate effect on ADL	-severe effect on ADL
	-1 functional domain affected	->1 functional domain affected	->1 functional domain affected
	-no or mild motor/cerebellar involvement	-moderate motor/cerebellar involvement	-severe motor/cerebellar involvement
Recovery	-prompt recovery	-incomplete recovery at 3 months	-incomplete recovery at 6 months
	-no functional deficit	-some functional impairment	-functional impairment

Recommendations for determining the level of concern when considering treatment modification based **disability progression**:

Criteria	Level of Concern		
EDSS score:	Low	Medium	High
≤ 3.5	≤ 1 points	2 points at 6months	>2 points at 6months 2 points at 12months
4-5	<1 point	1 point at 6 months	>1 point at 6months 1 point at 12months
≥5.5		0.5 points at 6months	>0.5 points at 6 months
Clinically Documented Progression	No motor Minor sensory	Some motor, cerebellar or cognitive Multiple EDSS domains affected	Pronounced motor, cerebellar or cognitive Multiple EDSS domains affected
T25FW	≤ 20% confirmed at 6months	>20% and ,100% increase confirmed at 6months	≥ 100% increase confirmed at 6 months

Recommendations for determining the level of concern when considering treatment modification based on annual MRI findings:

Criteria	Level of Concern		
	Low	Medium	High
Activity on MRI:			
New Gd-enhancing Lesions OR accumulation Of new T2 lesions per year	1 lesion	2 lesion	≥3 lesions

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Goodin DS, Cohen BA, O'Connor P, Kappos L, Stevens JC; Therapeutics and Technology Assessment Subcommittee of the **American Academy of Neurology**. Assessment: the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008 Sep 2;71(10):766-73. The **PML** risk in a pooled clinical trial cohort has been estimated to be 1 person for every 1,000 patients treated for an average of 17.9 months, although this figure could change in either direction with more experience with the drug.

December 17, 2008 — Biogen Idec and Élan reported to the United States Securities and Exchange Commission (SEC) that "relevant regulatory agencies" had been informed of another case of progressive multifocal leukoencephalopathy (PML) with natalizumab (Tysabri) monotherapy in a patient with multiple sclerosis (MS). The case was found through surveillance, the companies note, and the patient is stable. The male patient is from Germany and had been on natalizumab monotherapy for 26 months. He is reported to be stable and under the care of his physician. The companies released information on their December 11 Form 8-K report to the SEC December 15.

Health Canada Feb/09 New Safety Information Regarding Progressive Multifocal Leukoencephalopathy (PML) Associated with Tysabri (natalizumab) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-_avis/prof/_2009/tysabri_2_hpc-cps-eng.php

Biogen http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9ODc0MXxDaGlsZElEPS0xfFR5cGU9Mw==&t=1

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FDA Sep/09 documents 13 PML cases http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107198.htm

October 27, 2009 — The European Medicines Agency (EMEA) disclosed October 23 that it has begun a review of the risk–benefit balance for use of natalizumab (*Tysabri*, Biogen Idec/Elan) in relapsing-remitting multiple sclerosis in light of new cases of progressive multifocal leukoencephalopathy (PML) with treatment. The EMEA notes it started a review of the benefits and risks of natalizumab because reports of PML cases worldwide have climbed now to 23 since the drug was reinstated in the market in 2006. "This review is initiated to discuss any additional measures necessary to ensure the safe use of Tysabri and how to balance the risks to the patients against the benefits of the treatment," a press release from EMEA notes. The release was a round-up of EMEA activities as of October 2009. Natalizumab was taken off the market in February 2005 after the first 3 cases of PML were reported. On September 23, 2009, the US Food and Drug Administration (FDA) reported that the count for confirmed cases of PML worldwide in patients treated with natalizumab as monotherapy had reached 13. They have now confirmed the new total case count at 23.

Jan 21,2010 (Dow Jones)--As of Wednesday, there have been 31 cases of a rare brain infection in multiple sclerosis patients on Tysabri, sold by Biogen Idec Inc. (BIIB) and Elan Corp. (ELN), according to a review by a European regulatory panel. The European Medicines Agency's Committee for Medicinal Products for Human Use, known as CHMP, reported the cases of progressive multifocal leukoencephalopathy, or PML, in a review of the drug that concluded its rewards outweigh its risks and the drug should stay on the market. Of the **31 cases**, 23 of the patients were on the drug for more than two years, which puts the infection rate at about 1 in 1,000 patients for those exceeding that duration. This assertion is the same held by the company and implied by the drug's label.

FDA Feb/10 notified healthcare professionals and patients that the risk of developing progressive multifocal leukoencephalopathy (PML) increases with the number of Tysabri infusions received. This new safety information, based on reports of 31 confirmed cases of PML received by the FDA as of January 21, 2010, will now be included in the Tysabri drug label and patient *Medication Guide*.

March 18, 2010 9:22 AM EDT Biogen Idec (Nasdaq: BIIB) disclosed that the number of PML cases involving those taking its Tysabri drug has increased to 42 patients with 9 who have died.

May/10 Biogen Idec Canada Inc., has updated the Tysabri product information with new information on Progressive Multifocal Leukoencephalopathy (PML). The risk of PML increases with increasing duration of treatment with Tysabri. After 24 infusions, physicians are to review with their patients, the benefits and risk of continuing Tysabri treatment.

Schröder A, Lee DH, Hellwig K, Lukas C, Linker RA, Gold R. **Successful Management of Natalizumab**-Associated Progressive Multifocal Leukoencephalopathy and Immune Reconstitution Syndrome in a Patient With Multiple Sclerosis. Arch Neurol. 2010 Jul 12.

Oct 22/10 - Two more patients taking Biogen Idec Inc's multiple sclerosis drug Tysabri (natalizumab) have developed progressive multifocal leukoencephalopathy (PML), the company said on Wednesday. The Cambridge, Massachusetts-based biotechnology company said in its latest monthly update that as of Oct. 1, there have been **70 confirmed cases of PML**, up from 68 as of Sept. 2. Of those, 14 have died and 56 are alive with varying degrees of disability ranging from mild to severe. There were no additional deaths in October. As of June 30, about 71,400 patients had received Tysabri since it was launched.

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FDA Jan/12 JC virus is common and usually harmless, the agency said, but its presence — along with either of the other two PML risk factors — can be dangerous in patients taking immunomodulating drugs like natalizumab. The other risk factors are treatment with natalizumab for longer than 2 years, and previous treatment with immunosuppressant drugs such as methotrexate or cyclophosphamide. The FDA estimates that patients with all three risk factors face about a 1% risk for PML (11 cases per 1000 patients treated).

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FDA May/12 warned clinicians on Thursday that "**liberation therapy**," an experimental procedure that uses angioplasty balloons or stents to open narrowed veins in the chest and neck, has not been approved to treat chronic cerebrospinal venous insufficiency (**CCSVI**) and could be dangerous. Liberation therapy has been associated with one death due to a brain hemorrhage and one stroke, says the FDA. Other possible risks include blood clots, cranial nerve damage, and migrating stents.

FDA is alerting the public that a patient in Europe diagnosed with possible multiple sclerosis (MS) has developed a rare and serious brain infection after taking the drug Gilenya (fingolimod). This is the first case of progressive multifocal leukoencephalopathy (**PML**), reported following the administration of **Gilenya** to a patient who had not previously received Tysabri (natalizumab), an MS drug associated with a higher risk of PML.

FDA Nov/14 is warning that a patient with multiple sclerosis (MS) who was being treated with **Tecfidera (dimethyl fumarate)** developed a rare and serious brain infection called progressive multifocal leukoencephalopathy (**PML**), and later died. The patient who died was not taking any other drugs that affect the immune system or drugs that are thought to be associated with PML.

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Health Canada Aug/12 GILENYA (**fingolimod**) - Stronger recommendations regarding first-dose **cardiovascular monitoring** and use in patients with pre-existing cardiovascular conditions.
Health Canada Feb/15: **TECFIDERA and the risk of PML** is being communicated to health professionals and to the public.
Health Canada Sep/15 is informing Canadians that the drug label (product monograph) for the multiple sclerosis drug **Gilenya** (**fingolimod**) has been updated with new safety information on the risk of **skin cancer**, as well as a rare brain infection known as **progressive multifocal leukoencephalopathy (PML).**
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Approach to Migraine: Considerations

- ACUTE:
  - may consider metoclopramide or domperidone 1st; NSAID and/or triptan also recommended first line;
  - in very severe attacks, SC sumatriptan likely to be most effective & rapid; consider need for rapid onset vs recurrence, GI tolerance of po form, etc.
  - Link to Review Article in AFP Feb 2011: http://www.aafp.org/afp/2011/0201/p271.html
  - Published case reports of 7 successfully treated patients with beta blocker eye drops. (Oral beta blockers not effective for acute migraine.) Mo Med 2014 Jul-Aug;111(4):283-8.
- PROPHYLAXIS: 1st line: beta-blockers (propranolol, metoprolol), TCAs, valproic acid, topiramate.
- MENSTRUAL Related Migraine (MRM): - severity may be increased; duration of headache may be longer and may be harder to treat than regular migraine
  - may consider NSAID or triptan for short-term treatment, several days before and during menstruation [20].

Agents not effective or too many side effects:

- SSRIs, clonidine, methylsergide, oxcarbazepine, melatonin

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326. Arevalo-Rodriguez I, Ciapponi A, Roque I Figuls M, et al. Posture and fluids for preventing **post-dural puncture headache**.Cochrane Database Syst Rev. 2016 Mar 7;3:CD009199. Since the previous version of this review, we found one new study for inclusion, but the conclusion remains unchanged. We considered the quality of the evidence for most of the outcomes assessed in this review to be low to moderate. As identified studies had shortcomings on aspects related to randomization and blinding of outcome assessment, we therefore downgraded the quality of the evidence. In general, there was no evidence suggesting that routine bed rest after dural puncture is beneficial for the prevention of PDPH onset. The role of fluid supplementation in the prevention of PDPH remains unclear.
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- **EXTRAS for MIGRAINE Overview of Preventive & Acute Therapies:**

Alternative Therapies: behavioural therapies include the mastery of relaxation techniques, cognitive behavioural therapy including stress management, biofeedback, and the mastery of pacing and self monitoring skills

Patient Factors	**Red Flags for Serious Headaches**[17] "This is the worst headache ever…"
Age of onset	middle-aged to elderly patients
Type of onset	severe & abrupt; presents suddenly "like a thunderclap"
Temporal sequence	progressive severity or increased frequency
Pattern	significant change in headache pattern
Neurologic signs	stiff neck, focal signs, reduced consciousness
Systemic signs	fever, appears sick, abnormal exam, myalgias, weight loss
Caution: If headache does not fit typical pattern, a serious diagnosis can be missed.	

The **diagnosis of migraine** is clinically based upon a compatible history, physical examination, and fulfillment of diagnostic criteria.
Gold Standard for Diagnosis: The International Classification of Headache Disorders (2nd ed.)[18]
http://www.ihs-headache.org/upload/ct_clas/ihc_II_main_no_print.pdf

How to distinguish a migraine from other headache types?[19]
Findings suggest that the best criteria differentiating migraine with other headache types are the presence of nausea and/or vomiting in combination with 2 of the following 3 symptoms: photophobia[light], phonophobia[loud noises], and osmophobia[odour] *{see no evil, hear no evil, smell no evil}*

Different types of headache
1° migraine (included hormone related) with or without aura, tension-type headache, cluster headache & other trigeminal autonomic cephalgias, others (cough, exertion, etc…)
2° attributed to head and/or neck trauma, attributed to a substance or its withdrawal, attributed to a psychiatric disorder, etc…

Clinical Features of Migraine
Many patients with chronic migraine have a pattern of daily or near-daily headaches of low to moderate severity, associated with less prominent migrainous features. Superimposed on this baseline are exacerbations of pain with more prominent migrainous features such as photophobia, phonophobia, osmophobia, nausea, vomiting, and cutaneous allodynia (i.e. the perception of pain produced by innocuous stimulation of normal skin).

ER setting[20]
- Use parenteral NSAIDS, sumatriptan, metoclopramide, or neuroleptics for initial symptom control
- Consider dihydroergotamine for severe cases
- Dexamethasone for possible prophylaxis against recurrence

Other resources:

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FDA Sep/12 notified healthcare profesionals about a possible increased risk of **heart failure with Mirapex (pramipexole)**. Results of recent studies suggest a potential risk of heart failure that needs further review of available data.

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FDA Mar/11 notified healthcare professionals and patients of an increased risk of development of cleft lip and/or cleft palate (oral clefts) in infants born to women treated with

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Primidone and levetiracetam probably transfer into breast milk in clinically important amounts. Valproate, phenobarbital, phenytoin, and carbamazepine probably are not transferred into breast milk in clinically important amounts. Pregnancy probably causes an increase in the clearance and a decrease in the concentrations of

lamotrigine, phenytoin, and, to a lesser extent carbamazepine, and possibly decreases the level of levetiracetam and the active oxcarbazepine metabolite, the monohydroxy derivative (MHD). Supplementing WWE with at least 0.4 mg of folic acid before pregnancy may be considered. Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered, and monitoring of levetiracetam and oxcarbazepine (as MHD) levels may be considered.

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Adverse Effect on:		Most; and Least Likely Agents
Brain	Cognition	Barbs, Benzos
	Coordination	Barbs, Benzos, CBZ Phenytoin; 2nd gen less so and least with Levetiracetam, Gabapentin
	Language	Topiramate
	Behavior, Personality	Barbs, Levetiracetam, Topiramate, Vigabatrin (+ psychiatric history increase risk)
Blood		CBZ, Phenytoin, Valproate
Bone		CBZ, Valproate
Liver, Pancreas		Valproate
Skin		CBZ, OxyCarb, Lamotrigine, Phenytoin (also related to Asian/genetics, age – Peds and Geriatrics, prior hx of skin rx, high initial dose or rapid dose esculation, immune system disorders, Herpes virus reactivation)
Weight (gain also associated with ↑ risk of CVD)		↑: Gabapentin, Pregabalin, Vigabatrin, Valproate, CBZ (moderate); ↓:Topiramate
Pregnancy		Barbs, Topiramate,Valproate; CBZ, Phenytoin, Lamotrigine
Female Hormones		Valproate (↑Polycystic Ovarian Syndrome and Hirsuitism in ♀);Levetiracetam least effect on OCs
Metabolic Enzyme **Induction** (**Increased** metabolic clearance of other substrates and reduced efficacy)		Barbs, CBZ, Phenytoin (reduce levels of antimicrobials, immunosuppressants, OCs, cardiovascular meds, psychotropics, antineoplastics, antiepileptics)
Metabolic Enzyme **Inhibition** (**Decreased** metabolic clearance of other substrates and increased/prolonged effects)		Valproate (TCAs, Barbs, Benzos, CBZ, lamotrigine, warfarin, zidovudine)

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Further investigations for Special Circumstances

Bleeding Disorders- ↑ suspicion when initial onset of menses is heavy & regular bleeding patterns or presents with suggestive sx: postpartum hemorrhage; surgery-related bleeding, & bleeding associated with dental procedures; or frequent bruising, epistaxis, and bleeding gums. Further investigations: platelet count, PTT, INR, von Willebrand factor,& ristocetin factor

Peri-menopausal- consider endometrial sampling first line due to ↑ risk of endometrial hyperplasia/carcinoma in patients >45yrs or <45 WITH hx of unopposed estrogen exposure, failed medical management, or persistent AUB

Uterine Fibroids & AUB Treatment[32,33,34,35]

Uterine fibroids are commonly found in women in the middle to later reproductive years & are associated with symptoms such as heavy bleeding, menstrual pain, pressure in the lower abdomen, infertiliy, & recurrent miscarriages. Uterine fibroids are thought to be estrogen and progesterone dependent because they shrink after menopause. Traditionally treatment has been the surgical route (myomectomy or hysterectomy), but drug treatments are becoming more relevant:

Agents currently used for Uterine Fibroids

1. GnRH agonists: ↓ uterine fibroid size (by ≤50%) & ↓ uterine fibroid-related symptoms, but treatment restricted to 3-6 months due to hypoestrogenic AE & fibroids return to pretreatment size once agents are stopped
2. LNG-IUS MIRENA: ↓ menstrual blood loss related to uterine fibroids & ↑ hemoglobin in women with anemia, but is not beneficial for uterine regression
3. Ulipristal FIBRISTAL: selective progesterone receptor modulator; ↓ uterine fibroid volume (≤31% vs placebo ↑ 3%); controls bleeding & faster onset of amenorrhea (noninferior & more sustained effect than leuprolide acetate); no serious side effects

Agents in the Clinical Trial Pipeline for the indication of Uterine Fibroid Associated Abnormal Uterine Bleeding:

- Mifepristone MIFEPREX: competitively binds & antagonizes progesterone receptors; inconsistent evidence on effect of uterine size reduction (0 to 50%); ↑ endometrial hyperplasia with no atypia (unsure of clinical implications)
- Asoprisnil: selective progesterone receptor modulator with high receptor & tissue specificity; 25mg/day ↓ volume by ≤36%; ↓ bloating, pelvic pain, & uterine artery blood flow; minimal hypoestrogenic effects
- Telapristone PROELLEX: selective progesterone modulator; doses of 12.5, 25, & 50mg ↓ fibroid size by 10.6, 32.6, & 40.3% respectively (leuprolide acetate 32.6% & placebo 10.6% ↓)
- Aromatase inhibitors (letrozole, anastrozole, fadrozole): antiestrogen; ↓ size of fibroid & symptoms (menstrual volume, duration of menstruation, & dysmenorrhea); no serious side effects reported

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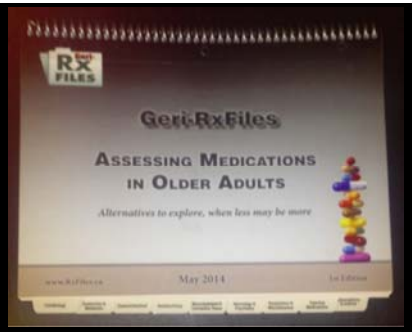

RxFiles – Abnormal Uterine Bleeding – Tx Chart

Developed by Kellie Towriss, BSP (Pharmacy Resident, Saskatoon Health Region (2013; last revised, June 2015)

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Extras for Hormonal Contraception:

Preventing Gaps when Switching Contraceptives. Lesnewski '11

Switching from →	Switching to	Comments
Combined OC, progestin only pill	Combined OC, progestin only pill	♦switch **directly** from one pill to another; do not miss a day
Combined OC	Patch or Ring	♦start patch **day before** last pill; start ring **day after** last pill ♦Do not need to complete pill cycle before switch
Patch or Ring	Combined OC	♦start pill day **before** scheduled to remove patch/ring; i.e. no more than 8 days after last patch (effective up to 9 days) or 34 days after ring (effective up to 35days) ♦Do not need to complete full cycle for patch/ring before pill starts
Patch	Ring	♦insert ring & remove patch on **same day**
Ring	Patch	♦Apply patch **2 days before** ring removal
Combined OC, patch or ring	Progestin IUD or injection	♦Continue pill, patch or ring x **7days** (or use barrier)
Copper IUD	Progestin IUD (i.e Mirena)	♦Use barrier **x 7 days**; return to fertility may be immediate
Copper IUD	Progestin injection (i.e. Depo-Provera)	♦Give injection **7 days before** IUD removal; if done on same day, use **barrier x 7days**
Copper IUD	Combined OC, patch, or ring	♦Start new method **7 days before** removal of IUD or use **barrier x 7days**
Progestin IUD (i.e. Mirena) or injection (i.e. Depo-Provera)	Combined OC, patch, or ring	♦Start new method **7 days before** removal of IUD or next injection (i.e. may start new method **up to 15 weeks after** last injection)
Combined OC, patch or ring	Copper IUD	♦Can insert copper IUD up to **five days** after stopping pill, patch or ring
Progestin IUD (i.e. Mirena)	Copper IUD	♦Can insert copper IUD **right after removing** progestin IUD
Progestin injection (i.e. Depo-Provera)	Copper IUD	♦Can insert copper IUD **up to 16weeks after** the last shot

Consider: Abstain from sexual intercourse or use a barrier method (condoms +/- spermicide) if no overlap in methods for a minimum of 7days for most switches (see above table for exact number of days in bold print)

Consider EC when OC pills missed: (SOGC Clinical Practice Guideline – Emergency Contraception in J Obstet Gynaecol Can 2012;34(9): 873.)

- 1 missed combined oral contraceptive pill in the first week
- 3 or more combined oral contraceptive pills missed in the 2nd or 3rd week
- 1 or more pills missed on Progestin only pill

Or when Depo-Provera injection late by 2weeks or more.

"Patient Friendly" Statistics for Contraceptive Failure Rates: http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118465.htm#hormonal

Out of 100 women who use the following method for 1 year:

- Injection, progestin IUD – 1 may get pregnant
- COC, POP, patch & ring – 5 may get pregnant
- Male condoms – 11 to 16 may get pregnant
- Diaphragm – 15 may get pregnant
- Sponge – 16 to 32 may get pregnant
- Female condoms – 20 may get pregnant
- Spermicide along – 30 may get pregnant

Contraceptive Choices for Post-Partum and Breastfeeding: (Woodhams, E in Contraception 2012)

• Generally advisable to avoid sexual acitivity for 6 weeks post-partum although many women resume sexual activity earlier
• Avoid estrogen containing formulations (pills, patch, vaginal ring) for first 3-6 weeks regardless of whether breastfeeding (due to increased VTE risk); if breastfeeding, wait minimum 30days until lactation well established; if other risk factors for VTE, wait 6 weeks
• Progestin only methods (injection, implant, IUD, pill) can all be started immediately post-partum (recent data shows unlikely to interfere with breastfeeding)
• IUD can be inserted immediately post-placental delivery although expulsion rate can be as high as 20% ; if not placed within 10min of placental delivery, wait 6wks
• Diaphragms and cervical caps will need re-fitting after delivery; all other barrier methods can be used immediately post-partum

After Emergency Contraception SOGC'15:

Health care providers should **discuss a plan for ongoing contraception** with women who use pills for emergency contraception (EC) & should provide appropriate methods if desired.
Hormonal contraception should be started within 24hrs of taking **levonorgestrel** for EC, & back-up contraception or abstinence should be used for the first 7 days after starting hormonal contraception.
Women who use **ulipristal**-EC should start hormonal contraception 5 days after using ulipristal-EC. Ulipristal-EC users must use back-up contraception or abstinence for the first 5 days after taking ulipristal-EC & then for the first 14 days after starting hormonal contraception.

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FDA Apr/12 has completed its review of recent observational (epidemiologic) studies regarding the risk of blood clots in women taking drospirenone-containing birth control pills.Based on this review, FDA has concluded that **drospirenone**-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills. . Report that some epidemiologic studies reported as high as a three-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or some other progestins, whereas other epidemiological studies found no additional risk of blood clots with drospirenone-containing products.
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Health Canada Dec/11 has completed a safety review of drospirenone-containing oral contraceptives (marketed under the brand names Yasmin and Yaz) with respect to the risk of blood clots (venous thromboembolism, or VTE). The review determined that **drospirenone-containing birth** control pills may be associated with a risk of blood clots that is **1.5 to 3 times higher than other birth control pills**.
Health Canada May/13: **Diane-35** supports current labelling and use. The review of the safety of the anti-acne medication Diane-35 has found that the drug's benefits continue to outweigh the risks, when used as authorized.
Health Canada Sep/13 **Freya-28**, an oral contraceptive (birth control product), is being voluntarily recalled from the Canadian market by Mylan Pharmaceuticals after a pharmacy reported that a placebo pill was found in place of an active pill in one package.
Health Canada Sep/13 **Esme-28** (DIN 02388146), an oral contraceptive (birth control product), is being voluntarily recalled from the Canadian market by Mylan Pharmaceuticals.
Health Canada Mar/14 has asked companies to add new warnings to product packages advising that Emergency contraceptive pills, also known as the "morning after" pill,are less effective in **women weighing 165 to 176 pounds (75-80 kg),** and are **not effective** in women over 176 pounds (**80 kg**).
Health Canada May/16 **ESSURE** (permanent birth control system) – Risk of Serious Complications - Bayer Inc. These include changes in menstrual bleeding, unintended pregnancy, chronic pain, perforation and migration of device, allergy and sensitivity or immune-type reactions. Some complications may be considered serious.
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Extras:

Preventing Gaps when Switching Contraceptives. Lesnewski '11

Switching from →	Switching to	Comments
Combined OC, progestin only pill	Combined OC, progestin only pill	♦switch directly from one pill to another; do not miss a day
Combined OC	Patch or Ring	♦start patch day before last pill; start ring day after last pill ♦Do not need to complete pill cycle before switch
Patch or Ring	Combined OC	♦start pill day before scheduled to remove patch/ring; i.e. no more than 8 days after last patch (effective up to 9 days) or 34 days after ring (effective up to 35days) ♦Do not need to complete full cycle for patch/ring before pill starts
Patch	Ring	♦insert ring & remove patch on same day
Ring	Patch	♦Apply patch 2 days before ring removal
Combined OC, patch or ring	Progestin IUD or injection	♦Continue pill, patch or ring x 7days (or use barrier)
Copper IUD	Progestin IUD (i.e Mirena)	♦Use barrier x 7 days; return to fertility may be immediate
Copper IUD	Progestin injection (i.e. Depo-Provera)	♦Give injection 7 days before IUD removal; if done on same day, use barrier x 7days
Copper IUD	Combined OC, patch, or ring	♦Start new method 7 days before removal of IUD or use barrier x 7days
Progestin IUD (i.e. Mirena) or injection (i.e. Depo-Provera)	Combined OC, patch, or ring	♦Start new method 7 days before removal of IUD or next injection (i.e. may start new method up to 15 weeks after last injection)
Combined OC, patch or ring	Copper IUD	♦Can insert copper IUD up to five days after stopping pill, patch or ring
Progestin IUD (i.e. Mirena)	Copper IUD	♦Can insert copper IUD right after removing progestin IUD
Progestin injection (i.e. Depo-Provera)	Copper IUD	♦Can insert copper IUD up to 16weeks after the last shot

Consider: Abstain from sexual intercourse or use a barrier method (condoms +/- spermicide) if no overlap in methods for a minimum of 7days for most switches (see above table for exact number of days in bold print)

"Patient Friendly" Statistics for Contraceptive Failure Rates: http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118465.htm#hormonal

Out of 100 women who use the following method for 1 year:

- Injection, progestin IUD – 1 may get pregnant
- COC, POP, patch & ring – 5 may get pregnant
- Male condoms – 11 to 16 may get pregnant
- Diaphragm – 15 may get pregnant
- Sponge – 16 to 32 may get pregnant
- Female condoms – 20 may get pregnant
- Spermicide along – 30 may get pregnant

♦Study with **IMPLANON** USA found that lactogenisis not affected by early postpartum (on day 1-3) insertion.

Considerations for Specific Conditions

Age >35yrs

- ☐ Can be used if healthy & non-smoking
- ☐ May provide peri-menopausal benefits (↑bone mass, ↓vasomotor symptoms, etc.)
- ☐ ↓ in ovarian & endometrial ca
- ☐ However VTE risk ↑ with age

Epilepsy (carbamazepine, phenytoin, phenobarbital, oxcarbazepine, primidone, topirimate >200mg/day)

- ☐ DIs with common antiepileptics due mostly to hepatic enzyme induction
- ☐ DMPA & IUD may be preferred
- ☐ If on COC, consider 1) shorten hormone free period to 4 days instead of 7; or 2) consider long-cycle use
- ☐ Do not recommend progestin only pill

IBD

- ☐ Oral options may not be adequately absorbed if diarrhea

Migraines

- ☐ COCs contraindicated if migraine with aura or neurologic symptoms
- ☐ If no aura, caution if other risk factor for stroke

Smoking

- ☐ COC contraindicated in ♀ ≥ 35yrs who smoke ≥ 15 cigarettes/day

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FDA Apr/12 has completed its review of recent observational (epidemiologic) studies regarding the risk of blood clots in women taking drospirenone-containing birth control pills.Based on this review, FDA has concluded that **drospirenone**-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills. . Report that some epidemiologic studies reported as high as a three-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or some other progestins, whereas other epidemiological studies found no additional risk of blood clots with drospirenone-containing products.
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Health Canada Dec/11 has completed a safety review of drospirenone-containing oral contraceptives (marketed under the brand names Yasmin and Yaz) with respect to the risk of blood clots (venous thromboembolism, or VTE). The review determined that **drospirenone-containing birth** control pills may be associated with a risk of blood clots that is **1.5 to 3 times higher than other birth control pills**.
Health Canada Sep/13 **Freya-28**, an oral contraceptive (birth control product), is being voluntarily recalled from the Canadian market by Mylan Pharmaceuticals after a pharmacy reported that a placebo pill was found in place of an active pill in one package.
Health Canada Sep/13 **Esme-28** (DIN 02388146), an oral contraceptive (birth control product), is being voluntarily recalled from the Canadian market by Mylan Pharmaceuticals.
Health Canada May/16 **ESSURE** (permanent birth control system) – Risk of Serious Complications - Bayer Inc. These include changes in menstrual bleeding, unintended pregnancy, chronic pain, perforation and migration of device, allergy and sensitivity or immune-type reactions. Some complications may be considered serious.
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Original Reviewers of Herbal Options for Postmenopausal Symptoms in Women:
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Online Extras

Pearls for post-menopausal hormone therapy (HT):

- ♀ without hx of hysterectomy who are on estrogen should use a progestogen to protect against endometrial hyperplasia & carcinoma
- If last menstrual period < 1yr prior, a sequential combined regimen recommended (e.g. continuous estrogen with 12-14 days progestogen/month)
- If last menstrual period > 1yr prior, ♀ who wish to avoid monthly withdrawal bleed, may start continuous combined regimen
- If breakthrough bleeding occurs following switch to continuous combined & does not settle within 3-6months, consider switch back to sequential for 1 or more years
- If bleeding is heavy or erratic on sequential regimen, consider ↑ dose of progestagen (e.g. double)
- Persistent bleeding beyond 6 months warrant referral/investigation
- 90% of ♀ persisting with regimens will eventually be bleed free
- If AEs 2° to progestagen (mood swings, PMS like effects, androgenic effects), may ↓ dose by ½ &/or ↓ duration to 7 -10 days
- HT prescribed before age 60 has a favorable benefit/risk profile
- If using HT after age 60 lower doses (lowest effective dose) especially prudent due to gradually increasing risk
- Venlafaxine (75mg/day) was equal to low dose estrogen (estradiol 0.5mg/day) for treatment of vasomotor symptoms in a RCT.[Joffe H et al., 2014.]

Original derivations of herbal products: black cohosh = rhizome/root; chasteberry = fruit; dong quai = root; evening primorse oil = seed; red clover = flower top; wild yam = rhizome/root; valerian = root

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Health Canada Aug/06 & Jan/10 is advising consumers about a possible link between health products containing herbal medicine **black cohosh** and liver damage. A number of international case reports of liver damage suspected to be associated with the use of black cohosh, including three case reports in Canada and one published case of death in the United States. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html , http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v20n1-eng.php#_Black_cohosh_products
Health Canada Jan/08 is warning Canadians not to use the unauthorized product **RGC-RMC Rheumax Capsule** (batch number REM1-SI93016N). This batch of RGC-RMC Rheumax Capsule has been found to contain **progesterone**, a steroid hormone that can have adverse effects on the brain, breast and skin and should only be taken if prescribed by a health professional.
Health Canada Dec/13 General Nutrition Centres Company (GNC), in consultation with Health Canada, is voluntarily recalling its natural health product "**Women's Phytoestrogen Formula**" – used for the relief of menopausal symptoms – due to possible contamination with chloramphenicol.
Health Canada May/14 has requested that Christmas Natural Foods Ltd. stop selling and recall its unauthorized health product, **Heartland Natural Wild Yam Moisturizing Cream**, after testing conducted by the Department identified a undisclosed prescription drug ingredient, progesterone.
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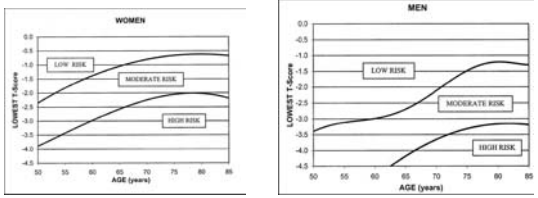

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http://nccam.nih.gov/news/19972000/121100/qa.htm (InfoPOEMs: Glucosamine HCl and chondroitin provides modest if any symptomatic benefit for patients with mild osteoarthritis of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (LOE = 1b))
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	Pre-Pregnancy (~3 months prior) &/or Potential for Pregnancy	Pregnancy Pregnancy P Safe, P Likely Safe, P Caution, P CI, P Unknown	Postpartum & Lactation Lactation L Safe, L Likely Safe, L Caution, L CI, L Unknown
Activity [33]	⇨Encourage activity as part of a healthy lifestyle. ⇨Goal is ≥2.5 hours of activity/week, broken into ≥10 minute sessions. ⇨Decreases risk of pregnancy complications see Body Weight section **~ ½ of pregnancies (⅔ of diabetic pregnancies) are unplanned. Treat every patient visit with females of childbearing potential as an opportunity for preconception counseling.**	⇨PARmed-X Pregnancy Questionnaire: a screening tool for assessing safety, type & intensity of exercise during pregnancy. (http://www.csep.ca/cmfiles/publications/parq/parmed-xpreg.pdf) ⇨Recommend activities which ↓ risk of falls/fetal impact: P Walking, stationary cycling, swimming, low-impact aerobics P Running; Yoga & Pilates inform instructor, avoid compression of the abdomen & strong twists, as well as lying on back during last 4 months of pregnancy. P Horseback riding, skiing, hockey, gymnastics, sauna, hot tub/yoga P Scuba diving ⇨Stop exercising & see physician if: excessive SOB, chest pain, contractions, vaginal bleeding or gush of fluid, dizzy or faint. ⇨Targeted heart rate during pregnancy: age (beats/min) <20 (140-155), 20-29 (135-150), 30-39 (130-145), ≥40 (125-140) If **obese** (BMI ≥30kg/m^2): age 20-29 (102-124), 30-39 (101-120) ⇨ "Talk test" can also be used to monitor intensity • Goal: ability to maintain a conversation while exercising	⇨ Pelvic floor exercises (i.e. **Kegel**): start immediately postpartum to ↓ risk of future stress urinary incontinence. ⇨ Assess ability to (re)start exercise at 6 week postpartum visit for both vaginal & cesarean deliveries. • May need to ↓ or limit intensity & duration of exercise. ⇨ Lactation: moderate exercise will not impact quantity or composition of breast milk. • Maximal intensity workouts: ↑ lactic acid in breast milk → ? may be less palatable to infant.
Nutrition [1,2,3,4] see chart pg 97	P L **Ca^{++}** Total 1300mg/day ≤18 yrs, 1000mg/day ≥19 yrs; P L **Vitamin D** Total 600 IU/day^{IOM} – 2000 IU/day^{CPS}, consider periodic 25(OH) level; P L **Vitamin A** retinol > 10,000 IU or 3000mcg/day (teratogenic) Vitamin D deficiency risk factors: dark skin, ↓ sunlight north of 55th parallel (i.e. LaRonge, Edmonton), ↓ sun exposure (SPF≥8, institutionalized, occlusive clothes), elderly, obese, malabsorption or renal dx, medications e.g. anticonvulsants, antiretrovirals, cholestyramine, corticosteroids, rifampin ⇨ P **Folic acid: dose based on risk of neural tube defect** SOGC'15 • Low risk no risk factors: 0.4mg po daily, for ≥2-3 months prior • Moderate risk*: 1mg po daily, initiate 3 months prior * hx of congenital defect or family hx of NTD for ♀ or ♂, DM, medications e.g. anticonvulsants, methotrexate, sulfonamide, trimethoprim, GI malabsorption • High risk**: 4-5mg po daily for ♀, initiate 3 months prior ** personal history of NTD or NTD pregnancy for either ♀ or ♂ **Other risk factors**: BMI >35kg/m^2, epilepsy, hemolytic anemia, smoker **Is too much folic acid harmful?** Likely not (water-soluble vitamin). May mask vitamin B_{12} deficiency; consider maternal multivitamin with vitamin B_{12} 2.6µg/day. Conflicting studies on potential ↑ risk of cancer. **Calcium Supplements:** Carbonate – least expensive, highest % of elemental Ca^{++}, take with food. Citrate – less GI side effects. **Material Multivitamins**: generic & store brands available $4-8/month - **MATERNA**▼ Fe^{++} 27mg, folic acid 1mg, Ca^{++} 250mg, Vit D 400IU, I$^-$ 220µg, $8 - **PregVit/PregVit folic 5**$^{Rx✗⊗}$ Fe^{++} 35mg, folic acid 1.1/5mg, Ca^{++} 300mg, Vit D 250IU, I$^-$150µg. Pink tab (Fe^{++}) in am, blue tab (Ca^{++}, folic acid) in pm. $33/$44 - **PALAFER CF** Fe^{++} 100mg, folic acid 0.5mg, $18 - **Folic Acid** 0.4mg$^{OTC,✗⊗}$ $2, 1mg$^{OTC,✗▼}$ $2, and 5mg$^{Rx, on SPDP,▼}$ $8	⇨ P **Folic acid: daily dose based on risk of neural tube defect** • 1st trimester: low risk 0.4mg, moderate risk 1mg, high risk 4-5mg • 2nd & 3rd trimester: 0.4 - 1mg po daily for all pregnant ♀ ⇨ P **Iron**: supplementation with 16-30mg elemental po daily in non-anemic patients (UL 45mg/day). Use tx doses if anemic. • Consider risk of iron deficiency anemia in early pregnancy → ? ↑ risk of pre-term delivery, low-birth weight, & fetal death ⇨ **Iodine:** 150-250µg/d from diet & maternal multivit with ≥150µg. Eat "twice as healthy" not "twice as much" ⇨**Caloric intake**: ↑ by 340 calories/day during the 2nd trimester & by 450 calories/day during the 3rd trimester. 2-3 extra Food Guide servings per day are all that is needed (e.g. 1 large glass of milk & 1 piece of fruit). Health Canada Pregnancy Good Guide Serving Tracker available on-line	⇨ L Folic acid: continue 6 weeks postpartum or as long a breastfeeding continues. ⇨ **Vitamin D** for term infants during 1st year: 400 IU/day, or **800 IU/day October to April** if at risk of vitamin D deficiency (see above). Infant formulas provide 400 IU/L (1L=34oz). Supplement [e.g. Ddrops] breastfed infants & formula fed infants at risk of vitamin D deficiency. **Premature infants**: 200IU/kg/day (max 400 IU/day). See RxFiles Vitamin D Q&A: http://www.rxfiles.ca/rxfiles/uploads/documents/Vitamin-D-Overview-QandA.pdf ⇨ Fe^{++} (iron-rich food/cereals, supplements) in breastfed infants ≥4-6 mos ⇨ **Caloric intake during lactation:** ↑ by 330 calories/day 0-6 months postpartum, & ↑ by 400 calories/day 7-12 months postpartum.
		Fish & Mercury Levels during Pregnancy & Breastfeeding: Health Canada recommends 2 servings of fish/week (75g=2.5oz=½ cup). Limit fish with high mercury levels (fresh/frozen tuna, shark, swordfish, marlin, orange roughy, escolar) to 150g/month. Limit canned albacore (white) tuna to 300g/week.[34] Refer to Health Canada's Food Safety for Pregnancy Women for information on other foods to avoid (e.g. certain cheeses, deli meats, etc) http://www.hc-sc.gc.ca/hl-vs/alt_formats/pdf/iyh-vsv/food-aliment/pregnant-enceintes-mar-2010-eng.pdf	
Body Weight [35]	⇨Encourage BMI <30kg/m^2 (ideal 18.5-24.9kg/m^2). Promote diet & exercise to ↓ weight. If obese, start folic acid see above. ⇨Screen: diabetes (i.e. FBG, A1C) ⇨Pregnancy complications with BMI >30kg/m^2 include: • ↑ risk of infertility, c-section, stillbirth, preterm birth & blood clots • 2-fold increase in neural tube defects, and ↑ risk of other malformations • Miscarriage Odds Ratio (OR) 3.5 (95% CI 1.03-12.01) • Spontaneous abortion OR 1.2 (95% CI 1.01-1.46) • Hypertension OR 3.0 (95% CI 2.29-2.62) • Gestational diabetes OR 2.6 (95% CI 2.1-3.4) • Large infant birth weight (>4500g) OR 2.0 (95% CI 1.4-3)	<table><tr><th>Pre-pregnancy BMI[36]</th><th>**Rate** of weight gain (mean) 2nd & 3rd trimester kg (lb)/week</th><th>**Total** weight gain kg (lb) (based on ≤2kg (4.4lb) weight gain in 1st trimester)</th></tr><tr><td><18.5</td><td>0.5 (1)</td><td>12.5-18 (28-40)</td></tr><tr><td>18.5-24.9</td><td>0.4 (1)</td><td>11.5-16 (25-35)</td></tr><tr><td>25-29.9</td><td>0.3 (0.6)</td><td>7-11.5 (15-25)</td></tr><tr><td>≥30</td><td>0.2 (0.5)</td><td>5-9 (11-20)</td></tr></table> ⇨Ultrasound to assess anatomic structures: if obese, consider scheduling at 20-22 weeks as obesity ↓ visibility of structures. ⇨Bariatric surgery hx: assess for nutritional deficiencies Fe^{++}, Ca^{++}, vitamin B12, folate, & vitamin D	⇨Lactation: obesity has been linked to breastfeeding challenges such as ↓ prolactin response and delayed lactogenesis. • Refer mother to a Lactation Consultant if she is experiencing difficulties with breastfeeding (e.g. LaLeche League www.llc.ca) ⇨Breastfeeding promotes postpartum weight loss. Breastfeeding burns 500-600 calories/day.

Alcohol [37]

- ♦ No safe amount has been identified; studies searching for a threshold are conflicting.
- ♦ Abstinence is the safest choice. Fetal Alcohol Syndrome (FAS) occurs with prolonged heavy drinking.
- ♦ Some alcohol ingestion prior to knowledge of pregnancy is unlikely to cause harm.
- ♦ Hold breastfeeding ≥2 hours/drink to avoid infant exposure to alcohol. Monitor infant for sedation & impaired motor skills. Alcohol may ↓ milk production & alter taste of milk ↓ infant milk ingestion.

Caffeine [38]

- ♦ Ok if ≤300mg/day (~2 x 8oz cups of coffee) during pre-conception, pregnancy & breastfeeding

Smoking [39] see chart pg 115 Ask, Advise, Assess, Assist & Arrange

- ♦ P L Tobacco – avoid maternal & second-hand smoke during pregnancy as it ↑ risk fetal/infant morbidity & mortality. Smoking during lactation ↓ milk production & ↑ risk of infant colic.
- ♦ **Smoking cessation**: 1st line – counseling; success rates with high vs low intensity were non-significant. Advise at minimum.
  - 2nd line - P L nicotine replacement (NRT). {1 RCT; no effect on cessation or birth wt.[Berlin]} ↓Exposure: gum, lozenge, limit patch to 16 hrs/d. ↑metabolism of nicotine in 3rd trimester – may require ↑ in NRT doses.
  - Other options: P L nortriptyline or P L bupropion may be preferred in depressed patients; P L varenicline

Contraception [40] see charts pg 86-88

Pre-pregnancy:

⇨After stopping hormonal contraception, fertility is restored in:

- 1-3 months with combined oral contraceptives
- 9 months (range 4-11) with medroxyprogesterone DEPO-PROVERA. Rate of conception after the last injection is 50% at 10 months, & 90% at 24 months.

⇨Intrauterine device (IUD) MIRENA, NOVA-T does not ↑ risk of infertility

Pregnancy: IUD does not ↑ risk of ectopic pregnancy. However, if conception occurs while an IUD is inserted, assess for an ectopic pregnancy.

Postpartum/Lactation:

⇨Lactational amenorrhea method is 98% effective for contraception **IF** 1) menses has not returned, 2) almost exclusive breastfeeding, 3) baby <6months, & 4) time between feedings are ≤4h during the day & ≤6h at night.

⇨ Progestin-only products often preferred postpartum as there is no impact on lactation, and thought to have less VTE risk versus combined oral contraceptives. The oral contraceptive pill MICRONOR (taken every day, no pill-free interval), injection DEPO-PROVERA & implant IMPLANON (US only) can be started immediately after delivery as a contraceptive, ±breastfeeding. Wait 6 weeks postpartum before inserting an IUD MIRENA; may be inserted immediately if cesarean.

⇨ There is insufficient evidence to determine if combined oral contraceptives impact the quality & quantity of breast milk. Assess on an individual patient basis.

⇨ L Avoid combined oral contraceptive pills during the first 3 weeks postpartum. Avoid during the first 6 weeks **IF** at risk of venous thromboembolism (VTE) age≥35, smoker, thrombophilia, immobility, previous VTE, preeclampsia, recent cesarean, stillbirth, preterm birth, BMI ≥30kg/m^2; postpartum hemorrhage may increase risk of asymptomatic VTE.

Galactagogues for Breastfeeding [41]

⇨Medications should never replace support, education & assessment of breastfeeding technique.

⇨Frequent feeds & complete milk removal at regular intervals will increase milk production.

⇨There is insufficient evidence to recommend the use of pharmacologic or herbal galactagogues. Trials investigating domperidone & metoclopramide were primarily of poor quality, small numbers ≤50 patients, short duration ≤4 weeks, & had high-drop out rates.

⇨There is no evidence that ↑ prolactin levels equate to ↑ milk production.

⇨Anecdotally, medications may be of some benefit in adoptive mothers who wish to breastfeed, to re-establish breastfeeding after weaning, or mothers of babies in neonatal intensive care. Refer other mothers experiencing difficulties with breastfeeding to a Lactation Consultant before trialing drug therapy (e.g. LaLeche League www.lllc.ca).

⇨Domperidone MOTILIUM 10mg po TID [max 60mg/day]. There is no evidence that doses >30mg/day are more effective, & risk of side effects ↑ (e.g. QT prolongation). May take up to 4 days for improvement. Trial for 6 weeks. Taper by ↓ 1 pill q4-7 days. Preferred over metoclopramide due to ↓ side effects.

⇨Metoclopramide MAXERAN 10mg po TID-QID x 7-14 days, then taper by ↓ 1 pill q5-7 days.

⇨Herbals: even less data than prescription galactagogues. Several herbal galactagogues are not recommended during breastfeeding (e.g. fenugreek, blessed thistle, fennel, caraway, Goat's rue).

⇨Beer: the barley component of beer may ↑ prolactin, but there is insufficient evidence to recommend & alcohol may ↓ milk production.

⇨Bromocriptine PARLODEL is not recommended for the suppression of lactation due to an ↑ risk of stroke and myocardial infarctions when used postpartum.

Polycystic Ovary Syndrome (PCOS) [42] Up to 74% of PCOS females experience infertility

⇨↑ risk of pregnancy complications: gestational diabetes, HTN, preeclampsia, and neural tube defects if obese & pre-existing DM. Use folic acid if trying to conceive, or if on metformin & sexually active (see Folic Acid above for dosing).

⇨1st line: Weight loss via diet & exercise (if obese); a ↓ in body weight of 5-10% can restore ovulation.

⇨**Clomiphene CLOMID: 1st line for drug-induced ovulation**

- Dose: 50mg po daily x 5 days (start on day 5 of menses). If pregnancy does not occur, repeat. If ovulation occurs, continue at same dose. If ovulation does not occur, ↑ to 100mg /day. Max 250mg/day ↑ risk of side effects.
- Conception rates: 50% on 50mg, 75% on 100mg & 85% on 150mg. Consider ineffective if conception does not occur within 3 cycles of maximum dose. Limit to 12 cycles (↑ risk of ovarian tumours).
- Precautions: ↑ rate of twins (~8%) and triplets (0.3%), hot flashes (>10%), visual blurring/after images (≤2%).

⇨ **Metformin: 2nd line as adjuvant (off-label indication)**

- Versus placebo, metformin ↑ ovulation rates but non-significant for pregnancy rates. However, anecdotally, some PCOS patients do become pregnant shortly after starting metformin.
- Consider adding it to clomiphene in clomiphene-resistant patients who are older & have visceral obesity.
- Dose: start 250-500mg po daily with food. Titrate up q2weeks to 750-850mg po TID as tolerated.
- Lack of evidence to support continued metformin use during pregnancy; however, likely safe.

⇨**Other options**: referral for gonadotropin injections, ovarian drilling (laparoscopic procedure in which the ovary is punctured leading to less testosterone production), in vitro fertilization.

Hypertension in Pregnancy [7]

- Types of Hypertension during Pregnancy:
  - **Pre-existing HTN**: HTN diagnosed prior to conception or before 20 weeks gestation
  - **Pre-existing HTN + Preeclampsia**: occurs after 20 weeks gestation with 1 or more of the following:
    - resistant HTN (≥3 antihypertensive drugs), or new or worsening proteinuria, or ≥1 adverse condition* or ≥1 severe complication** SOGC 2014
  - **Gestational HTN:** HTN diagnosed ≥20 weeks
    - **Gestational HTN + Preeclampsia:** new onset proteinuria, or ≥1 adverse condition*, or ≥1 severe complication** SOGC 2014
  - **Blood pressure targets:** no comorbidities 130-155/80-105mmHg, with comorbidities (diabetes, renal disease, cerebrovascular disease) 130-139/80-89mmHg. May also consider:
    - Pre-existing HTN: consider SBP 130-140mmHg
    - Gestational HTN: consider SBP 140-150mmHg

*** Table 1: Adverse Conditions Pertaining to Preeclampsia** SOGC 2014

Maternal Symptoms: Persistent/new/unusual headache, visual disturbances, persistent abdominal or right upper quadrant pain, ↓ oxygen sats, severe nausea or vomiting, chest pain or dyspnea.

Maternal Signs of End-Organ Damage: Eclampsia, severe hypertension, pulmonary edema, suspected placental abruption, seizures (also see below).

Abnormal Maternal Laboratory Tests: ↑ SCr, INR, WBC, AST, ALT, or LDH with symptoms; ↓ platelets or albumin

**** Table 2: Severe Complications (warrants delivery)** SOGC 2014

Maternal symptoms: eclampsia; stroke, TIA, or MI; uncontrolled HTN (>12hrs while using ≥3 antihypertensive drugs); low oxygen sats (<90%); pulmonary edema; ↓ platelets (<50 x 10^9/L; ↑ INR or transfusion; ↑ SCr (>150 µM) or new dialysis

Fetal Morbidity or mortality

- Defining the type of HTN is important for non-BP management & follow-up screening during pregnancy & postpartum. However, blood pressure targets are similar and antihypertensive therapy is the same regardless of type.

- Supplements for the prevention of preeclampsia:
  - Fish oils: supplements (e.g. evening primrose) have not been shown to ↓ risk of preeclampsia.
  - P Watch mercury levels in dietary fish (see Extras). Evening primrose may delay rupture of membranes, augment oxytocin, etc.
  - Vitamin E & C: does not ↓ risk of preeclampsia; may ↑ risk of GestHTN and premature rupture of
  - P membranes.

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TSH Trimester Specific Targets for Hypothyroidism

The 2011 American Thyroid Association (ATA) Guideline recommends a first trimester TSH target of <2.5mIU/L, and second & third trimester TSH targets of <3mIU/L.[12] These goals are often attainable with an increase in the levothyroxine dose, especially when the targets are met in early pregnancy. However, in clinical practice, there may be the rare occasion when it is difficult to reach the second & third trimester TSH target of <3mIU/L. This may occur when the levothyroxine dose required to achieve a TSH <3mIU/L results in symptoms of hyperthyroidism (e.g. maternal palpitations, failure to gain weight in either mother and/or fetus, or the development of maternal mood disorders). It may also result when pregnant patients are non-compliant with their levothyroxine as they are hesitant to take medications or increase their doses during pregnancy. In these rare situations, if a second and third trimester TSH <3mIU/L cannot be tolerated or attained, a TSH of <3.5mIU/L may be reasonable.

In 2012, the ATA & American Association of Clinical Endocrinologists released guidelines suggestion the following TSH targets: first trimester ≤ 2.5mIU/L, second trimester ≤ 3mIU/L & third trimester ≤ 3.5mIU/L.[12]

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conclusions. In view of the limited evidence base, further randomised trials are required to determine the most effective and safe interventions for asthma in pregnancy. Future trials must be sufficiently powered, and well-designed, to allow differences in important outcomes for mothers and babies to be detected. The impact on health services requires evaluation. Any further trials assessing pharmacological interventions should assess novel agents or those used in current practice. Encouragingly, at least five trials have been identified as planned or underway.

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However, for some women VPA is the most effective drug at controlling seizures. Informed treatment decisions require detailed counselling about these risks at treatment initiation and at pre-conceptual counselling. We have insufficient data about newer AEDs, some of which are commonly prescribed, and further research is required. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk.

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http://nccam.nih.gov/news/19972000/121100/qa.htm (InfoPOEMs: Glucosamine HCl and chondroitin provides modest if any symptomatic benefit for patients with mild osteoarthritis of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (LOE = 1b))
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Herbal Drug Interactions: Online Extras 💻

Useful Herbal Websites

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www.ars-grin.gov/duke
www.quackwatch.com
www.ncahf.org
www.herbmed.org
www.consumerlab.com
www.naturaldatabase.com
www.mskcc.org/aboutherbs
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www.herbs.org medlineplus.gov/druginfo/herb_All.html
Linus Pauling Institute lpi.oregonstate.edu;
National Center for Complementary and Integrative Health (NIH) nccih.nih.gov
Mayo Clinic www.mayoclinic.org/drugs-supplements

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Alfalfa: Patients may ask about a widely reported recall of Caldwell Fresh Foods alfalfa sprouts. The company has recalled all of its raw sprouts (marketed under the brands Caldwell Fresh Foods, California Exotics, and Nature's Choice) because they may be contaminated with a strain of **salmonella**. Since March, at least 22 cases of salmonella infections in 10 states have been linked to the sprouts, according to the FDA. California has 11 confirmed cases; the 9 other affected states are Arizona, Colorado, Idaho, Illinois, Missouri, New Mexico, Nevada, Oregon, & Wisconsin. Six people have been hospitalized; no deaths have been reported. FDA news release (Free) Manufacturer press release (Free)

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Australian Therapeutic Goods May/15: **Maxman Cialis** tablets contains undeclared sildenafil.

Australian Therapeutic Goods May/15: **Top Gun for Men** tablets contain undeclared tadalafil; **Power 1 tablets, Dr. Ming's Chinese capsule & Maxman Domina Tu Pareja** tablets contains undeclared sildenafil.

Australain Therapeutic Good Administration July/15 **Enhanced Vegetal Vigra capsules, Gold Viagra capsules, Majestic Lovezone tablets, Niu Mo Wang 'Bull Monster' tablets, North West Wolf capsules, Strong Horses capsules, Strong-SX capsules & USA Gold Ant** capsules contains sildenafil. **Gold Viagra** tablets (packaged as "**Kangaroo Sexually Invigorating Essence**") contains undeclared sildenafiland tadalafil.
Australain Therapeutic Good Administration:**OMG Slim** capsules contains Undeclaredsibutramine and orlistat.
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DMAA: July 25/12- Manufacturers of some sports supplements are falsely claiming a compound known as DMAA is a natural substance derived from geraniums, researchers say. Instead, research shows that DMAA is synthetic, consisting of four compounds called stereoisomers. DMAA (1,3-dimethylamylamine) is a stimulant found in some nutritional and sport supplements.

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Elderberry extract has long been used as a folk remedy for cold and influenza symptoms. A recent randomized trial provides evidence for its efficacy (level 2 [mid-level] evidence). During the spring 2009 influenza season in China, 64 patients with ≥ 3 influenza-like symptoms (fever, headache, myalgias, coughing, nasal mucus discharge, nasal congestion) were randomized within 24 hours of symptom onset to elderberry extract lozenge (175 mg) vs. placebo orally 4 times daily for 2 days. After 48 hours, the rate of complete symptom relief was higher in the elderberry group (28% vs. 0%, no p value reported), with at least some symptom relief (only 0-2 mild symptoms remaining) reported in 88% vs. 16% for placebo (no p value reported). Elderberry extract was associated with significantly improved symptom severity scores for headache, nasal congestion, muscle aches, and fever at 24 hours ($p < 0.001$) and for all symptoms at 48 hours ($p < 0.001$). The elderberry group had higher symptom scores at baseline, however, suggesting that the groups may have been at different stages in their overall illness course despite randomization within 24 hours (Online J Pharmacol Pharmacokin 2009;5:32).

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

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

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

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

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

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

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

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

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

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

FDA Nov/08 Balanced Health Products, Inc. announced a recall of **STARCAPS** due to the presence of an undeclared drug ingredient, Bumetanide. Bumetanide is a diuretic indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease including nephrotic syndrome.

FDA Nov/08 Fashion Sanctuary announced a recall of **Zhen De Shou Fat Loss** Capsules because FDA analysis found the product to contain undeclared sibutramine, an FDA approved drug used as an appetite suppressant for weight loss.

FDA Dec/08 alerted consumers not to purchase or consume more than **25 different products** marketed for weight loss because they contain undeclared, active pharmaceutical ingredients that may put consumers' health at risk. The undeclared active pharmaceutical ingredients in some of these products include sibutramine (a controlled substance), rimonabant (a drug not approved for marketing in the USA), phenytoin (an anti-seizure medication), and phenolphthalein (a solution used in chemical experiments and a suspected cancer causing agent). The weight loss products, some of which are marked as "dietary supplements," are promoted and sold on various web sites and in some retail stores. FDA advises consumers who use the products to stop taking them and consult their healthcare professional immediately as the health risks posed by these products can be serious (for example, high blood pressure, seizures, tachycardia, palpitations, heart attack or stroke). FDA also encourages consumers to seek guidance from healthcare professional before purchasing weight loss products. See the FDA News Release for a listing of the names of the 25 referenced products. Read the MedWatch 2008 safety summary, including links to the News Release and Questions and Answers, at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Weight

FDA Jan/09 notified consumers not to take **Venom HYPERDRIVE 3.0**, a product sold as a dietary supplement but containing sibutramine.

FDA Apr/09: **ABC Beauty Supply** & FDA notified consumers and healthcare professionals of a recall of 34 dietary supplement products. FDA lab analyses identified undeclared **sibutramine**, an FDA- approved drug, used as an appetite suppressant for weight loss. http://www.fda.gov/oc/po/firmrecalls/universalabc04_09.html

FDA Apr/09 Nature & Health Co. and FDA notified healthcare professionals of a recall of a supplement product, **Libimax**. FDA analysis found the product contains tadalafil

FDA May/09 warned consumers to immediately stop using **Hydroxycut** products by Iovate Health Sciences, Inc. Hydroxycut products are associated with a number of serious **liver injuries**. Hydroxycut products are dietary supplements that are marketed for weight-loss, as fat burners, as energy-enhancers, as low carb diet aids, and for water loss under the **Iovate and MuscleTech brand** names. FDA has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, an indicator of potential liver injury, to liver damage requiring liver transplant. One death due to liver failure has been reported to FDA. Other health problems reported include seizures; cardiovascular disorders; and rhabdomyolysis, a type of muscle damage that can lead to other serious health problems such as kidney failure.

FDA June/09 notified consumers and healthcare professionals to discontinue use of three **Zicam Nasal Gel/Nasal Swab** products sold over-the-counter as cold remedies because they are associated with the loss of sense of smell that may be long-lasting or permanent.

FDA July/09 and Haloteco notified healthcare professionals and consumers of a nationwide voluntary recall of Libipower Plus. Lab analysis of **Libipower Plus** samples were found to contain undeclared Tadalalafil.

FDA July/09 notified healthcare professionals that four weight loss dietary supplements sold and marketed by the firm (**Slimbionic, One Weight Loss Pill, SlimDemand Capsules, Botanical Weight Loss**) contain sibutramine.

FDA Aug/09 not to use body-building products marketed as containing steroids or steroid-like substances. The affected products are TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, and TT-40-Xtreme..

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

FDA Nov/09 & GMP Herbal Products notified consumers and healthcare professionals of a recall of **Pai You Guo**, a weight loss dietary supplement, due to the presence sibutramine & phenolphthalein.

FDA Nov/09 & RockHard Laboratories notified consumers that **RockHard Weekend**, a product sold as a dietary supplement, contains sulfoaildenafil, an analogue of sildenafil.

FDA Nov/09 & IDS Sports notified consumers that five of the IDS's dietary supplement products (**Bromodrol, Dual Action Grow Tabs, Grow Tabs, Mass Tabs, and Ripped Tabs TR**) contain the following undeclared substances, which FDA considers to be steroids: “Madol,” “Turinabol,” “Superdrol,” &/or “Androstenedione.”

FDA Dec/09 for **S-DROL**: a voluntary recall by the manufacturer of one lot (lot# 810481, expiry date 01/2012) of S-DROL after FDA testing found it to contain undeclared desoxymethyltestosterone.

FDA Dec/09 warned consumers to stop using bodybuilding products manufactured by American Cellular Labs after they were found to contain unauthorized synthetic steroids in **TREN-Xtreme, MASS Xtreme, ESTRO Xtreme, AH-89-Xtreme, HMG Xtreme, MMA-3 Xtreme, VNS-9 Xtreme, TT-40-Xtreme.**

FDA Dec/09 warned that **Atlas Operations, Inc**. notified consumers of a nationwide recall of the company's dietary supplements for sexual enhancement. These products are sold as dietary supplements throughout the USA. FDA lab analyses found that the products tested from certain batches contain Sulfoaildenafil.

FDA Dec/09 The Texas Department of State Health Services and FDA notified healthcare professionals and consumers, especially pregnant or breastfeeding women, to avoid consuming a product called “**Nzu**”, taken as a traditional remedy for morning sickness,because of the potential health risks from high levels of lead and arsenic, noted on laboratory analysis by Texas DSHS. Nzu, which is sold at African specialty stores is also called Calabash clay, Calabar stone, Mabele, Argile and La Craie. It generally resembles balls of clay or mud and is usually sold in small plastic bags with a handwritten label identifying it as “Nzu” or “Salted Nzu.”

FDA Jan/10 & **MuscleMaster(dot)com**, Inc. notified consumers and healthcare professionals of the voluntary nationwide recall of all lots and expiration dates of the seventeen

dietary supplements listed in the firm press release, sold between June 1, 2009 and November 17, 2009. FDA informed MuscleMaster(dot)com that it believes that the recalled products contain ingredients that are **steroids**.

FDA Jan/10 notified consumers and healthcare professionals about a counterfeit and potentially harmful version of **Alli 60 mg capsules** (120 count refill kit). The **counterfeit** version contained the controlled substance sibutramine and did not contain orlistat, the active ingredient.

FDA Mar/10 & Natural Wellness notified consumers that **MasXtreme**, a product sold as a dietary supplement contains aildenafil close in structure to sildenafil and is expected to possess a similar pharmacological and adverse event profile as well as the drug phentolamine which is an alpha-adrenergic blocker.

FDA Apr/10 & Kanec USA notified healthcare professionals of a nationwide recall of **Stud Capsule For Men** [Lot #060607-01/060108-01, Exp 6-2013], after being informed by FDA that laboratory analysis of a sample found the product to be adulterated with sildenafil, an FDA approved drug.

FDA May/10 notified healthcare professionals, their patients, and consumers not to consume **Vita Breath**, a dietary supplement manufactured by American Herbal Lab and marketed at health fairs and on the Internet, because the product may contain hazardous levels of lead.

FDA June/10 **Magic Power Coffee**: Product marketed as a dietary supplement for sexual enhancement contains the drug ingredient hydroxythiohomosildenafil.

FDA July/10 analysis of **Que She** found that it contains: fenfluramine – a stimulant drug withdrawn from the U.S. market in 1997 after studies demonstrated that it caused serious heart valve damage, propranolol – a prescription beta blocker drug that can pose a risk to people with bronchial asthma and certain heart conditions, sibutramine – a controlled substance and prescription weight loss drug, sibutramine was the subject of a recent study whose preliminary findings showed an association between sibutramine use and increased risk of heart attack and stroke in patients who have a history of heart disease, & ephedrine – a stimulant drug that is legally marketed over-the-counter for temporary relief of asthma but can pose a risk to people with certain cardiovascular conditions.

FDA Aug/10 lab analysis of **Solo Slim** was found to contain the undeclared drug ingredient Didesmethyl Sibutramine.

FDA Aug/10 lab analysis of **Revivexxx Extra Strength** was found to contain undeclared tadalafil.

FDA Aug/10 notified Novacare LLC that certain products appear to contain sulfoaildenafil: **Stiff Nights, Aziffa, Size Matters, Erex, Mojo, Hard Drive, Eyeful, Red Magic, Straight Up, Zotrex, Monster Excyte, WOW, Xaitrex, Verect, Prolatis, Xytamax, Maxyte, Libidinal, OMG, OMG45, and Zilex (with Golden Spear) summers**.

FDA July/10 lab analysis of **Slim-30** Herb Supplement distributed by the company was found to contain undeclared N-Desmethyl Sibutramine and traces of Sibutramine.

FDA July/10 & Good Health, Inc. is conducting a voluntary recall after FDA lab analyses found that the product tested from certain batches of **Vialipro** contain Sulfoaildenafil.

FDA July/10 lab analysis of this herb supplement, **Joyful Slim** Herb Supplement, was found to contain the undeclared drug, desmethyl sibutramine.

FDA July/10 warned consumers not to consume or use **Miracle Mineral Solution**, an oral liquid solution also known as "Miracle Mineral Supplement" or "**MMS**." The product, when used as directed, produces an industrial bleach.

FDA July/10 notified consumers that lab analysis of lots of ejaculoid **XXTREME** and **stimuloid II** found that the products, sold as dietary supplements, contain sulfoaildenafil FDA Aug/10 had Lab analysis of **Mr. Magic** to contain hydroxythiohomosildenafil and sulfoaildenafil.

FDA Aug/10 analyzed **TimeOut** and determined that it contains hydroxythiohomosildenafil.

FDA Sep/10: Products marketed as dietary supplements contain **aromatase inhibitors**, commonly known as "ATD." Adverse events associated with the use of aromatase inhibitors could include the following: decreased rate of bone maturation and growth, decreased sperm production, infertility, aggressive behavior, adrenal insufficiency, kidney failure, and liver dysfunction. Advanced Muscle Science (Arom-X, Arom-X UTT, Arom-XL, 4-AD, and Decavol), ArimaDex, Clomed, Off Cycle II Hardcore, iForce – Reversitol.

FDA Oct/10 advised consumers to avoid "**chelation**" products that are marketed over-the-counter (OTC) to prevent or treat diseases. There are serious safety issues associated with chelation products. Depending on the condition, when relying on unproven OTC chelation products to treat serious conditions, patients may delay seeking effective medical care. Even when used under medical supervision, these products can cause serious harm, including dehydration, kidney failure, and death.

FDA Nov/10 ISSUE: Lab analysis has found **Duro Extend** Capsules for Men to contain Sulfoaidenafil, an analogue of Sildenafil.

FDA Dec/10 warned consumers not to use **Man Up Now** capsules, marketed as a dietary supplement for sexual enhancement, because FDA analysis determined that the product contains sulfoaildenafil.

FDA Dec/10 notified the public that testing determined that **RockHard Weekend** Lot Numbers 100159 and 100260 sold as blister packs, 3ct bottles and 8ct bottles & **Pandora** Lot Numbers 100378 sold as blister packs & **Passion Coffee** contain an analogue of sildenafil.

FDA Dec/10 has received multiple reports of adverse events associated with the use of **Fruta Planta**, including several cardiac events and one death. FDA laboratory analysis confirmed that Fruta Planta contains sibutramine.

FDA Jan/11 laboratory analysis confirmed that **Celerite Slimming Capsules** contain sibutramine

FDA Mar/11 lab analysis of **Svelte 30** orange & gray capsules determined that the product contains Sibutramine.

FDA Mar/11 notified Biotab Nutraceuticals, Inc. that two lots of counterfeit product purporting to be **Extenze** contain undeclared drug ingredients. Specifically, lot 0709241 contains tadalafil and sildenafil, and lot 0509075 contains tadalafil and sibutramine.

FDA Mar/11 laboratory analysis confirmed that **Black Ant** contains sildenafil.

FDA Mar/11 **:** USA Far Ocean Group, Inc. issues voluntary nationwide recall of **U-Prosta**, a product marketed as a dietary supplement that contains undeclared terazosin.

FDA Mar/11 ISSUE: Tested samples of **Soladek** contained levels of vitamin A and vitamin D that were many times the recommended daily allowances for these vitamins.

FDA Mar/11 laboratory analyses of **Celerite Slimming Tea**: Recall - were found to contain undeclared Sibutramine.

FDA Mar/11 ISSUE: FDA lab analysis of **X-Hero** found the product contains sulfosildenafil, the analogue of the active ingredient of an FDA-approved drug. In addition, FDA analysis of **Male Enhancer** sample found the product contains tadalafil.

FDA Apr/11 Lab analyses of **Best Enhancer** found that the product contain Sulfoaildenafil.

FDA Apr/11 "**U-Prosta Natural support for prostate health**" is being voluntarily recalled in Canada by Sunnylife International Inc. after the U.S. Food and Drug Administration (FDA) found the product contains undeclared terazosin.

FDA May/11 **Regenerect**: Recall - Undeclared Drug Ingredient of lab confirmed the presence of Sulfoaildenafil.

FDA May/11 laboratory analysis confirmed that "**Slim Xtreme Herbal Slimming Capsule**" contains sibutramine.

FDA June/11 lab analyses found Via **Xtreme Ultimate Sexual Enhancer Dietary** Supplement for Men to contain sulfoaildenafil methanesulfonate.

FDA June/11 Nature Relief and FDA notified the public of a recall of **Nature Relief Instant Wart and Mole Remover**. FDA has advised that the active ingredient, calcium oxide, can cause severe burns of the skin, particularly to areas of thin or sensitive skin, such as the face, area around the eyes, and genitalia.

FDA July/11 is advising consumers not to purchase or use "**Slim Forte Slimming Capsules**," "**Slim Forte Slimming Coffee**," and "**Botanical Slimming Soft Gel & Slim Forte Double Power Slimming Capsules.** FDA laboratory analysis confirmed that these products contain sibutramine.

FDA Oct/11 notified the manufacturer that lab analyses found that the product; **Uprizing 2.0** , sold as a testosterone booster, contains superdrol, a synthetic steroid, making it an unapproved new drug.

FDA Nov/11 lab analysis for Lot 10090571 found **Virility Max** to contain sulfoaildenafil.

FDA Dec/11 Eclectic Institute is voluntarily recalling specific lots of its freeze-dried capsules containing **Gotu Kola** (Centella asiatica) and **Bladderwrack** (Fucus vesiculosus) capsules because of potential Salmonella contamination.

FDA Feb/12 Healthy People Co. notified the public of a recall of the company's dietary supplements sold under the brand names Healthy People Co. FDA lab analysis confirmed the presence of Sibutramine and Tadalafil, making these products unapproved new drugs. (Mince Belle Dietary Supplement, PERFECT Men Dietary Supplement , EVERLAX Dietary Supplement, EVER Slim Dietary Supplement, Herbal Drink Acai-man Mangosteen Dietary Supplement, EVER SLIM Shake Mix Dietary Supplement)

FDA Feb/12 Regeneca, Inc. notifed the public of a nationwide recall of **RegenArouse**, Lot Number 130100. FDA lab analysis confirmed the presence of Tadalafil.

FDA Feb/12 is advising consumers not to purchase or use "**Hard Ten Days**," & "**Man King**" a product for sexual enhancement sold on various websites. FDA laboratory analysis confirmed that "Hard Ten Days" contains sildenafil

FDA Feb/12 is advising consumers not to purchase or use "**Japan Weight Loss Blue**," a product for weight loss sold on various websites, laboratory analysis confirmed that "Japan Weight Loss Blue" contains sibutramine, analogs of sibutramine, and ephedrine alkaloids.

FDA Mar/12 notified healthcare professionals and warned consumers not to use skin creams, beauty and antiseptic soaps, or lotions that might contain **mercury**. The products are marketed as **skin lighteners and anti-aging** treatments that remove age spots, freckles, blemishes and wrinkles. Adolescents also may use these products as acne treatments.

FDA Apr/12 laboratory analysis confirmed that "**Japan Rapid Weight Loss Diet Pills Yellow**" contains sibutramine and phenolphthalein.

FDA Apr/12 laboratory analysis confirmed that "**France T253**" contains sildenafil.

FDA Apr/12 is advising consumers not to purchase or use "**X-Rock**," a product for sexual enhancement manufactured by CRM Laboratories and sold on various websites, including www.xrockme.com. FDA laboratory analysis confirmed that "X-Rock" contains sildenafil and hydroxythiohomosildenafil.

FDA Apr/12 laboratory analysis confirmed that "**Instant Hard Rod**" contains aminotadalafil. FDA laboratory analysis confirmed that "**ZenMaxx**" contains aminotadalafil. FDA laboratory analysis confirmed that "**RigiRx Plus**" contains aminotadalafil.

FDA May/12 is advising consumers not to purchase or use "**VMaxx Rx**," a product for sexual enhancement sold on various websites, including www.vmaxxrx.com. FDA laboratory analysis confirmed that "VMaxx Rx" contains the undeclared ingredient sulfoaildenafil. FDA is also advising consumers not to purchase or use "**Boost — Ultra Sexual Enhancement Formula**." This product is promoted and sold on various websites, including www.boostultra.biz. FDA laboratory analysis confirmed that "Boost—Ultra Sexual Enhancement Formula" contains sildenafil. FDA is also advising consumers not to purchase or use "**Firminite**," a product for sexual enhancement sold on various websites, including **www.firminite.com.** FDA laboratory analysis confirmed that "Firminite" contains tadalafil.

FDA May/12 West Coast Nutritionals, Ltd. is conducting a recall of all lots of their dietary supplements **Firminite, Extra Strength Instant Hot Rod, and Libidron** to the consumer level. An FDA lab analysis of Firminite was found to contain undeclared Tadalafil.

FDA May/12 is advising consumers not to purchase or use "**EreXite**," a product for sexual enhancement sold on various websites, including www.amazon.com. FDA laboratory analysis confirmed that "EreXite" contains tadalafil.

FDA June/12 cautioned late last week against using **Reumofan Plus**, a dietary supplement marketed as a "natural" pain reliever for arthritis, osteoporosis, and other conditions. The drug, which is made in Mexico but available online, contains unlabeled and potentially harmful pharmaceutical ingredients: diclofenac, methocarbamol & sometimes dexamethasone. (Dec/12 FDA: Reumofan Plus is being relabeled and sold under the name "**WOW**.")

FDA June/12 Botanical Laboratories Inc. and FDA notified consumers and healthcare professionals of a recall of **Wellesse Digestive 3 in 1 Health liquid dietary supplement**. A supplier of one of the ingredients indicated the ingredient has the potential to be contaminated with Salmonella.

FDA Aug/12 CRM Laboratories is conducting a consumer/user level recall of all X-ROCK 3 Day Pill For Men and Z-ROCK products sold between October, 2011 and April, 2012. Finished product of **X-ROCK 3 Day Pill for Men and Z-ROCK** was tested and found to contain an analogue of an ingredient in an FDA-approved drug. Analytical tests conducted by the FDA concluded that the products contained sildenafil and hydroxythiohomosildenafil.

FDA Aug/12 is issuing an updated alert that **Reumofan Plus and Reumofan Plus Premium** contain undeclared active ingredients found in prescription drugs that should be used only under the supervision of a health care professional. It contains Diclofenac Sodium and Methocarbamol.

FDA Sep/12 Brand New Energy and FDA notified the public of a recall of all lot codes of **EphBurn 25**. One lot of EphBurn 25 sampled by the FDA was found to contain ephedrine alkaloids, making it an unapproved drug.

FDA Sep/12: Body Basics Inc. announced that it is conducting a voluntary nationwide recall of **ACTRA-Sx 500 Dietary Supplement Capsules**, Lot 008-A, Expiration December 2013. The Company, through independent lab analysis, has confirmed the presence of Sildenafil Citrate.

FDA Sep/12 is warning consumers not to use **Intestinomicina**, a drug product manufactured in El Salvador, because it contains the prescription drug ingredient, Chloramphenicol.

FDA Sep/12 Evol Nutrition Associates, Inc./Red Dawn ("Evol Nutrition") notified the public of a nationwide recall of all lots of two dietary supplement products distributed by the company under the names **Mojo Nights and Mojo Nights for Her** to the consumer level. Testing by the FDA revealed the presence of undeclared tadalafil and sildenafil in Mojo Nights (Evol Nutrition is also recalling Mojo Nights for Her).

FDA Oct/12 is advising consumers not to purchase or use "**Ultimate Formula Bee Pollen Capsules (Ultimate Formula)**," or "**Zi Xiu Tang Bee Pollen Capsules**," also referred to as "**Zi Xiu Tang Beauty, Face & Figure Capsule**," a product promoted and sold for weight loss because they contain sibutramine.

FDA Dec/12: **Libigrow, Libigrow XXXtreme, Blue Diamond, Blue Diamond Platinum, Mojo Nights, Mojo Nights Supreme, And Casanova**: Recall - Undeclared Ingredients Sulfoaildenafil and Thioaildenafil.

FDA Dec/12 is advising consumers not to purchase or use "**SLIMDIA Revolution**," a product promoted and sold for weight loss on various websites, including www.pinkfatty.com, and in some retail stores since it contains Sibutramine.

FDA Jan/13 is advising consumers not to purchase or use "**MAXILOSS** Weight Advanced," a product promoted and sold for weight loss on various websites, includingwww.dreamlifeweightloss.com, and in some retail stores since it contains sibutramine.

FDA Jan/13 Freedom Trading is conducting a voluntary consumer recall of a product sold as a dietary supplement under the brand name of **Super Power**. This product was sold between August 2012 and January 2013 nationwide & the products contained trace amounts of sildenafil.

FDA Feb/13 Olaax Corp announced a nationwide recall of the company's dietary supplement sold under the brand name **Maxiloss Weight Advanced Softgels** to the user level, because FDA testing found the Maxiloss Weight Advanced product to contain Sibutramine.

FDA Mar/13 Green Planet, Inc. notified the public of a recall of its dietary supplement product **Night Bullet**. Analytical tests conducted by the FDA found that the product contains trace amounts of Sulfohydroxyhomosildenafil and Aminotadalafil, which are analogues of sildenafil.

FDA Apr/13 laboratory analysis confirmed that "**Ninja Mojo"& "Love Rider**" contains tadalafil. FDA also confirmed that "**AFFIRM XL**" contains the undeclared ingredient sulfoaildenafil.

FDA Apr/13 Consumer Concepts, Inc. notified the public of a consumer/user level recall of all **ROCK-It MAN** Male Enhancement Capsules sold between October, 2012 and April, 2013. Analytical tests conducted by the FDA concluded that the product contained hydroxythiohomosildenafil.

FDA Apr/13 **Affirm XL**, Inc. is conducting a voluntary recall to the consumer level after FDA lab analysis testing found the product to contain an analogue of sildenafil.

FDA Apr/13 says it wants to make sure that supplements containing the **stimulant dimethylamylamine (DMAA)** are not distributed or sold in the U.S. The agency's action comes after reports of illness and death associated with DMAA-containing supplements. It has warned companies that use of DMAA in dietary supplements is illegal. One company, USPLabs, has defended its use. The company makes "**Jack3d**," which contains DMAA and is described as a "pre-exercise CNS-carnosine-ATP augmentor." It's sold on the Web.

FDA Apr/13 laboratory analysis confirmed that "**Sex Plus**" contains undeclared sildenafil, tadalafil, sulfosildenafil and dimethylacetildenafil. FDA laboratory analysis confirmed that "**Zoom-Zooma-Zoom**" contains sildenafil, the active ingredient in the FDA-approved prescription drug Viagra.

FDA May/13 American Lifestyle is announcing that it is conducting a voluntary recall of all lots of **Vicerex** UPC 893490820087 and **Black Ant** UPC 4026666142546. Laboratory analysis conducted by the FDA has determined the Vicerex product contains undeclared tadalafil and the Black Ant product contains undeclared sildenafil.

FDA May/13 is advising consumers not to purchase or use "**Bullet Proof**," a product promoted and sold for sexual enhancement on various websites and in some retail stores. FDA laboratory analysis confirmed that "Bullet Proof" contains tadalafil. Plus Chang Kwung announced today that it is conducting a voluntary nationwide recall of the company's dietary supplements sold under the brand name **Lightning Rod** (500 mg per capsule packaged in 3-count, UPC 6 89076 20257 2 and 12-count bottles, UPC 6 89076 20297 8), because FDA testing found the Lightning Rod Capsules to contain an analogue of Sildenafil.

FDA May/13: BeaMonstar Products notified the public that it is recalling its **SexVoltz, Velextra, and Amerect** capsules. Laboratory analysis conducted by the FDA on SexVoltz and Velextra has determined these products contain undeclared tadalafil.

FDA Jun/13 FDA laboratory analysis confirmed that "**Bethel 30**", & "**XIYOUJI QINGZHI CAPSULE**" & **JaDera** contains sibutramine. .

FDA Jun/13 laboratory analysis confirmed that "**Reload**" , "**Cave Diver**" , "**Super Cheetah**", "**Nights to Remember**" , & "**X Zen Platinum**", contains sildenafil.

FDA Jun/13 A sample of **Extreme Body Slim, Fat Zero, Fruit & Plant Slimming, & Paiyouji Plus** all contains silbutramine.

FDA Jun/13 A sample of **Royal Dragon Herbal Tonic Balls** contains vardenafil.

FDA Jun/13 Beta Labs has recalled certain lots of **Oxyphen, Phentalene, Phen FX, and Red Vipers** because they contain 1,3 dimethylamylamine (DMAA), the FDA announced over the weekend. The products are used as pre-workout stimulants and for weight loss, but the agency has previously warned that DMAA can be dangerous: it can elevate blood pressure and lead to cardiovascular complications. One distributor, GNC, faces FDA seizure of over 3000 cases of two other DMAA-containing products, **Jack3d and OxyElitePro**. Although the manufacturer of those supplements has ceased production, GNC continues to sell its remaining stocks, according to the *New York Times*.

FDA July/13 **Clalis, Exten 1300 & MaxTreme Zen** contains sildenafil, while **MVP Mega** contains talalafil.

FDA July/13 **Meizi Revolution, Strawberry Balance** contains silbutramine. **Silver Sword** & **Clalis** contains sildenafil.

FDA Aug/13 Volcano Company is recalling all lots of **Volcano Male Enhancement Liquid and Volcano Male Enhancement Capsules** to the consumer level. FDA test results revealed the Volcano Male Enhancement Liquid has been found to contain undeclared Desmethyl Carbodenafil, Dimethylsildenafil, and Dapoxetine.

FDA Aug/13 Purity First Health Products is recalling two lots of **Healthy Life Chemistry B-50** (100 capsules), one lot of **Healthy Life Chemistry Multi-Mineral** (200 capsules) and all lot numbers for **Healthy Life Chemistry Vitamin C** (200 capsules). The B-50 capsules were found on testing by FDA to contain Methasterone (a schedule III controlled substance) and Dimethazine. Testing of the Multi-Mineral and Vitamin C capsules appear to indicate the presence of Dimethyltestosterone.

FDA Aug/13 Herbal Give Care LLC issued a voluntarily recall of all lots of **Esbelin silouttee** and **Esbelin siloutte Herbal Blend with L-Carnitine** (30 Capsules), to the consumer level. The products have been found to contain undeclared Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine.

FDA Aug/13 Bethel Nutritional Consulting, Inc., New York, NY, is voluntarily recalling **Quick Thin and Bethel Advance** to the consumer level. These products have been found to contain Sibutramine and Phenolphthalein, and may pose a threat to consumers.

FDA Aug/13 Health and Beyond LLC is voluntarily recalling quantity lots of product **Tranquility**. The products have been found to contain a trace of Doxepin which is a pharmaceutical for sleep and Chlorpormazine for psychotic disorders.

FDA Aug/13 CTV Best Group announced that it is conducting a voluntary nationwide recall of all lots of a dietary supplement products distributed by the company under the names **BEST SLIM 40 Pills** to the consumer level. Testing by FDA revealed the presence of Sibutramine in Best Slim.

FDA Aig/13 Herbal Give Care LLC is voluntarily recalling all lots of **Esbelder man (30 capsules), Esbelder fem (30 capsules) and Esbelder siloutte** (30 capsules) to the consumer level. The products have been found to contain undeclared Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine.

FDA Aug/13: Jack Rabbit Inc. announced that it is conducting a voluntary nationwide recall of one lot of the company's dietary supplement product sold under the name **Jack Rabbit**. FDA lab analysis of the product was found to contain Sildenafil and Tadalafil.

FDA Aug/13 laboratory analysis confirmed that **Ortiga** contains the prescription drug ingredient, diclofenac.

FDA Aug/13 Hardmenstore.com is voluntarily recalling 1000 lots of **72HP, Evil Root and Pro Power Max** at the consumer level. According to representatives of the FDA, 72HP, Evil Root and Pro Power Max have reportedly been found to contain amounts of the PDE-5 Inhibitor, sildenafil.

FDA Sep/13 Ge Pharma, LLC is recalling **Creafuse Powder Grape** Lot# GE4568 and Creafuse Powder Fruit Punch Lot #GE4570, because they contain 1,3 dimethylamylamine (DMAA). DMAA is commonly used as a stimulant, pre-workout, and weight loss ingredient in dietary supplement products.

FDA Sep/13 laboratory analysis confirmed that **Shou Fu Ti Tun Guo Xiang Xing Jian Fei Jiao Nang** contains sibutramine.

FDA Sep/13 is advising consumers not to purchase or use **XZone Premium**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that XZone Premium contains sildenafil, tadalafil, and dapoxetine.

FDA Sep/13 is advising consumers not to purchase or use **Wood-E**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that Wood-E contains sildenafil.

FDA Sep/13 is advising consumers not to purchase or use **Xzen 1200, Xzen Gold or Xzen XPress**, products promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that it contains either sildenafil & tadalafil.

FDA Sep/13 Haute Health, LLC is voluntarily recalling all lots of **Virilis Pro, PHUK and Prolifta** at the retail and consumer level. Virilis Pro, PHUK and Prolifta have been found to contain amounts of the PDE-5 Inhibitor sildenafil.

FDA Oct/13 along with the Centers for Disease Control and Prevention (CDC) and the Hawaii Department of Health (DOH), are investigating a growing number of reports of acute non-viral hepatitis in Hawaii. The Hawaii DOH has reported that 24 of these cases share a common link to a dietary supplement product labeled as **OxyElite Pro**.

FDA Oct/13: B@B Trade, Inc., Florida is voluntarily recalling all lots of **Slim Fortune, Lidiy, and Slim Expert** to the consumer level. The FDA laboratory analysis of these dietary supplements found to contain undeclared Sibutramine,

FDA Oct/13 is advising consumers not to purchase or use **Perfect Body Solutions or Burn 7.** FDA laboratory analyses confirmed that Perfect Body Solutions and Burn 7 contain sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Dr. Mao Slimming Capsules**. FDA laboratory analysis confirmed that Dr. Mao Slimming Capsules contain sibutramine.

FDA Oct/13 is advising consumers not to purchase or use **Bella Vi Insane Amp'd or Bella Vi Amp'd Up & Be Inspired.** FDA laboratory analyses confirmed that Bella Vi Insane Amp'd and Bella Vi Amp'd Up contain sibutramine.

FDA Nov/13: Fossil Fuel Products, LLC, is recalling lots QL110714A102 and QL110408B046 of "**RezzRX**." Laboratory analysis conducted by the FDA determined the RezzRX lot QL110714A102 contains undeclared hydroxylthiohomosildenafil and aminotadalafil and RezzRX lot QL110408B046 contains undeclared hydroxylthiohomosildenafil.

FDA Nov/13: Jobbers Wholesale is recalling Lot No. KWAKPMC030505175957019 of **Rhino 5 Plus**, Lot No. JBP-L-1270-70 of **Maxtremezen** and Lot No. KWAKPMC03050517 of **Extenzone**. FDA analysis found these products to contain undeclared desmethylcarbondenafil and dapoxetine, making these products unapproved new drugs.

FDA Nov/13 Vitality Research Labs is recalling lots K58Q and F50Q of **VitaliKOR Fast Acting**. FDA laboratory analysis on VitaliKOR has determined that this product contains undeclared Vardenafil and Tadalafil.

FDA Nov/13: Tendex is voluntarily recalling Lot# F51Q of P-Boost and Lot # F51Q of NatuRECT to the consumer level. FDA laboratory analysis on Lot# F51Q of **P-Boost**, which the firm also labels as **NatuRECT**, has determined that this product contains undeclared tadalafil.

FDA Nov/13 **SlimExtra Herbal** capsules contain silbutramine.

FDA Nov/13 **Alpha Male** contains sildenafil & other analogs.

FDA Dec/13 IQ Formulations, of Sunrise, Florida is initiating a recall of all lots of its 45-capsule bottles of **Hydravax** due to potential inclusion of an unlisted ingredient. The FDA has advised IQ Formulations that an analysis of a sample from one lot of Hydravax (Lot # 2458, Exp # 07/16) revealed the presence of an undeclared ingredient – a diuretic.

FDA Dec/13 is advising consumers to immediately stop using a product called **Mass Destruction**, marketed as a dietary supplement for muscle growth. The product is labeled to contain at least one synthetic anabolic steroid and has been linked to at least one reported serious illness.

FDA Dec/13 laboratory analysis found the **Burn 7 Capsules** to contain undeclared Sibutramine.

FDA Jan/14 Midwest Wholesale is voluntarily recalling the following products Boost**: Ultra, XZone Gold, Sexy Monkey, Triple MiracleZen Platinum, Magic for Men, "New" Extenze, and New XZen Platinum**. FDA analysis found these products to contain undeclared Sildenafil and/or Tadalafil.

FDA Jan/14 is advising consumers not to purchase or use **Magic Slim or Dream Body Slimming Capsule**, products promoted and sold for weight loss and sold on various websites and in some stores, since FDA lab analysis confirmed they contains sibutramine.

FDA Jan/14: **JINQIANGBUDOR Red Dragon** & **Tiger King** contains sildenafil; **Bali Mojo** & **Vimax** contains tadalafil; SexRx Contains both sildenafil and tadalafil.

FDA Jan/14 **Citrus Fit Gold**, **Hot Detox** & **Thinogenics** contains sibutramine. **Tonic Life BP** contains phenolphthalein.

FDA Mar/14 is advising consumers not to purchase or use **Vitaccino Coffee**, a product promoted and sold for weight loss. FDA laboratory analysis confirmed that Vitaccino Coffee contains sibutramine.

FDA Mar/14 Terra-Medica, Inc. is voluntarily recalling 56 lots of **Pleo-FORT, Pleo-QUENT, Pleo-NOT, Pleo-STOLO, Pleo-NOTA-QUENT, and Pleo-EX homeopathic** drug products in liquid, tablet, capsule, ointment, and suppository forms to the consumer level. FDA has determined that these products have the potential to contain penicillin or derivatives of penicillin.

FDA Mar/14: New Life Nutritional Center is recalling all lots of "**Super Fat Burner capsules, Maxi Gold capsules and Esmeralda softgels**" to the user level after FDA analysis revealed the products contain undeclared active pharmaceutical ingredients: sibutramine, phenolphthalein or a combination of both sibutramine and phenolphthalein.

FDA Mar/14: **Bella Vi Insane Bee Pollen Capsules, Bella Vi BTrim Ultimate Boost, Bella Vi BTrim Max, Bella Vi Extreme Accelerator, Bella Vi Insane Amp'd, and Bella Vi Amp'd U**, contain silbutramine with or without phenolphthalein.

FDA Mar/14: Nova Products, Inc. issued a voluntary recall of the following products: **African Black Ant (Lot# 2006-000926), Black Ant (Lot# 2006-3627878), XZen Gold (Lot# 130310GL), ZXen Platinum (Lot# 130520PL), XZen 1200 (Lot# 13051012), XZone Gold (Lot# 131110GL), and XZone 1200 (Lot# 13071012)** at the retail level. FDA laboratory analysis on these products has determined that they contain undeclared amounts of sildenafil and tadalafil.

FDA Apr/14: FDA analysis on **New You** contains silbutramine.

FDA Apr/14 has tested multiple **Zi Xiu Tang Bee Pollen** products from various distributors in the United States (US). All products that have been tested, including those that claim to be "genuine" and "anti-counterfeit," have been found to contain one or both of the undeclared drug ingredients sibutramine and Phenolphthalein.

FDA Apr/14 laboratory analysis confirmed that **Infinity** & **Lite Fit** USA contains sibutramine.

FDA apr/14 is advising consumers not to purchase or use **S.W.A.G,** a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that S.W.A.G contains sildenafil.

FDA Apr/14: Nature's Universe notified the public it is recalling all lots of **Thinogenics** product sold prior to February 6, 2014 to the user level after FDA analysis revealed that the affected product contained undeclared sibutramine.

FDA Apr/14: Nano Well-being Health Inc. issued a voluntary recall of **Super Arthgold**, 500 mg capsules to the consumer level. FDA laboratory analysis has found the product to contain chlorzoxazone, diclofenac and indomethacin.

FDA May/14 laboratory analysis confirmed that **Slim Trim U** & **Natural Body Solution** contains sibutramine.

FDA May/14: Eugene Oregon, Inc. is voluntarily conducting this recall because FDA analysis of **African Black Ant, Black Ant, and Mojo Risen** distributed to a third party revealed that the distributed products contained undeclared amounts of the active pharmaceutical ingredients sildenafil and tadalafil.

FDA May/14 is advising consumers not to purchase or use **Asset Bee Pollen**, a product promoted and sold for weight loss because it contains sibutramine.

FDA May/14 is advising consumers not to purchase or use **Asset Bold**, a product promoted and sold for weight loss. FDA laboratory analysis confirmed that Asset Bold contains sibutramine.

FDA May/14 is advising consumers not to purchase or use **MV5 Days**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that MV5 Days contains sildenafil.

FDA Jun/14: advising consumers not to purchase or use **Eyeful** contains hydroxythiohomosildenafil; **Liu Bian Li** contains sildenafil; **Dick's Hard Up** contains tadalafil; **3 Hard Knights** contains sildenafil and thiosildenafil; **Full Throttle On Demand** contains propoxyphenyl sildenafil; GoldReallas contains sildenafil and thiosildenafil.

FDA June/14 laboratory analysis confirmed that **Zhen Gong Fu** contains sildenafil.

FDA Jun/14 laboratory analysis confirmed that **La Jiao Shou Shen** contains sibutramine

FDA Jun/14 laboratory analysis confirmed that **Gold Vigra & Miraculous Evil Root** contains sildenafil. FDA laboratory analysis confirmed that **Sport Burner & Toxin Discharged** Tea contains fluoxetine. FDA laboratory analysis confirmed that **Sliming Diet** contains sibutramine.

FDA July/14 laboratory analysis confirmed that **Mix Fruit Slimming, Lingzhi Cleansed Slim Tea, 24 Ince, Lipo 8 Burn Slim, Sliming (sic) Diet By Pretty, & Trim-Fast Slimming Softgel** contains sibutramine.

FDA July/14: **Lian Zhan Qi Tian capsules & Weekend Warrior** contains thiosildenafil.

FDA July/14: **Vitaccino Coffee, Collagen Slim, & Sulami** contains sibutramine.

FDA July/14: **Fruta Bio, Jianfeijindan Activity Girl, & LTD Japanese Chinese Formula** pill for weight reduction contains sibutramine and/or phenolphthalein.

FDA Aug/14 Regeneca Worldwide a division of VivaCeuticals, Inc., is conducting a voluntary nationwide recall of its **RegenESlim** appetite control dietary supplement, lot # EX0616R15814 and lot #11414RE5516, because FDA analysis confirmed the presence of DMAA.

FDA Aug/14 is advising consumers not to purchase or use **Arize**, a product promoted and sold for sexual enhancement. FDA laboratory analysis confirmed that Arize contains sulfoaildenafil; and Herbal Vigor Quick Fix contains tadalafil.

FDA Sep/14 laboratory analysis confirmed that **Best Line Suplemento Alimenticio Capsules** contains sibutramine.

FDA Sep/14 laboratory analysis confirmed that **LX1** contains undeclared DMAA, also known as 1,3-dimethylamylamine, methylhexanamine or geranium extract.

FDA Sep/14 laboratory analysis confirmed that **Mezo** contains benzylsibutramine, a substance structurally similar to sibutramine.

FDA Sep/14 laboratory analysis confirmed that **Japan Hokkaido Slimming Weight Loss Pills** contain sibutramine, benzocaine, phenolphthalein and diclofenac.

FDA Sep/14 warns parents and caregivers not to use "**Bo Ying compound**" manufactured by Eu Yan Sang (Hong Kong) Ltd. due to the potential lead poisoning risk associated with the product.

FDA Oct/14 laboratory analysis confirmed that **Sit and Slim II** contains sibutramine.

FDA Nov/14 is advising consumers not to purchase or use **V26 Slimming Coffee**. FDA laboratory analysis confirmed that V26 Slimming Coffee contains sibutramine.

FDA Oct/14 laboratory analysis found that "**Ginseng Kianpi Pil**" contains dexamethasone, a corticosteroid commonly used to treat inflammatory conditions, and cyproheptadine.

FDA Nov/14 is advising consumers not to purchase or use **Mayhem**, a product labeled as a dietary supplement that is promoted to increase appetite and muscle growth, because it contains an undeclared dexamethasone and cyproheptadine.

FDA Nov/14 Solgar, Inc. is voluntarily recalling **ABC Dophilus Powder**. Testing conducted by the Centers for Disease Control revealed the presence of Rhizopus oryzae in 1.75 oz (50 g) containers of Solgar ABC Dophilus Powder, which may cause Mucormycosis.

FDA Nov/14: REFA Enterprises is voluntarily recalling one lot each of: **Forever Beautiful Bee Pollen** (UPC # 6333090804632), **Forever Beautiful Infinity** (UPC # 633090804649). The products have been found to contain undeclared Sibutramine or a combination of both Sibutramine and Phenolphthalein through FDA laboratory analyses.

FDA Nov/14 is advising consumers not to purchase or use **Bee Slim, Bee Thin & Super Extreme Accelerator**. FDA laboratory analysis confirmed that they contain sibutramine.

FDA Nov/14 is advising consumers not to purchase or use **Black Storm**. FDA laboratory analysis confirmed that Black Storm contains sildenafil.

FDA Nov/14 laboratory analysis confirmed that **Slim-Vie** containssibutramine.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **SLIM-K Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of SLIM-K collected and tested by the FDA was found to contain sibutramine, desmethylsibutramine, and phenolphthalein.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **B-Lipo Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of B-Lipo Capsules collected and tested by the FDA was found to contain lorcaserin.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **SLIM-K Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of SLIM-K collected and tested by the FDA was found to contain sibutramine, desmethylsibutramine, and phenolphthalein.

FDA Dec/14 Bethel Nutritional Consulting, Inc. is recalling one lot of **B-Lipo Capsules** to the consumer level. The firm was informed by the US Food and Drug Administration (FDA) that a sample of B-Lipo Capsules collected and tested by the FDA was found to contain lorcaserin.

FDA Dec/14 is warning health professionals of the risks associated with the regarding use of dietary supplements containing live bacteria or yeast in immunocompromised persons. A premature infant administered a dietary supplement, ABC Dophilus Powder

(**Solgar**), as part of in-hospital course of treatment, developed gastrointestinal mucormycosis caused by the mold Rhizopus oryzae and died. Rhizopus oryzae mold was found to be present as a contaminant in an unopened container of the ABC Dophilus Powder, which is formulated to contain three species of live bacteria.

FDAJan/15 is alerting consumers and health care professionals that **counterfeit versions of Cialis 20 mg tablets** were found in the mail on its way to a U.S. consumer.

FDAJan/15 laboratory analysis confirmed that **Happy Passengers** contains sildenafil.

FDA Feb/15 laboratory analysis confirmed that **Black King Kong, Germany Niubian, Tibet Babao, 72HP, Night Man, & Libigrow XXX Treme** contains sildenafil.

FDA Feb/15 laboratory analysis confirmed that **Botanical Slimming (Red), & Oxy ELITE Pro Super Thermogenic** (Lot# 216732, Exp. 04/17) contains fluoxetine.

FDA Feb/15 laboratory analysis confirmed that **Lean Body Extreme** contains sibutramine, desmethyl sibutramine, phenolphthalein, and sildenafil.

FDA Feb/15 laboratory analysis confirmed that **Nine Slim, & Seven Slim** contains phenolphthalein.

FDA Mar/15 laboratory analysis confirmed that **Santi Scalper, Vigra, Vigour 300, Sex Men, Super Hard, Plant Vigra, MME MAXMAN, Hard Wang & FX3000** contains sildenafil.

FDA Mar/15 laboratory analysis confirmed that **Elimulating Weight & Toxin Keeping Beauty** contains sibutramine

FDA Mar/15 laboratory analysis confirmed that **Bigger Longer More Time More Sperms (sic), Black Ant King, African Superman & Black Mamba Premium c**ontains sildenafil.

FDA Mar/15 laboratory analysis confirmed that **Black Mamba Hyperrush & L-Carnitine Sob Strengthening Version Slimming Miracle Capsule** contains sibutramine.

FDA Apri/15 A dietary supplement marketed to body builders and purported to contain **anabolic steroids** is linked to serious liver injury, the FDA warned on Monday. The agency has so far received three reports of adverse events associated with **Tri-Methyl Xtreme**, which is sold on the internet and in some retail stores and gyms.

FDA May/15 laboratory analysis confirmed that **Asihuri Plus Fortecontains** dexamethasone, a corticosteroid, and phenylbutazone.

FDA May/15 laboratory analysis confirmed that **Ginseng She Lian Wan** contains dexamethasone, a corticosteroid, and chlorpheniramine.

FDA May/15 laboratory analysis confirmed that **Jianbu Huqian Wan** contains dexamethasone, a corticosteroid, chlorpheniramine, and furosemide.

FDA May/15 laboratory analysis confirmed that **Saurean Fong Sep Lin** contains dexamethasone, a corticosteroid, and cyproheptadine.

FDA May/15 laboratory analysis confirmed that **Black Panther** contains sildenafil.

FDA May/15 laboratory analysis confirmed that **Viagra 007c**ontains sildenafil.

FDA May/15 laboratory analysis confirmed that **King of Romance** contains sildenafil.

FDA May/15 laboratory analysis confirmed that **Li Da Dai Dai Hua Slimming Capsule** contains sibutramine.

FDA May/15 laboratory analysis confirmed that **Slim Forte Slimming** Capsule contains sibutramine.

FDA Apr/15 laboratory analysis confirmed that **Superior** contains sibutramine.

FDA Apr/15 laboratory analysis confirmed that **Fatloss Slimming Beauty** contains sildenafil.

FDA Apr/15 laboratory analysis confirmed that **Extreme Diamond 3000** contains desmethyl carbodenafil and dapoxetine.

FDA May/15 **Samurai-X, Happy Passengers, & AMPD Gold Bee Pollen** contains undeclared sildenafil.

FDA May/15 **Yanhee Slim & iNSANE Bee Pollen** contains undeclared lorcaserin; **EDGE Amplified Weight Release** contains undeclared phenolphthalein and fluoxetine; **iNDiGO & BtRim Max** contains undeclared phenolphthalein.

FDA May/15: **Black King Kong, Tibet Babao, Vigour 300, Hard Wang**, **FX3000, Sex Men, Vigra, Plant Vigra, Santi Scalper, Baolong, Rhino Blitz Gold 3000, Vim-25, Black Mamba Premium, Bigger Longer More Time More Sperms (sic), Herb Viagra, & La Pepa Negra** contains undeclared sildenafil.

FDA May/15: **Male Silkworm Moth Nourishing Oral Liquid** contains undeclared vardenafil.

FDA May/15: **Nine Slim & Seven Slim** contains undeclared phenolphthalein.

FDA May/15: **Oxy ELITE Pro Super Thermogenic** contains undeclared fluoxetine.

FDA May/15: **Elimulating Weight & Toxin Keeping Beauty & L-Carnitine Sob Strengthening Version Slimming Miracle Capsule** contains undeclared sibutramine.

FDA May/15: **Lean Body Extreme** contains undeclared sibutramine, desmethyl sibutramine, phenolphthalein & sildenafil.

FDA May/15: **Diablos Eca Fire Caps** contains undeclared sildenafil, phenolphthalein, sibutramine & deisobutylbenzylsibutramine.

FDA July 15: **Extreme Diamond 3000** contains Undeclared desmethyl carbodenafil and dapoxetine.

FDA July 15: **Black Mamba Hyperrush & Ultra ZX** contains Undeclared sibutramine and phenolphthalein.

FDA July 15:**Botanical Slimming (Red) & Xcel** contains Undeclared fluoxetine.

FDA July 15:**Green Algae Combination** by Crane Beauty contains Undeclared lorcaserin.

FDA July 15:**Natural Max Slimming** contains Undeclared sildenafil, fluoxetine, and sibutramine.

FDA July 15: **Ultimate Boost & Xcel Advanced** contains Undeclared phenolphthalein.

FDA Aug/15 R Thomas Marketing, through its websites www.herbviagra.com and www.herbsviagra.com, sold the supplements under the names **Black Ant, Herb Viagra, Real Skill and Stree Overlord**. All four items contain undeclared sildenafil.

FDA Oct/15 **Kaboom Action Strips** 12 Pack contains undeclared sulfoaildenafil.

FDA Oct/15 **Lida DaiDaiHua** contains undeclared sibutramine & phenolphthalein.

FDA Sep/15: Consumers who have used any of the **Baidyanath brand Ayurvedic dietary supplements** listed in theConsumer Advice Notice should stop using them and consult their health care provider. Testing by the New York Department of Health and the U.S. Food and Drug Administration (FDA) has found that these products contain high levels of lead and/or mercury,

FDA Sep/15: **Miracle Diet 30** has been found to contain undeclared phenolphthalein,

FDA Sep/15: **Miracle Rock 48** has been found to contain undeclared thiosildenafil.

FDA Oct/15 laboratory analysis confirmed that **Wild Sexx Capsules** contains sildenafil and tadalafil.

FDA Oct/15 laboratory analysis confirmed that **Ultra SX Capsules, Super Dragon 6000 Capsules, Sex-Love Secret Code Capsules, Paradise Suplemento Natural Ultra Plus Capsules, APEXXX, & S.W.A.G.G.E.R Extreme Capsules** contains sildenafil.

FDA Oct/15 laboratory analysis confirmed that **Fuel Up High Octane, & Fuel Up Plus** contains hydroxythiohomosildenafil.

FDA Oct/15 laboratory analysis confirmed that **Xtreme Fat Burner Capsules** contains phenolphthalein.

FDA Oct/15 laboratory analysis confirmed that **Tip-Top Shape, Lishou Slimming Coffee, & Basha Nut 100% Fruit Soft Gel Capsules** contains sibutramine.

FDA Nov/15 laboratory analysis confirmed that **Perfect Slim Fast Track Slim & Slyn** Both contains fluoxetine.

FDA Nov/15 laboratory analysis confirmed that **Super Herbs** contains sibutramine and desmethylsiburamine.

FDA Nov/15 laboratory analysis confirmed that **Zero Fat & SPCARET Princess Diet** contains sibutramine.

FDA Nov/15 laboratory analysis confirmed that **Rhino X, Effective Viagra, Sex Drive Capsules, XForMan Plus & Australia Kangaroo Essence** contains sildenafil.

FDA Dec/15 Lucy's Weight Loss System is voluntarily recalling all lots of **Pink Bikini White powder Capsules**, 30 white (750MG per capsule) to the consumer level. Pink Bikini has been found positive for diclofenac.

FDA Dec/15 Lipo Escultura Corp. of Brooklyn, NY (dba JAT Productos Naturales Corp., and JAT Natural Products Corp.) are voluntarily recalling all **Lipo Escultura** within expiry to the consumer level since contains sibutramine and diclofenac.

FDA Dec/15 has warned five dietary supplement makers nationwide for their use of the substance Picamilon as an ingredient in their products. **Picamilon** is not a dietary ingredient, the FDA says, and therefore declaring it as such in product labeling causes the companies' products to be misbranded.

FDA Dec/15 laboratory analysis confirmed that **Rhino Big Horn 3000** contains desmethyl carbodenafil and sildenafil.

FDA Dec/15 laboratory analysis confirmed that **OrgaZen 3000, OrgaZen 3500, & Rhino 7 Blue 9000** contains tadalafil.

FDA Dec/15 laboratory analysis confirmed that **Triple Power Zen Gold 2000, Triple Power Zen Plus 2000, Xtra Zone 2200, Xtra Zone 2400, Xtra Zone 2600, & Diamond 3500** contains sildenafil and tadalafil.

FDA Dec/15 laboratory analysis confirmed that **Triple MiracleZen Extreme 1750 mg, MiracleZen Gold 1750 mg & Triple MiracleZen Plus 1500 mg** contains sildenafil, tadalafil and dapoxetine.

FDA Dec/15 laboratory analysis confirmed that **Eros Power Zone 1900** contains desmethyl carbodenafil and dapoxetine.

FDA Dec/15 laboratory analysis confirmed that **X Again Platinum** contains sildenafil, tadalafil and dapoxetine.

FDA Dec/15 laboratory analysis confirmed that **Evolve Bee Pollen, Jenesis, Prime Bee Pollen & Oasis Bee Pollen** contains sibutramine.

FDA Dec/15: laboratory analysis confirmed that **La'Trim Plus** contains sibutramine.

FDA Dec/15: Nuway Distributors llc is voluntarily recalling all lots of **Apexxx** tablets to the consumer level. FDA analysis found Apexxx to contain amounts of the PDE-5 Inhibitor, sildenafil.
FDA's Dec/15 analysis found the **Smart Lipo** products to contain undeclared sibutramine, desmethylsibutramine, and phenolphthalein.
FDA Dec/15 laboratory analysis confirmed that **Thirty Plus** contains sibutramine.
FDA Dec/15 laboratory analysis confirmed that **Power Tiger-X** contains sulfoaildenafil.
FDA Dec/15 BeeXtreme LLC is recalling all lots of **La' Trim Plus, Jenesis and Oasis products** from the market. Recent Analysis by the Food and Drug Administration has found undeclared Sibutramine and Phenolphthalein.
FDA: Jan/16 U.S. Marshals have seized nearly a half a million dollars' worth of dietary supplements containing **kratom (Mitragyna speciosa),** a plant-based substance that people use recreationally or to self-treat opioid addiction. The supplement (marketed as RelaKzpro) could pose a risk to public health, the FDA says, because it has narcotic-like effects and can potentially be abused. Kratom, which grows in Southeast Asia, affects the brain the same way opiates do. Risks associated with consuming the substance include nervousness, respiratory depression, and vomiting. Additionally, withdrawal can cause aggression, hostility, muscle and bone aches, and jerky limb movements. Importation of kratom was banned by the FDA in 2014. The agency says there is "inadequate information" that supplements with kratom don't present a risk for illness or injury, and it warns people not to use the substance. FDA news release (Free)
FDA Jan/16: Shakti Group USA LLC is recalling 50 gm and 100 gm sizes of L.G Compounded **Asafoetida Powder**, both coded with Lot Number: 2323 because it has the potential to be contaminated with Salmonella, an organism which can cause serious and sometimes fatal infections in young children, frail or elderly people, and others with weakened immune systems.
FDA Jan/16: R Thomas Marketing LLC is voluntarily recalling all lots of the following products to the consumer level: **Black Ant, Herb Viagra, Real Skill, Stree Overlord, Weekend Prince, & African Black Ant**. These products were tested by the FDA and found to contain sildenafil.
FDA Jan/16 is warning consumers not to use **Licorice Coughing Liquid**, a cough syrup product sold over-the-counter, because it contains unidentified morphine.
FDA Jan/16 laboratory analysis confirmed that **Wonder-Erect Male Gum & Wonder-Erect Male Pills** contains vardenafil.
FDA Jan/16 is warning consumers not to purchase or use a skin whitening cream called "Crema Piel De Seda," due to the risk of mercury poisoning.
FDA Jan/16 is warning consumers not to use "**Bentonite Me Baby**" by Alikay Naturals because of a potential lead poisoning risk.
FDA Jan/16 analysis of **Pink Bikini** (white capsules, blue capsules and gold capsules) and Shorts on the Beach (blue capsules and gold capsules) found these products to be tainted with Sibutramine, Phenolphthalein, and/or Diclofenac.
FDA Jan/16 is warning consumers not to purchase or use a skin whitening cream called "**Crema Piel De Seda**," due to the risk of mercury poisoning.
FDA laboratory analysis confirmed that Ginseng Power-X contains sildenafil and sulfoaildenafil.
FDA Feb/16 laboratory analysis confirmed that **Ninja-X** contains sildenafil and thiosildenafil.
FDA lFeb/16 aboratory analysis confirmed that **Golden Night** contains sildenafil and hydroxythiohomosildenafil.
FDA laboratory analysis confirmed that **Boss Number #Six** contains tadalafil.
FDA Feb/16 laboratory analysis confirmed that **Mamba is Hero** contains sildenafil, desmethyl carbodenafil, and dapoxetine
FDA Feb/16 laboratory analysis confirmed that **Zhong Hua Niu Bian, Weekend Prince, Bull & Bull's Genital** contains sildenafil.
FDA Mar/16 laboratory analysis confirmed that **Sextra** contains sildenafil.
FDA Mar/16 laboratory analysis confirmed that **ENVY BP** contains sibutramine.
FDA Mar/16 laboratory analysis confirmed that **Propell Platinum** contains sibutramine.
FDA Apr/16 Invisiblu International LLC is voluntarily recalling one lot of **Continuum Labs LGD-Xtreme**, 3 mg to the retail and consumer level. The product has been found to contain LGD-4033 Ligandrol, an investigational drug not approved for use. The risks of using this product are unknown.
FDA Apr/16 Super Herbs is voluntarily recalling all bottles of **SUPER HERBS**, light green and dark green capsules to the consumer level after FDA laboratory testing found SUPER HERBS to contain sibutramine, desmethylsibutramine, and/or phenolphthalein.
FDA Apr/16 laboratory analysis confirmed that **3rd Degree & Black Gold X** contains sibutramine.
FDA Apr/16 laboratory analysis confirmed that **Black Label X** contains sildenafil.
FDA May/16 laboratory analysis confirmed that **Step 2** contains sibutramine.
FDA May/16: SOS Telecom, Inc. is voluntarily recalling all lots of the following products (**Tiger-X, Ninja-X, Ginseng Power-X, & Super Samurai-X**) to the consumer level because these products were tested by the FDA and found to contain sildenafil.
FDA June/16: Pharmavite LLC is recalling specific lots of **Nature Made** products due to possible Salmonella or Staphylococcus aureus contamination.
FDA June/16: The **Body Shot Bar** is voluntarily recalling all lots distributed March 1- May 6 2016 of Step 2 60 gold capsule (350MG per) capsules to the consumer level. Step 2 has been found positive for Sibutramine after FDA sampling and testing.
FDA July/16 laboratory analysis confirmed that **Xcelerated Weight Loss Charged Up, Xcelerated Weight Loss Turbo Charge** contains sibutramine.
FDA July/16 laboratory analysis confirmed that **Xcelerated Weight Loss Ultra Max** contains phenolphthalein and sildenafil.
FDA July 16 laboratory analysis confirmed **Super Shangai, Shangai Ultra X & Power Spring (XXX) Oral Liquid** contains sildenafil.
FDA July 16 laboratory analysis confirmed that **Slim Fit X, & Mang Luk Power Slim Detox** contains sibutramine and desmethylsibutramine.
FDA July 16 laboratory analysis confirmed that **Mang Luk Power Slim, Maxx Easy** contains sibutramine.
FDA July/16: Dream Body Weight Loss is voluntarily recalling all lots of **Dream Body Extreme Gold 800mg 30 gold capsules, Dream Body 450mg 30 white capsules, and Dream Body Advanced 400mg 30 purple capsules to the consumer level. The Dream Body Extreme 800mg Gold, Dream Body 450mg and Dream Body Advanced 400mg** have been found to contain sibutramine.
FDA July/16: FDA laboratory analysis confirmed that **Dream Body Advanced + Acai Weight Loss & Cleanse** contains sibutramine, fluoxetine and sildenafil.
FDA July/16: FDA laboratory analysis confirmed that **Dream Body Extreme Gold** contains sibutramine, fluoxetine and sildenafil.
FDA July/16: FDA laboratory analysis confirmed that **Dream Body Original Formula, SBF Bee Pollen & Extra Slim Plus Acai Berry Weight Loss Formula** contains sibutramine.
FDA Jul/16 laboratory analysis confirmed that **Ziyinzhuangyang** contains sildenafil.
FDA Jul/16 laboratory analysis confirmed that **Zi Xiu Tang Beauty Face & Figure Capsule** contains phenolphthalein and fluoxetine.
FDA Jul/16 Laboratory analysis confirmed that **Weili (一炮到天亮or Yi Pao Dao Tian Liang)** contains sildenafil.
FDA Jul/16 laboratory analysis confirmed that **Ultimate Lean** contains sibutramine and desmethylsibutramine.
FDA Aug/16 laboratory analysis confirmed that **One More Knight 1750** contains tadalfil and dapoxetine.
FDA Aug/16 laboratory analysis confirmed that **Master Zone 1500** contains sildenafil and tadalfil.
FDA Aug/16 laboratory analysis confirmed that **Love4Long** contains sildenafil.
FDA Aug/16 laboratory analysis confirmed that **Natural Eruption** contains sibutramine.
FDA Aug/16 Ton Shen Health of Chicago, IL, is recalling its "**DHZC-2**" Tablets because they have the potential to be contaminated with elevated levels of lead.
FDA Aug/16 laboratory analysis confirmed that **De Guo Hei Bei (德国黑倍), Boss-Rhino Gold X-tra Strength, & Anaconda Strong Formula** contains sildenafil.
FDA Aug/16 laboratory analysis confirmed that **Citrus' Fit** contains sibutramine and desmethylsibutramine.
FDA Aug/16 laboratory analysis confirmed that **Adelgazantes R-II** contains sibutramine.
FDA Aug/16 is investigating **DHZC-2** tablets by Ton Shen Health/Life Rising for lead and other hazardous material and is also investigating to see if other Life Rising products from this company may be similarly affected.
FDA Aug/16 laboratory analysis confirmed that **Kopi Jantan Tradisional Natural Herbs Coffee** contains desmethyl carbodenafil.
FDA Oct/16 laboratory analysis confirmed **that Zi Su Body Fat Health II** contains sibutramine and phenolphthalein.
FDA Nov/16: Ton Shen Health of Chicago, IL, is recalling its Life Rising brand "**Side Head Regulator TT**" Tablets because they have tested positive for elevated levels of lead for children under the age of 18.
FDA Nov/16: Love My Tru Body is voluntarily recalling all of **Skinny Bee Diet 500 mg** to the consumer level after FDA laboratory testing found Skinny Bee Diet to contain sibutramine, desmethylsibutramine, and/phenolphthalein.
FDA Nov/16 laboratory analysis confirmed that ABX Weight Loss contains sibutramine.
FDA Nov/16 Nutra Manufacturing, Inc. announced a nationwide, voluntary recall of one lot of **GNC Women's Ultra Mega Time Release dietary supplement** product sold in 180 count containers UPC 048107158910, lot number 3044FQ2024, with an expiration date of June 2018 due to the fact the product may contain an undeclared major food allergen, milk.
FDA Nov/16: Raritan Pharmaceuticals is a contract manufacturer of these products for **Homeolab USA that supplies the belladonna blends to Raritan Pharmaceuticals**. These products were distributed Nationwide: 1) Product: **CVS Homeopathic Infants' Teething Tablet** 135 tablets, UPC: 050428424162, Lots: 41116 and 43436; 2) Product: **Kids Relief Homeopathic Ear Relief Oral Liquid** 0.85 fl. oz., UPC: 778159090639, Lot: 35254 3) Product: **CVS Homeopathic Kids' Ear Relief Liquid** 0.85 fl. oz., UPC: 050428441633, Lot: 33149.

FDA Nov/16: NutriVitaShop, also doing business as Naturecom Inc. Lake Forest, CA is requesting the nationwide recall of its **DMAA net weight 500g** because there may be presence of DMAA. Lot numbers include #20141102, 20150715, 20151022, 20160226, 20160701, 20161017 and 20150323. DMAA net weight 500g is packaged in approximately 8" x 11" silver and clear mylar ziplock bags that contain 500g of DMAA. DMAA is also known as 1,3-dimethylamylamine, methylhexanamine, or geranium extract.

FDA Dec/16 Ultimate Body–Tox is voluntarily recalling all lots of **Ultimate Body Tox PRO** capsules to the consumer level. FDA analyses of this product found it to contain undeclared sibutramine.

Fish Oil Testing: Independent test for contaminants Nutrasource Diagnostics at the University of Guelp www.nutrasource.ca/ifos_new

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Health Canada is warning Aril/06 consumers not to not to use advises consumers not to use unauthorized products containing **anabolic steroids** (Five products containing illegal anabolic steroids, as they can potentially cause serious health issues such as liver disorders and heart problems. The five products are: Anabolic Xtreme Superdrol, Methyl-1-P, Ergomax LMG, Prostanozoland, and FiniGenX Magnum Liquid.)
Health Canada is warning consumers not to not to use **Kaizen Ephedrine HCL tablets for weight loss Dec/05** http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_138_e.html
Health Canada is warning consumers not to ingest the herb **chaparral** in the form of loose leaves, teas, capsules or bulk herbal products because of the risk of liver and kidney problems. Dec/05 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_135_e.html
Health Canada is warning consumers not to use certain **Ayurvedic medicinal** products because they contain high levels of heavy metals such as lead, mercury and/or arsenic. July/05 http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_80.html
Health Canada Jan/06 Natural health product **Libidfit** may pose health risks (promoted for sexual enhancement and erectile dysfunction, but contains an undeclared amount of a pharmaceutical ingredient similar to sildenafil) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_02_e.html
Health Canada is warning consumers Feb/06: Not to use the Chinese medicinal product White Peony Scar-repairing pills, manufactured in Hong Kong by White Peony Pharmaceuticals Limited, due to high levels of lead. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_05_e.html
Health Canada is warning consumers Feb/06 not to use 13 Chinese herbal products manufactured by the Hong Kong Chi Chun Tang Herbal Factory due to bacterial contamination that could lead to serious health risks. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_08_e.html
Health Canada advises consumers April/06 not to use Super Fat Burning and LiDa Daidaihua Slimming Capsules for weight loss because they have been found to contain sibutramine http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_15_e.html
Health Canada is advising consumers Apr/06 not to use unapproved products containing **yohimbine or yohimbe bark**, including Strauss Energy SIX capsules. Yohimbine is a prescription substance that can pose serious health risks for people with underlying risk factors. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_16_e.html
Health Canada is advising consumers Apr/06 not to use unapproved Miracle Bion products as it could be contaminated with bacteria such as *E. coli*. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_23_e.html
Health Canada May/06 is warning consumers not to use the product **Nasutra** because it has been found to contain the sildenafil (chemical name for Viagra) that could lead to serious health risks, especially for patients with existing medical conditions such as heart problems, those who may be taking heart medications, or those who may be at risk for strokes.
Health Canada May/06 is advising consumers not to use Ocean Plasma **Isotonic Living Water and Ocean Plasma Hypertonic Living Water** because they are unapproved products that contain unacceptable amounts of aerobic bacteria.
Health Canada June/06 is advising consumers not to use four unapproved **Ayurvedic medicinal products** from India because they contain high levels of lead and/or mercury. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_46_e.html
Health Canada July/06 is advising Fat Rapid Loss Capsules (Xin Yan Zi Pai Mei Zi Jiao Nang) because may contain sibutramine http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_55_e.html
Health Canada July/06 is advising consumers not to use 4 foreign health products due to concerns about possible side-effects: **Zhuifeng Tougu Wan** & **Fufang LuHui Jiaonang**, two traditional Chinese medicines that contain toxic levels of mercury; **Safi**, a herbal product manufactured in India and Pakistan that contains toxic levels of arsenic; and **Baike Wan**, a herbal product from Malaysia that contains the prescription drugs piroxicam and frusemide, and the over-the- counter drug chlorpheniramine.
Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well Dietary Supplement** because a sample has been found to contain **estazolam.**
Health Canada Warns Consumers August 04, 2006 Not To Use **Neophase** Formula For Men Due To Potential Health Risks which has been found to contain an undeclared ingredient similar to the active pharmaceutical ingredient found in Viagra. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_67_e.html
Health Canada Aug/06 is reminding consumers not to use Miracle II Miracle Neutralizer or any other products exported or sold by Tedco, Inc. of Louisiana because they could contain harmful bacteria. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_68_e.html
Health Canada Aug/06 is advising consumers about a possible link between health products containing the herbal medicine **black cohosh and liver damage**. There have been a number of international case reports of liver damage suspected to be associated with the use of black cohosh, including three case reports in Canada and one published case of death in the United States. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html
Health Canada Aug/06 is advising consumers not to use four foreign health products due to concerns about possible side-effects: **Reduce Weight**, a proprietary Chinese Medicine marketed as a weight-loss product. Contains the prescription drug sibutramine (the generic name for Meridia) **Yixinjiaonang**, a proprietary Chinese medicine marketed as a sexual enhancement & erectile dysfunction product, contains the prescription drug tadalafil (the generic name for Cialis) **Meng Rong**, a proprietary Chinese medicine marketed as a sexual enhancement and erectile dysfunction product, contains the prescription drug sildenafil (the generic name for Viagra) **VG**, a proprietary Chinese medicine marketed as a sexual enhancement and erectile dysfunction product, contains the prescription drug sildenafil (the generic name for Viagra) http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/index_e.html
Health Canada Aug/06 is advising consumers not to use **Salt Spring Herbals Sleep Well** Dietary Supplement because a sample analyzed by Health Canada has been found to contain the undeclared drug Estazolam. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_82_e.html
Health Canada Aug/06 is advising consumers not to use two foreign health products due to concerns about possible side-effects: **Chao Nongsu Qingzhi Jiaonang** (OPC Care) is promoted as a weight-loss product. The product is adulterated with sibutramine and mazindol, two prescription medications used to suppress appetite. **Conting Qianweisu Slimming Herbs** Capsule is marketed as a weight-loss product. The product is adulterated with sibutramine, a prescription medication used to suppress appetite. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/2006/2006_84_e.html http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/fpa-ape/2006/2006_83_e.html
Health Canada Sept/06 advises against use of the **Ayurvedic medicinal product Jambrulin** due to lead content http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_89_e.html
Health Canada Sept/06 is warning consumers not to use the natural health product **Libidus** because it contains an undeclared pharmaceutical ingredient, a modified form of vardenafil.
Health Canada Oct/06 is advising consumers not to use the unauthorized natural health products **Emperor's Tea Pill (Tian Huang Bu Xin Wan)** and **Hepatico Extract (Shu Gan Wan)** because certain lots of these products contain high levels of lead and mercury. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_98_e.html
Heath Canada Nov/ 06 is warning Canadians not to use the unauthorized product **Embrun de mer** promoted for the treatment of skin irritation in newborns and adults because it contains unacceptable amounts of harmful bacteria.
Health Canada Dec/06 is advising consumers not to use a product called **Eden Herbal Formulations Sleep Ease Dietary Supplement**, because it was found to contain an undeclared drug estazolam

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_127_e.html

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Health Canada Feb/08 warning Canadians not to use Foreign Products: 1) **Jingzhi Kesou Tanchuan; Guanxin Suhe capsules**; **Qing Re An Cang Wan**; & **Guan Xin Su He** 2) **Xiao Qin Long Capsules** 3) **Xiao Qin Long Wan**; **Chuan Xiong Cha Tiao Wan Tablets**; **Bai Tou Weng Wan** 4) **Wannianqing Pai Danggui Niantong Tang** (batch number 050401) These products have been found to contain aristolochic acid, a toxin associated with serious and potentially fatal health effects.

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

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

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

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

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

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

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

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

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

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

Health Canada May/08 is reminding consumers who choose to use unapproved Ayurvedic medicinal products that some of these products may contain high levels of heavy

metals. Consumption of excessive amounts of heavy metals, such as lead, mercury, and arsenic, pose serious health risks.

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

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

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

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

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

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

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

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

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

Health Canada Sep/08 is advising consumers not to use 3 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lover Liquid Nutriment Herbal Supplement and Onyo** because they were found to contain undeclared pharmaceutical ingredients. **Lover Liquid Nutriment Herbal Supplement** was found to contain sildenafil while Onyo was found to contain sildenafil, as well as unapproved substances with structures similar to sildenafil and vardenafil. The U.S. Food and Drug Administration warned consumers not to use the product **Rose 4 Her** because it was found to contain an undeclared ingredient similar to the prescription drug sildenafil.

Health Canada Sep/08 is advising consumers not to use 6 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Dr. Life** or **Chong Cao Ju Wang** because they were found to contain undeclared pharmaceutical ingredients. Dr. Life contains an unauthorised substance similar in structure to tadalafil while Chong Cao Ju Wang contains sildenafil. The Hong Kong Department of Health warned against the use of **Hanguo shoushen yihao** (meiti xing) because it was found to contain the undeclared pharmaceutical ingredient sibutramine. The U.S. Food and Drug Administration alerted consumers to a voluntary recall of 32-ounce plastic bottles of **Liquimax Complete Nutrition Multivitamin Formula** (UPC codes 7497052290, 7497023607 or 7497023696) because the product may contain undeclared fish (not shellfish), tree nuts (almonds, pecans, and/or walnuts), and wheat. People with sensitivities to fish, tree nuts and/or wheat may risk serious or life-threatening allergic reactions if they consume these products. The Hong Kong Department of Health warned against the use of **ARMA - Sin Gang San** and **New ARMA - Sin Gang San** because they were found to contain the undeclared pharmaceutical ingredients sibutramine and fenfluramine.

Health Canada Oct/08 is advising consumers not to use 2 foreign health products due to concerns about possible side-effects: Swissmedic warned consumers not to buy or use the product **Powertabs** because it contains an unauthorised substance similar in structure to sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Sweet Energizer Vitality** Candy because it was found to contain an unauthorised substance similar in structure to tadalafil.

Health Canada Nov/08 is advising consumers not to use 5 foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lu Quan** because it contains undeclared glibenclamide and sildenafil. The Hong Kong Department of Health warned consumers not to buy or use **Fat Killer, Carbohydrate Cut and Sugar-Carbohydrate Cut** because they contain sibutramine and an unauthorised substance similar in structure to sibutramine, and **Zhuang Yao Gu Shen** Capsule because it contains sildenafil.

Health Canada Nov/08 is advising consumers not to use 13 foreign health products due to concerns about possible side-effects: The U.S. FDA warned consumers not to buy or use **Viapro** because it contains an unauthorised substance similar in structure to sildenafil. Sildenafil is a prescription drug used in the treatment of erectile dysfunction and should only be used under the supervision of a health care practitioner.

The U.S. Food and Drug Administration informed consumers of a voluntary manufacturer recall of these 12 products because they contain human **placenta, aristolochic acid and/or ephedra**, and may pose serious health risks. All 12 products are manufactured by **Jen-On Herbal Science**

International Inc. (also known as **Herbal Science International Inc**.). Consumers who had purchased these products were advised to discontinue their use immediately and return them to the place of purchase for a full refund.

Health Canada Nov/08 is warning consumers not to use **Firm Dose** and **Granite Rooster**, two products promoted to enhance male sexual performance, as these products may pose serious health risks. Firm Dose was found to contain similar to sildenafil, while Granite Rooster was found to contain similar to tadalafil.

Health Canada Nov/08 is advising consumers not to use the unauthorized product, Kwan Loong Medicated Oil, as it contains chloroform. Foreign Product Alerts: Seng Jong Tzu Tong Tan,Tou Tong San (Headache Formula),Du Huo Ji Sheng ,Tang (Du Huo Joint Relief), Wu Yao Shun Qi San, Qing Bi Tang (Nasal Cleanser), Zhong Fong Huo Luo Wan (Stroke Revito Formula), Xiao Qing Long Tang (Little Green Dragon), Ding Chuan Tang (Breathe Smooth), Xiao Xu Ming Tang, Feng Shi Zhi Tong Wan (Joint Relief),,Guo Min Bi Yan Wan, Fang Feng Tong Sheng San.

Health Canada Jan 2009 is advising consumers not to use 4 foreign products: **Zhuang Tjar Gere** because it contains the undeclared prescription drugs sildenafil & tadalafil, **Zhixhue** Capsules manufactured by Vital Pharmaceutical Holdings Ltd. due to concerns of serious side- effects including liver dysfunction, **Tonik Warisan Banjar** because it contains undeclared dexamethasone & **Healthily Slim** because it contains sibutramine.

Health Canada Mar/09 Foreign Product Alerts: **68 Weight Loss Products**; Best-life Fat Burning Capsules; Bevidan;Huiji Yin Chiao Chieh Tu Pien; Relacore -plus Lami, Linglongquxian, Menergy M-Essence, Nyal Day & Night Cold & Flu Fighter (AUST L 146264), Nyal Cold & Flu Fighter (AUST L 146263), 999 Radix Notoginseng, Batch no. 0807021, Slim Pure, Carbohydrate, Kalomee, K Carbohydrate, K Tighten Slim, & K Slimming Pills. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_fpa-ape_2009/index-eng.php

Health Canada June/09 Foreign Product Alerts: **Fangocur Mineral Drink** (undeclared arsenic); **Jia Yi Jian** (undeclared sibutramine & tadalafil);**Fortodol**, which is also sold under the names (undeclared nimesulide with liver concern) of Donsbach Miradin, Lepicol Miradin, Leppin Miradin, & Miradin; **Shan Dian Qiang Xiao Shou** (undeclared sibutramine & phenolphthalein); **Zencore Plus** (undeclared benzamidenafil) & **Zhong Guo Shen Fang** (undeclared med like sildenafil).

Health Canada June/09 is warning consumers not to use the unauthorized product **Slim Magic Herbal**, which is promoted as a weight-loss product, as it was found to contain an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning consumers not to use the unauthorized product **Nutural Slim**, which is promoted as a weight-loss product, as it was found to contain the undeclared pharmaceutical ingredient sibutramine and also an undeclared pharmaceutical ingredient similar to sibutramine.

Health Canada June/09 warns of foreign Product Alerts: **Herbal Xenicol** because it contains undeclared cetilistat. **BioEmagrecim**, which the FDA had previously warned contained sibutramine, was also found to contain fluoxetine, furosemide and fenproporex. Products: **Slimbionic, Xsvelten, 999 Fitness Essence, 24" ince, Light Some, Paiyouji, Pearl White Slimming, & Reducing Weight Easily** contain undeclared pharmaceutical ingredients (sibutramine and/or phenolphthalein) and/or excessive levels of lead, and may cause serious health effects..

Health Canada July/09 is warning consumers not to use the unauthorized health product labelled as **Specific-Formula Arthro-Ace** as it was found to contain undeclared dexamethasone and may cause serious health effects.

Health Canada July/09 is warning that the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **Air Ikan Haruan** after it was found to contain undeclared dexamethasone. The Hong Kong Department of Health warned consumers not to buy or use the product **Neovidan** after it was found to contain undeclared prednisolone and mefenamic acid. Plus the Singapore Health Sciences Authority (HSA) warned consumers to not buy or use **XP Tongkat Ali Supreme** after it was found to contain undeclared tadalafil.

Health Canada Aug/09 is advising via Singapore Health Sciences Authority (HSA) warned that **Delima Raja Urat** contains undeclared dexamethasone, chlorpheniramine, pheniramine and sibutramine, while **Cao Gen Bai Lin Wan** contains undeclared dexamethasone and chlorpheniramine.

Health Canada Oct/09: **Bao Ling**- The Singapore Health Sciences Authority advised consumers not to buy or use since contained undeclared betamethasone, hydrochlorothiazide & chlorpheniramine. **Dynasty Worldwide Jinglida So Young Formula**- The Singapore Health Sciences Authority (HSA) warned consumers to not buy or use since contained undeclared aminotadalafil. **STEAM** lot#80214, 90260 -The U.S. FDA informed consumers of a voluntary manufacturer recall of two lots of STEAM after FDA testing found these lots to contain undeclared sulfoaildenafil (lot# 80214) & undeclared tadalafil (lot# 90260). **Syntrax Fyre (contained Yohimbine)**, **Texiao Fengshi Gutong Ling (contained indomethacin)**, **Kam Yuen Brand Wan Ying Yang Gan Wan (contained sildenafil)** - The Hong Kong Department of Health warned consumers not to buy or use these three products after they were found to contain undeclared pharmaceutical substances.

Health Canada Nov/09 is advising Canadians not to consume Chaotic Beverages sold under the brand names Mind Strike, Fearocity, Elixir of Tenacity and Power Pulse because they are unauthorized products marketed to a vulnerable population (children) with ingredients that may pose a health risk. **Mind Strike:** Contains an unknown amount of caffeine despite advertising that it is not an energy drink and contains several herbs which are not included in Health Canada's list of botanicals with a history of safe use in children. **Fearocity:** Contains an unknown amount of caffeine, several herbs not included in Health Canada's list of botanicals with a history of safe use in children, taurine at an unacceptable level for children, and niacin at a level three times higher than that recommended for children aged 1 to 13 years. **Elixir of Tenacity:** Contains green tea extract, which is not included in Health Canada's list of botanicals with a history of safe use in children, and vitamin A at a level unacceptable for children aged 1 to 8 years. **Power Pulse:** Contains chromium picolinate at levels of possible concern in a product taken by children.

Health Canada Nov/09 is warning consumers not to use Herblex "**Once More**"since it was found to contain sildenafil.

Health Canada Dec/09 is advising Canadians not to use certain Acai Berry products after a large number of shipments of adulterated products were stopped at the border. The product names include: **Anti-Aging Acai Berry, Guarana Blast, Brazillian Pure, Anti-aging Vital Rez V, Weight Loss VitalAcai, Dietary Supplement Acai Power Blast and Muscle Mass**. These products advertised for anti-aging and weight loss were found to contain undeclared sildenafil.

Health Canada Dec/09 is warning consumers not to use "**RevolutionDS Weight Loss**", an unauthorized health product promoted for weight loss, because it contains benzylpiperazine (BZP), and may pose serious health risks.

Health Canada Dec/09 is advising consumers not to use the following foreign health products: 1. **Power-Plus P**: The Singapore Health Sciences Authority issued a recall notice for Power-Plus P (expiry date 03/03/2011) after it was found to contain undeclared tadalafil. 2. **Show Party**: The Hong Kong Department of Health warned consumers not to buy or consume Show Party [shou-shen pai] after it was found to contain undeclared sibutramine and phenolphthalein. 3. **Zeng Da Yan Shi Wan**: The Hong Kong Department of Health warned consumers not to buy or use after it was found to contain undeclared sildenafil.

Health Canada Jan/10 informs that Finish Food Safety Authority: **Full Contact Max Potency** contains thio-sildenafil and thio-homosildenafil; Singapore Health Sciences Authority: **M-Action** contains desmethylacetildenafil and acetilacid. U.S. FDA: **RockHard Weekend** contains sulfoaildenafil; & **Pai You Guo** contains

sibutramine and phenolphthalein. Hong Kong Department of Health: **Ku Xiu Ba Xiang Jian Fei Wan** contains sibutramine and an unauthorized substance similar to sibutramine; **Super Slim (Yani)** contains sibutramine and phenolphthalein; **SHoufsy** contains sibutramine & **MIGAC (sic) FAT BURMING (sic) FACTOR** contains sibutramine.

Health Canada Jan/10 is advising consumers not to use the unauthorized product "**Stiff Nights**" after the U.S Food and Drug Administration (FDA) found that this product contains an undeclared substance similar to the prescription drug sildenafil.

Health Canada Jan/10 is warning consumers not to use the unauthorized product "**The Slimming Coffee**," which was previously sold as "**Lose Weight Coffee**," because it was found to contain sibutramine.

Health Canada Jan/10 is advising consumers not to use any unauthorized health products sold under the brand names **Natural Choice Vitamin B-17**, **Natural Choice Kava Kava** and **Natural Choice Lithium Orotate**. The unauthorized Natural Choice Vitamin B-17, according to what is listed on the product label, contains amygdalin which is a compound derived from bitter apricot kernels that has the potential to release cyanide when ingested by humans. The unauthorized Natural Choice Kava Kava, according to what is listed on the product label, contains kava lactones & agencies have received reports associating the use of kava with serious liver dysfunction.

Health Canada Jan/10 is advising Canadians that natural health products containing the ingredient **glucomannan** in tablet, capsule or powder form, which are currently on the Canadian market, have a potential for harm if taken without at least 8 ounces of water or other fluid.

Health Canada Feb/10 is advising consumers that the unauthorized product "**Complete 7-Day Cleanse**" is being recalled because it contains a number of active ingredients with a combined effect that may pose serious health risks. "Complete 7-Day Cleanse" is a multi-ingredient natural health product promoted for "cleansing" or removing toxins from the body. According to package labelling, the product contains over 30 active ingredients, some having a diuretic (water pill) or laxative (stimulant, and bulk-forming) effect.

Health Canada Feb/10: **2H & 2D**- Hong Kong Department of Health (HKDH) warned consumers not to buy or use 2H & 2Dafter it was found to contain undeclared tadalafil. Products distributed by **Atlas Operations Inc**. The FDA informed consumers of a voluntary recall by Atlas Operations Inc. of certain lots of some products that were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil. Products distributed by **Bodybuilding.com** The FDA informed consumers of a voluntary recall of 65 bodybuilding products as these products may contain the following anabolic steroids: "Superdrol," "Madol," "Tren," "Androstenedione," and/or "Turinabol." **STRO Emperor** Capsules The Irish Medicines Board warned consumers not to buy or use STRO Emperor Capsules after it was found to contain undeclared tadalafil. **Tian Yang Xu Huo Oral Ulcer** Capsule Singapore Health Sciences Authority issued a recall notice for one batch (batch number 0812003, expiry date 11.2011) of Tian Yang Xu Huo Oral Ulcer Capsuleafter it was found to contain undeclared aristolochic acid.

Health Canada Mar/10 is warning Canadians that an unapproved health product, **POWER-MAX** that contains sildenafil.

Health Canada Mar/10 is warning Canadians that an unauthorized health product, "**Herbal Diet Natural**" has been found on the Canadian market and contains an undeclared pharmaceutical ingredient similar to the prescription drug sibutramine.

Health Canada is warning Canadians that an unauthorized health product, "**West Pharm Therma Lean Fat Burner Energizer**" was found on the Canadian market. West Pharm Therma Lean Fat Burner Energizer contains Ephedrine and caffeine, which combined together, may cause serious and possibly fatal adverse effects.

Health Canada Apr/10 is warning Canadians that an unauthorized health product, "**Slim-30**" distributed in Ontario and Quebec by Duxx Enterprises Inc., contains an undeclared pharmaceutical ingredient similar to the prescription drug, sibutramine.

Health Canada May/10 consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Ba Bao Xiao Ke Dan** The Hong Kong Department of Health warned consumers not to buy or use Ba Bao Xiao Ke Dan after it was found to contain undeclared glibenclamide. 2. **Bao Shu Tang Wu Zi Yan Zong Wan** The Hong Kong Department of Health warned consumers not to buy or use Bao Shu Tang Wu Zi Yan Zong Wan after it was found to contain excessive levels of lead, a heavy metal. 3. **Lin Yan Yin Chiao** The Singapore Health Sciences Authority issued a recall notice for one batch (batch# JI0324, expiry date 03/2011) of Lin Yan Yin Chiao after it was found to contain undeclared chlorpheniramine and paracetamol (acetaminophen). 4. **Man Power** The Hong Kong Department of Health warned consumers not to buy or use Man Power product after it was found to contain undeclared tadalafil. 5. 17 products sold through **MuscleMaster.com** (see Foreign Product Alert for a complete product list) The FDA informed consumers of a voluntary recall of the 17 bodybuilding products as they may contain the following anabolic steroids: "Superdrol," "Madol," "Tren," "Androstenedione," and/or "Turinabol." 6. **Seven Slim 7 Seshou** (Qingchun Shaonüxing, Jieshixing, Guifurenxing, Songchixing), Shoushen Jiaoguan-Tinei Yundong Wan (Jian Xiabanshen, Jian Quanshen Feipang) The Hong Kong Department of Health warned consumers not to buy or use the six products listed above after they were found to contain undeclared sibutramine and phenolphthalein.

Health Canada May/10 is advising consumers not to use 1. **Botanical Slimming 100% Natural Soft Gel, also sold as Meizitang** The Australian Therapeutic Goods Administration warned consumers not to buy or use this product after it was found to contain undeclared sibutramine. 2. **Marsha Slim Plus** The Hong Kong Department of Health warned consumers not to buy or use Marsha Slim Plus after it was found to contain undeclared sibutramine, an unauthorized substance similar to sibutramine and phenolphthalein. 3. **S&S Super Slender** The Hong Kong Department of Health warned consumers not to buy or use S&S Super Slender after two samples were found to contain agent similar to sibutramine. One of the tested samples also contained undeclared sibutramine and phenolphthalein.

Health Canada June/10 is warning Canadians that the unauthorized health products "**Vigofit**" and "**Once More**," which are promoted to enhance male sexual performance, have been seized by Health Canada inspectors from retail stores in Abbotsford and Surrey, British Columbia. These two products contain sildenafil.

Health Canada June/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **COMECOO, ZHONGCAOYAO-JIANKANGJIANFEI** The Hong Kong Department of Health warned consumers not to buy or consume these two products after they were found to contain undeclared phenolphthalein, sibutramine and two unauthorized substances similar to sibutramine. 2. **Qingzhi Santian Shou** The Hong Kong Department of Health warned consumers not to buy or consume Qingzhi Santian Shou after it was found to contain undeclared sibutramine and an unauthorized substance similar to sibutramine. 3. **Vita Breath** The U.S. FDA warned consumers not to buy or consume Vita Breath because it may contain hazardous levels of lead, which is a heavy metal.

Health Canada July/10 is advising consumers not to use the following foreign health product(s) due to concerns about possible adverse reactions: 1. **Stud Capsule For Men** The U.S. FDA informed consumers of a voluntary recall of one lot (Lot #060607-01/060108-01 Exp 6-2013) after it was found to contain undeclared Sildenafil. 2. **Po Chai Pills** (capsule form) The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain undeclared sibutramine and phenolphthalein. Sibutramine is a prescription drug and should only be used under the supervision of a health care practitioner while phenolphthalein is no longer authorized for sale in Canada because it may cause cancer. Po Chai Pills (capsule form) has been recalled by the manufacturer. 3. **LiPO-8 Cap and Glucomi 600 Cap** The Hong Kong Department of Health warned consumers not to buy or use these products because they contain undeclared sibutramine.

Health Canada July/10 is advising Canadians about "**UP Ultimate Performance for Men**", an unauthorized health product containing undeclared sildenafil.

Health Canada July/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1 Body Beautiful** The Hong Kong Department of Health warned consumers not to buy or consume *1 Body Beautiful* after it was found to contain undeclared phenolphthalein and sibutramine. 2. **USA Yaku Cell Slimming Capsules, Dong Gua Pai You Su, Qing Gua Pai You Su, and Mu Gua Pai You Su** The Hong Kong Department of Health warned consumers not to buy or consume these four products after they were found to contain undeclared phenolphthalein, sibutramine and an unauthorized substance similar to sibutramine. 3. **Atlas Operations Inc. expands its U.S. recall of over 30 sexual enhancement supplements** The U.S. FDA informed consumers of an expanded recall of certain lots of products after some were found to contain undeclared sulfoaildenafil. The products are being voluntarily recalled nationwide in the U.S. by the company Atlas Operations Inc. 4. **Stallion, SZM Formula for Men, Tomcat Ali and Volcanic** New Zealand's Medsafe warned consumers not to buy or use these four products after they were found to contain undeclared tadalafil. 5. **Vitalex for men and Vitalex for women** The U.S. FDA informed consumers that the *Vitalex*products were found to contain acetildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada Aug/10 says **Fulda Unitang Herbs Sleep Plus**, an unauthorized product promoted as an herbal sleep aid, has been found to contain high levels of estazolam.

Health Canada July/10 Unauthorized Health Products Sold by **Marigold Natural Pharmacy Ltd**. May Pose Health Risks. These products (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_126bk-eng.php) were made available to Canadians via the company's pharmacy in Courtenay, British Columbia and via their website (http://www.marigoldnaturalpharmacy.com).

Health Canada July/10 is advising consumers not to use the following foreign health product(s): **Huo Luo Jing Dan** The Singapore Health Sciences Authority warned consumers not to buy or consume Huo Luo Jing Dan after it was found to contain undeclared indomethacin, dexamethasone and prednisolone. Kam Chik San The Hong Kong Department of Health (HKDH) cautioned against the use of **Kam Chik San** after samples were found to contain mercury at a level much higher than permitted by the HKDH. **Magic Power Coffee** The U.S. FDA warned consumers not to buy or use Magic Power Coffee after it was found to contain undeclared hydroxythiohomosildenafil, which is an unauthorized substance similar to sildenafil. **Que She** The U.S. FDA warned consumers not to buy or use Que She after it was found to contain undeclared fenfluramine, propranolol, sibutramine and ephedrine. **Sheng Yuan Fang** The Hong Kong Department of Health (HKDH) warned consumers not to buy or use Sheng Yuan Fang after it was found to contain undeclared phenolphthalein and sibutramine.

Health Canada July/10 is informing Canadians that **Marché Euromix**, a retail store in Pierrefonds (Montréal), was found to be selling a health product that was not authorized for sale by Health Canada and that closely resembled in appearance an authorized drug, Viagra.

Health Canada Aug/10: "**SeXXX DRIVE**", promoted as a herbal supplement to enhance male sexual performance, & Health Canada found hydroxyhomosildenafil.

Health Canada Aug/10 has seized the unauthorized sexual enhancement supplements "**Male Enhancement ExtenZe**" and "**Women ExtenZe**" imported and sold by the Happy Paradise Adult Store in Burnaby, British Columbia. The labels of each of these unauthorized products list the prescription ingredient pregnenolone and the controlled drug, DHEA (dehydroepiandrosterone). The labels of the unauthorized "Male Enhancement ExtenZe Nutritional Supplements" list the ingredient yohimbe extract (bark).

Health Canada Sep/10 **E.O.D. Erection on Demand**" being promoted as a herbal to enhance male sexual performance, the product was tested by Health Canada and found to contain tadalafil.

Health Canada Sep/10: "**Arth-Forth**", an unauthorized product promoted as an herbal supplement and distributed by Ka Wing Hong Ltd., was tested by Health Canada and found to contain a steroid prescription drug, dexamethasone.

Health Canada Sep/10 is advising consumers not to use : 1. **Golden aryuru, Baisheng wei ge, Zhonghua niubian, Ten ka dai 1 bou, Kuai gan bei zeng chao yue zi wo (Happy felling doubly increase [sic]), Ling tou lang, SkyFruit, Chu bi ho ken, Jinbolang, Suika Koso, Lov, I ka ou (2009 nen sin hoso) and/or I ka ou (saisinsui shutsu hoso)** The Japanese Ministry of Health, Labour and Welfare warned consumers not to buy or use the 12 products listed above because they were found to contain undeclared sildenafil and/or other unauthorized substances similar to sildenafil that may pose similar health risks (norhongdenafil, acetil acid, and tioqinapiperifil). 2. **Joyful Slim Herb** Supplement The U.S. FDA informed consumers of a recall of one lot (#101408) of Joyful Slim Herb Supplement after FDA tests found it to contain undeclared desmethyl sibutramine. The lot is being voluntarily recalled nationwide in the U.S. by the company J & H Besta Corp. 3. **Vialipro** The U.S. FDA informed consumers of a recall of certain lots of Vialipro after FDA tests found product samples to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada Sep/10 **Exemption number**: This will help with the backlog of applications for a licence. Exemptions will be given to natural products that have passed an initial assessment of safety, quality, and efficacy. These products will be given an exemption number (EN)...instead of a Natural Product Number (NPN) or Drug Identification Number-Homeopathic Medicine (DIN-HM)...until they are fully reviewed by Health Canada.

Health Canada Nov/10 **Amana Care Seven Slim Herbal Capsules**: The Israel Ministry of Health informed consumers that it found the product Amana Care Seven Slim Herbal Capsules to contain undeclared sibutramine and residue of sildenafil. Arrow Brand Medicated Oil & Embrocation: The U.S. FDA warned consumers not to buy or use **Arrow Brand Medicated Oil & Embrocation** because it contains ingredients that are potentially poisonous, particularly in children. **Beijing 101 Hair Consultants: Hair Growth Formula D-2653-Band Hair Growth Tonic E-0583-D**: The Singapore Health Sciences Authority advised consumers to stop using one batch of these products (Beijing 101 Hair Consultants Hair Growth Formula D-2653-B batch# 20091201, and Hair Growth Tonic E-0583-D batch# 20091201) after testing of these batches revealed the presence of undeclared minoxidil. **101 Zhangguang: Gold 101 Super Effective Hair Growth Agentand Fabao 101D Doctor Zhao's Chinese Traditional Herbal Hair Care Formula**: The Hong Kong Department of Health warned consumers not to buy or use these two products after they were found to contain undeclared minoxidil.

Health Canada Nov/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Goya–Bitter Melon - Miyura Fit'x Capsules** contained undeclared phenolphthalein and sibutramine **2. MasXtreme** contains undeclared aminotadalafil while the other (#911035) contains undeclared aildenafil and phentolamine **3. Mr. Magic Male Enhancer from Don Wands** contained hydroxythiohomosildenafil and sulfoaildenafil **4. So Hard for Men - Pulse8 for Women - The Rock – Tonic 66** contained the undeclared pharmaceutical substances tadalafil, sildenafil, and/or hydroxyhomosildenafil **5. Solo Slim Extra Strength - Revivexxx Extra Strength** contained undeclared didesmethyl sibutramine **6. TimeOut** contained undeclared hydroxythiohomosildenafil.

Health Canada Nov/10 "**Fat Burner No. 1**" (labelled in Chinese characters translated as "**Qian Mei Yin Zi**", an unauthorized Chinese herbal weight loss medicine, is being voluntarily recalled by Ying Tai TCM Supplying Ltd. after Health Canada lab tests revealed the product contains two pharmaceutical ingredients: a chemical similar to sibutramine (N,N- didesmethylsibutramine), and sildenafil.

Health Canada Dec/10 "**Durazest**" and "**Once More**": Certain lots of two male sex enhancement products recalled as they may pose serious health risks. Certain lots (listed below) of two health products promoted for male sexual enhancement, "Durazest for Men" and "Once More," have been voluntarily recalled by Natural Performance Products Ltd. Health Canada laboratory tests identified the presence of a chemical similar to tadalafil (nortadalafil) in one lot of each product.

Health Canada Dec/10 is informing Canadians that NorthRegentRx has begun to voluntarily recall its product, **ResurreXX** from the Canadian market. NorthRegentRx is requesting that wholesalers,

distributors and retailers stop sale of this product since contained an undeclared substance "hydroxyhomosildenafil".

Health Canada Dec/10 has been advised "**Flat Stomach Concept Extra**" is being voluntarily recalled by Les Produits Naturels Leblanc Inc due to missing label statements related to duration of use, risks and contraindications. Information missing from the label of Flat Stomach, a product contained within the Flat Stomach Concept Extra kit, may result in potential chronic use of aloe, which can lead to bowel dependence, and electrolyte imbalance.

Health Canada Dec/10 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: 1. **Slimming Beauty Bitter Orange Slimming Capsule** (Slimming Beauty) The U.S. Food and Drug Administration warned consumers not to buy or use Slimming Beauty after FDA lab tests revealed that this product contains undeclared sibutramine. 2. **Shaguar, Signature Signergy, VIGRX (green capsule), VIGRX (white capsule), VigRx, VigRX Plus** New Zealand's MedSafe warned consumers to not buy or use these products after they were found to contain undeclared sildenafil, hydroxyhomosildenafil, thiosildenafil, and/or tadalafil. 3. **ArimaDex**, **Clomed** The U.S. Food and Drug Administration informed consumers that ArimaDex and Clomed are being recalled in the U.S. because they may contain an aromatase inhibitor. ArimaDex and Clomed are being voluntarily recalled by G.E.T. and KiloSports Inc., respectively.

Health Canada Dec/10 Three Probiotic Natural Health Products May Pose Serious Health Risks to Canadians with Milk or Soy Allergies. Consumers with milk or soy allergies are advised that three probiotic natural health products are being voluntarily recalled from the market because they are labelled as not containing dairy(milk) and/or soy but may contain trace amounts of milk or soy protein from ingredients used in the production process. **Saccharomyces Boulardii** (NPN 80013551) Advanced Orthomolecular Research Inc. (AOR); **Herbasaurs Bifidophilus for Kids** (NPN 80015508) & **Acidophilus Bifidobacterium** (NPN 80015336) by Nature's Sunshine Products of Canada Ltd & **Cultures de Yogourt 2 Milliards** (NPN 80013273 Bio-Dis Inc.

Health Canada Jan/11 The product **Synerate**, manufactured for Strive and distributed by Upper 49th, is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. Synerate, a product used for weight loss or body building, contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Jan/11 **Nutrex Research Lipo 6X** is being voluntarily recalled from the Canadian market because of the risk of serious, potentially fatal adverse effects from the combination of the ingredients in the product. It contains caffeine and synephrine, which is similar to ephedrine.

Health Canada Feb/11 is advising consumers not to use the following foreign health products promoted for sexual enhancement due to the presence of unauthorized substances (PDE5 derivatives eg. sildenafil): **1. Aziffa, Erex, Eyeful, Hard Drive, Libidinal, Maxyte, Mojo, Monster Excyte, OMG, OMG45, Prolatis, Red Magic, Size Matters, Stiff Nights, Straight Up, Verect, WOW, Xaitrex, Xytamax, Zilex (with Golden Spear), Zotrex 2. Prolatis' Duro Extend Capsules For Men 3. Tiger King 4. Vigor-25, Man Up Now**

Health Canada Feb/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Fruta Planta, Reduce Weight Fruta Planta** The U.S. FDA warned consumers not to buy or use Fruta Planta and Reduce Weight Fruta Planta after FDA lab tests revealed that this product contains undeclared sibutramine. **2. RockHard Weekend (lots 100159 and 100260 sold as blister packs, 3-count bottles and 8-count bottles)** The U.S. FDA informed consumers of a nationwide voluntary recall of certain lots (see above) of RockHard Weekend and Pandora after lab tests confirmed the products contain an unauthorized substance similar to sildenafil that may pose similar heath risks. **3. Slimming Factor** The Australian TGA warned consumers not to buy or use Slimming Factor after TGA lab tests confirmed the presence of the undeclared substances sibutramine, fenfluramine and phenolphthalein. According to the TGA release, the product is sold over the Internet.

Health Canada Mar/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Celerite Slimming Capsules:** The U.S. FDA informed consumers of a company recall of Celerite™ Slimming Capsules after it was found to contain undeclared sibutramine. **2. Herbal Flos Lonicerae (Herbal Xenicol) Natural Weight Loss Formula:** The product was found to contain undeclared sibutramine at more than twice the dose that was normally prescribed before sibutramine was removed from the UK market in 2010. **3. Magicream:** The Irish Medicines Board warned consumers not to buy or use Magicream after it was found to contain undeclared clobetasol propionate and ketoconazole. **4. Nite Rider Maximum Sexual Enhancer for Men - STUD Capsule for Men:** The U.S. FDA informed consumers of a company recall of these products after they were found to contain undeclared sildenafil.

Health Canada April/11 Consumers with milk or soy allergies are advised that four probiotic natural health products {**Saccharomyces Boulardii (NPN 80013551), Herbasaurs Bifidophilus for Kids (NPN 80015508), Acidophilus Bifidobacterium (NPN 80015336), Cultures de Yogourt 2 Milliards (NPN 80013273)**} are being voluntarily recalled from the market because they are labelled as not containing dairy (milk) and/or soy but may contain trace amounts of milk or soy protein from ingredients used in the production process.

Health Canada Apr/11 has identified the presence of microbial contamination in "**Mary Ginseng House 100% Pure High Calibre Pow Sum Ontario Ginseng**", that may pose a health risk to immune-compromised individuals.

Health Canada May/11 "**Omega Alpha Kidney Flush**" Being Recalled from the Canadian Market: May Cause Serious Adverse Reactions in Pregnant Women and Kidney Disease Patients.

Health Canada May/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Dr. Health Series CM Factor** The Hong Kong Department of Health warned consumers not to buy or use this product after it was found to contain an unauthorized substance similar to sibutramine that may pose similar health risks. **2. Gold Seagull Long Zhi Wan, Venergy** The Hong Kong Department of Health advised consumers not to buy or use these products after Gold Seagull Long Zhi Wan was found to contain undeclared glibenclamide, while Venergy was found to contain undeclared sildenafil. **3. JianBu HuQian Wan** The HSA warned consumers not to buy or use JianBu HuQian Wan after it was found to contain undeclared dexamethasone and chlorpheniramine. **4. Rock Hard Extreme, Passion Coffee** The U.S. FDA advised consumers not to buy or use these products after they were found to contain undeclared sulfoaildenafil, which is an unauthorized substance similar to sildenafil and may pose similar health risks.

Health Canada July/11 "**Man Up Now**" Removed From Sale at Delta and Surrey Stores: May Pose Serious Health Risks to Canadians, was removed from sale at "O! Behave" retail stores in Delta and Surrey, B.C. after Health Canada's testing identified undeclared sildenafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products. These products were also removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. {**Sildenafil: in BAOLONG Switzerland Rolex 168 Prolong Time, BAOLONG Yilishen, Black Gold, Herbal Viagra, "Jin Chong Chao - Golden Cordyceps", Lubiangaowansu, MAGNA-RX, MAXMAN II capsules, Shenrong dabuwan, Traditional Chinese Medicine Viagra, V100, VIGER, VigRX for Men, VINIX capsules, Wolf, "XiongBaTian", Zang Gong Mi Lian Nan Bao} & Zeng Bei Jiu Zhan-Tadalafil.**

Health Canada July/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Beline Capsules** The U.K. Medicine and Healthcare products Regulatory Agency (MHRA) advised consumers not to use *Beline Capsules* after it was found to contain undeclared chlorpheniramine, an over-the-counter antihistamine drug. **2. Black Ant** The U.S. Food and Drug Administration warned consumers to immediately stop using *Black Ant* after it was found to contain undeclared sildenafil at an amount three times the starting dosage for the approved prescription drug product. **3. [Hua Tuo Brand] Youzhi Baoying Dan, [Lee Sze] Texiao Houtong Wan and Prolonged Man Power Essence** The Hong Kong Department of Health (HKDH) warned consumers to not use these products after they were found to contain excessive levels of mercury, lead, or arsenic, which are heavy metals. **4. Natural Vigra VIAGRA Tablets and Satibo Capsules** The Australian Therapeutic Goods Administration (TGA) advised consumers to stop using *Natural Vigra VIAGRA Tablets* after it was found to contain undeclared sildenafil, and *Satibo Capsules* after it was found to contain undeclared tadalafil and hydroxyhomosildenafil. **5. Slim Xtreme Herbal Slimming Capsules** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *Slim Xtreme Herbal Slimming Capsules* was found to contain undeclared sibutramine. **6. X-Hero and Male Enhancer** The U.S. Food and Drug Administration informed consumers of a voluntary recall after *X-Hero* was found to contain undeclared sulfosildenafil while *Male Enhancer* was found to contain undeclared tadalafil.

Health Canada July/11 is advising Canadians that we have updated our list of unauthorized health products to include a new product, **Tibet Babao**, which was found to contain undeclared sildenafil, a prescription erectile dysfunction drug. This product and several others have been removed from sale at the **Happy Paradise Adult Store in Burnaby, B.C**.

Health Canada Aug/11 is advising consumers not to use the following foreign health products due to concerns about possible adverse reactions: **1. Celerite Slimming Tea** The U.S. FDA informed consumers of a company recall of Celerite Slimming Tea after it was found to contain undeclared sibutramine. **2. Pink Lady for Women Capsules, St Nirvana Herbal Slimming Capsules** The Australian TGA warned consumers not to use these products after Pink Lady for Women Capsules was found to contain undeclared tadalafil while St Nirvana Herbal Slimming Capsules was found to contain undeclared sibutramine and phenolphthalein. According to the TGA advisories, these products are sold over the Internet. **3. Fifteen products**

promoted for weight loss The Hong Kong Department of Health (HKDH) warned consumers not to buy or use these 15 products after they were found to contain at least one of the following undeclared substances: phenolphthalein, sibutramine, and/or an unauthorized substance similar to sibutramine.

Health Canada Sep/11 **Bi Yan Pian** Recalled Due to Excessive Amount of Mercury. Wing Quon Enterprises Ltd has initiated a stop sale and is voluntarily recalling a natural health product, Bi Yan Pian (NPN# 80023876) from the Canadian market after the product was found to contain an excessive amount of mercury.

Health Canada Oct/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **Slim Forte Slimming Capsules**, **Slim Forte Double Power Slimming Capsules**, **Slim Forte Slimming Coffee** and **Meizitang Botanical Slimming Soft Gel**-The U.S. Food and Drug Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **OxyELITE Pro capsules and Pure Fat Three Days Reduce Weight capsules**- The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine), or a prescription drug (yohimbine). **SXL Sexcellence sachets**- The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains an unauthorized drug (sulfosildenafil). [W.S] **Gan Mao Ling and Chaisentomg Baby's Kam Chik San Powder** - The Hong Kong Department of Health warned that these Chinese health products contain excessive levels of heavy metals (lead or arsenic). **Huo Li Bao and Ren Sem Tu Chon Chin Kuo Pill** - The Singapore Health Sciences Authority warned that these Chinese pain-relief products contain prescription and/or over-the-counter drugs (furosemide, piroxicam, chlorpheniramine, and/or dexamethasone).

Health Canada Nov/11 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Zhui Feng Bao Wei San** The Singapore Health Sciences Authority warned that this health product contains excessive levels of microbial contamination. **2. Metabolic Advantage** The Singapore Health Sciences Authority warned that this weight-loss product contains prescription drugs (thyroid hormones). **3. Majun Dua Istimewa, Raja Maajun-Jerat Dan Seret Angin, and Horkut Chooi Foong Hor Lok Tan** The Singapore Health Sciences Authority warned that these traditional medicines contain undeclared prescription and over-the-counter drugs (dexamethasone, indomethacin, chlorpheniramine, dextromethorphan and acetaminophen). **4. Tian Ma Tu Chung Seven Leave Ginseng, Vall-Boon Tongkat Al, and Pao Ni Kang** The Singapore Health Sciences Authority warned that these traditional herbal products contain prescription and over-the-counter drugs (dexamethasone, ketoconazole, repaglinide, pheniramine, and chlorpheniramine). **5. Slimming Kapsul** The Hong Kong Department of Health warned that this weight-loss product contains an unauthorized drug (sibutramine) and a prescription drug (spironolactone). **6. Pancre-Plus** The Hong Kong Department of Health warned that this counterfeit Chinese medicine contains an unauthorized drug (phenformin) and a prescription drug (glyburide). **7. Maxidus capsules, Chao Jimengnan SuperPowerful Man tablets, Fu Yuan Chun capsules, and Qing Tian Zhu tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain prescription drugs (sildenafil, tadalafil) and/or unauthorized drugs (sulfohydroxyhomosildenafil, sulfosildenafil).

Health Canada Nov/11: An unauthorized health product, "**Stiff One Hard 169**" is being voluntarily recalled from the Canadian market after Health Canada's testing identified an undeclared prescription medication in the product (thiodimethylsildenafil, an undeclared substance similar to the prescription medication sildenafil).

Health Canada Dec/11 is advising "**Yanshiwang**", "**Jin Kong Fu**" and "**Chong Cao She Bian Zhuang Yang Dan**". These products were removed from sale at Male and Female Harmony retail stores in Richmond and Burnaby, B.C., along with the Happy Paradise Adult Store in Burnaby. These contained sildenafil.

Health Canada Jan/12 advises: 1)**17 weight loss products (see Alert for a complete list)** A-Slim 100% Natural Slimming Capsule, Acai Berry Soft Gel ABC, Advanced Slim 5 > DaiDaiHuaJiaoNang, Dream Body Slimming Capsule, Fruit Plant Lossing Fat Capsule, Health Slimming Coffee, Ja Dera 100% Natural Weight Loss Supplement, Leisure 18 Slimming Coffee, Lishou, Magic Slim Tea, Magic Slim Weight Reduction Capsule, P57 Hoodia, Pai You Guo Slim Tea, PhentraBurn Slimming Capsules, Slender Slim 11 Tengda. The U.S. Food and Drug Administration warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Uprizing 2.0** The U.S. Food and Drug Administration warned that this body building product contains a controlled prescription drug (superdrol). **3. Get Stiff, Maxi Mize** New Zealand's Medsafe warned that these sexual enhancement products contain prescription drugs (tadalafil, vardenafil, yohimbine) and/or unauthorized drugs (hydroxyhomosildenafil, hydroxythiohomosildenafil). **4. Ying Da Wang tablets** The Australian Therapeutic Goods Administration warned that this sexual enhancement product contains a prescription drug (sildenafil). **5. Slimina weightloss capsules, S-shape slim capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain prescription drugs (propranolol, nifedipine) and/or unauthorized drugs (sibutramine, fenfluramine, phenolphthalein). **6. Athri-Eze, Sear Heang Tienchi Tu Chung Wan, Wiku Jahe Kencur (Akur Mujarab), Cap Wijaya Kusuma (An Ki It)** The Singapore Health Sciences Authority warned that these Traditional Chinese or Traditional Malay Jamu products contain prescription and/or over-the-counter drugs (dexamethasone, prednisolone, furosemide, allopurinol, acetaminophen, chlorpheniramine), and/or an unauthorized drug (phenylbutazone). **7. Cardiotium, Paidusu, SlimEasy Herbs Capsule, Tianran Zuanshi Xianweisu** The Hong Kong Department of Health warned that these health products contain prescription drugs (losartan, atorvastatin, thyroxine) and/or unauthorized drugs (sibutramine, phenolphthalein). Consult a health care practitioner immediately if you have taken "Cardiotium" while pregnant. The use of losartan during pregnancy can cause injury and even death to the fetus. **8. [LuShenPai] Specific Hou Ton Qing, [AA] Pe Min Kan Wan** The Hong Kong Department of Health warned that these traditional Chinese health products contain excessive levels of heavy metals (arsenic or mercury).

Health Canada Feb/12 is advising Canadians that using "MMS", also known as **Miracle Mineral Solution or Miracle Mineral Supplement** may cause serious health problems. The product information lists sodium chlorite as an ingredient and is promoted as a substance that can cleanse toxins from the human body.

Health Canada Feb/12 seized a variety of **Stiff4Ever** and **PurePillz** products from The Love Shop retail outlets located in Ontario. These products are unauthorized drugs and are considered potentially dangerous to the health and safety of Canadians. Health Canada tested the Stiff4Ever products, advertised as male sexual stimulants, and identified sildenafil. The labels of the PurePillz products (see below) state that they contain BZP and TFMPP. Benzylpiperazine (BZP) is a synthetic substance with stimulant-like effects, while 3-trifluoromethylphenylpiperazine (TFMPP) is a synthetic substance with hallucinogen-like effects.

Health Canada Mar/12 **Power-X**" has been removed from a Canadian retail location after Health Canada's testing identified undeclared thiodimethylsildenafil which is similar to the prescription medication sildenafil.

Health Canada May/12: Unauthorized health products, **"X-Rock", "Kaboom" and "One For Her"** have been removed from sale from various retail outlets in British Columbia and Saskatchewan. Health Canada's testing identified undeclared prescription drugs sildenafil and tadalafil, and an undeclared substance, hydroxythiohomosildenafil, which is similar to sildenafil.

Health Canada May/12 **1. CanSui; Lexscl Fat Rapid Loss Capsule; The Extreme-thin Fat Burning Bomb; Xiu Zhi Su L-Carnitine Slimming Capsule** The Hong Kong Department of Health warned that these weight loss products contain unauthorized drugs (sibutramine, phenolphthalein). **2. Jin Yu Tang Tai Han Kang Pai Pu Ling Jiao Nang; TangBaoKouFuYiDaoSuJiaoNang; Tangren 365 Kangxunpai sangge huoyisu jiaonang; Tong Ren Xiu Fu Kou Fu Yi Dao Su** The Hong Kong Department of Health warned these products, promoted to control high blood sugar, contain a combination of prescription drugs (metformin, glibenclamide [also known as glyburide], rosiglitazone, glimepiride, hydrochlorothiazide) and unauthorized drugs (phenolphthalein, phenformin). **3. [Chung Lien Kulin Brand] Anshen Bunai Pian** The Hong Kong Department of Health warned that this traditional Chinese health product, used for insomnia, contains excessive levels of the heavy metal mercury. **4. Lipro Diet Pills; Xiyouji Qingzhi weight loss capsules** The Australian Therapeutic Goods Administration warned that these weight loss products contain an unauthorized drug (sibutramine). **5. AdvanceMen capsules; Miraculous Evil Root tablets** The Australian Therapeutic Goods Administration warned that these sexual enhancement products contain either a prescription drug (sildenafil) or an unauthorized drug (sulfoaildenafil).

Health Canada June/12 **1. African Black Ant; France T253; Hard Ten Days; Man King; Stree Overlord** : The U.S. Food and Drug Administration warned that these sexual enhancement products contain prescription drugs (sildenafil. One product also contains tadalafil). **2. RegenArouse; RegenErect:** The U.S. Food and Drug Administration informed of a recall because these sexual enhancement products contain a prescription drug (tadalafil). **3. Mince Belle; Everlax; Ever Slim; Ever Slim Shake Mix (Strawberry); Ever Slim Shake Mix (Chocolate); Acai-Man Mangosteen Herbal Drink; Perfect Men:** The U.S. Food and Drug Administration informed of a recall because these weight loss and sexual enhancement products contain prescription drugs (sibutramine or tadalafil). **4. Japan Weight Loss Blue, Japan Rapid Weight Loss Diet Pills Green; Japan Rapid Weight Loss Diet Pills Yellow:** The U.S. Food and Drug Administration warned that these weight loss products contain prescription drugs (sibutramine, ephedrine alkaloids) and unauthorized drugs (phenolphthalein, and substances similar to sibutramine). **5. Koff & Kold; Kold Sore:** The U.S. Food and Drug Administration informed of a recall because these cough and cold products were found to be non-sterile. **6. Ling Zhi She Xiang Tong Mai Dan:** The Hong Kong Department of Health warned this health product contains a prescription drug (dexamethasone). **7. Q & N Omega Tree:** The Singapore Health Sciences Authority informed of a recall after this product was found to contain controlled drug substances (cannabinol and tetrahydrocannabinol (THC)).

Health Canada June/12 **Natural Vigor Maximum** (Exemption Number: 138273) has been removed from sale from various retail outlets in Ontario after testing by Health Canada identified a hidden ingredient (dimethylhomosildenafil).

Health Canada Jun/12 testing has identified that the weight loss product "**ZXT Gold**" bee pollen capsules contain hidden pharmaceutical ingredients (sibutramine and phenolphthlalein).

Health Canada July/12 **Lightning Rod**, an unauthorized sexual enhancement product, has been removed from sale from various retail outlets in Ontario, British Columbia and Saskatchewan after testing by Health Canada identified a hidden ingredient (hydroxythiohomosildenafil).

Health Canada July/12 "**Fu Fang Zaoren Jiaonang**": A Potentially Dangerous Product for Pregnant Women. "Fu Fang Zaoren Jiaonang," an unauthorized natural health product promoted for anxiety and/or insomnia, has been removed from sale after testing by Health Canada confirmed the presence of the ingredient L-tetrahydropalmatine that could cause damage to vital organs such as the liver, most notably in pregnant women.

Health Canada July/12 **Vine Essence** has been recalled after testing by Health Canada identified a quantity of lead that exceeds Departmental acceptable limits and low levels of undeclared acetaminophen.

Health Canada Aug/12 These products are not authorized for sale in Canada and have not been found on the Canadian market, but they may have been brought into the country by travellers or purchased over the Internet. **1. Boost – Ultra Sexual Enhancement Formula; EreXite; Mojo Nights:** The U.S. Food and Drug Administration advised consumers not to buy or use these products after they were found to contain one or more of the following undeclared drug ingredients: tadalafil, sildenafil, and unauthorized substances similar to sildenafil that may pose similar health risks. **2. Firminite; Extra Strength Instant Hot Rod; Libidron:** The U.S. Food and Drug Administration informed consumers of a company recall after these products were found to contain undeclared tadalafil. **3. [Hu Qiu] Niu Huang Xiao Yan Wan:** The Hong Kong Department of Health warned consumers to not use this product after it was found to contain an excessive level of mercury. **4. Instant Hard Rod; RigiRx Plus; ZenMaxx**: The U.S. Food and Drug Administration advised consumers not to buy or use these products after they were found to contain undeclared aminotadalafil, which is similar to tadalafil and may pose similar health risks. **5. VMaxx Rx:** The U.S. Food and Drug Administration informed consumers of a company recall of certain lots of *VMaxx Rx* after the product was found to contain undeclared sulfoaildenafil.

Health Canada Aug/12: **Burnaby, B.C. Store (U-Box) Selling Potentially Dangerous Weight Loss Products.** Further to our previous communications, Health Canada is advising Canadians that four products promoted for weight loss have been seized from "U-Box," a store in Burnaby, B.C. Health Canada testing has identified they contain hidden drug ingredients (sibutramine and phenolphthalein) that may pose serious health risks. Caffeine was also found in some of the products and was not listed on the product label.

Health Canada Sep/12: **Zhuifeng Tougu Wan**", an unauthorized natural health product, is being voluntarily recalled after testing identified levels of mercury that are far beyond the allowable limit set by Health Canada.

Health Canada Oct/12 The natural health product "**Pollen Allergy**" (NPN 80035736), now sold as "**Tongqiao Biyan Pian**," is being recalled from the Canadian market after testing conducted by Health Canada identified levels of arsenic that exceed Departmental allowable limits.

Health Canada Dec/12 Three unauthorized health products -- "**Man Up Now", "Black Ant", "Triple Power Zen Gold 1200mg**"-- are being recalled by DVDXPRO after testing by Health Canada identified undeclared ingredients-sildenafil and/or tadalafil.

Health Canada Dec/12 is advising Canadians that three unauthorized products "**Goya Bittermelon", "S-organic Cocoa+L-carnitine", or "KaBaNa L-Carnitine 360 Slimming Coffee**", promoted for weight loss have been seized from "Cube Inc.", a box-store in Richmond, B.C. These products contain hidden drug ingredients (sibutramine and phenolphthalein) that may pose serious health risks. Caffeine was also found in two products and was not listed on the product label.

Health Canada Dec/12 is advising Four unauthorized natural health products have been removed from sale as they may pose serious risks to the health of Canadians. The "**ExtenZe**" products are promoted as sexual enhancement products and contain ingredients that legally require they be sold with a prescription in Canada. ExtenZe Max Strength Gelcaps, ExtenZe Original Tablets, ExtenZe Natural Female Tablets, and ExtenZe Big Cherry Flavour Liquid: Three of these unauthorized products list the prescription ingredient pregnenolone and the controlled drug DHEA (dehydroepiandrosterone) & three of these unauthorized products contain the prescription medication yohimbine (either as yohimbine HCl or as yohimbe extract).

Health Canada Jan/13: 1) **Muscletech Hydroxystim capsules**- The Australian Therapeutic Goods Administration (TGA) warned consumers not to purchase or use this product after it was found to contain 1,3-dimethylamylamine (DMAA), a drug that is not approved for sale in Canada. **2. [W.S.] Tian Ma Toutong Wan; Shi Hu Ye Guang Wan (Ye Guang Wan); Nai Chang Ming Yan Pills (Ming Yan Pills); [Fung Shing Pai] Tian-Ma Wan; Bak Foong Pills (11 products) .** The Hong Kong Department of Health has warned consumers not to purchase or use certain batches of these products after they were found to contain excessive levels of lead or mercury.

Health Canada Feb/13: Two unauthorized health products "**18 Again" and "Stiff 4 Hours**" were tested by Health Canada and were found to contain hidden ingredients (sildenafil or tadalafil) that may pose serious risks to the health of Canadians.

Health Canada Mar/13: An unauthorized natural health product, "**Libigrow**" was tested by Health Canada and found to contain hidden ingredients (sildenafil and tadalafil) that may pose serious risks to the health of Canadians. "Libigrow" was being sold at two retail locations in the province of Québec: Boutique Sexie folie Inc. (Sainte-Catherine) and at Boutique Érotique 5ième avenue Inc. (Valleyfield).

Health Canada Apr/13 **1. Diet Garcinia Forte; Shan Dian Shou; Aulura Energy Dietary Supplement** The Hong Kong Department of Health has advised consumers not to use these products after they were found to contain sibutramine and phenolphthalein, drug ingredients that were not declared on their product label. Shan Dian Shou also contains the undeclared prescription drug sildenafil. **2. Snake Powder Capsule for Rheumatism; Jia Rong Zhuang Gu Tong Bi Jiaonang; Long Ren Tang Fu She Gu Rang Jiao Nang** The Hong Kong Department of Health advised consumers not to use these products after they were found to contain multiple prescription and non-prescription drugs that were not declared on their product label. (prednisone, indomethacin, diclofenac, hydrochlorothiazide, cimetidine, prednisone, theophylline, dexamethasone etc). **3. Tinea Schwartz's; Tiao Jing Bu Xue Pills; Yeung Ng Tong Tin Hee Pills** The Hong Kong Department of Health advised consumers not to use these products after they were found to contain prescription drugs that were not declared on their product label (prednisone, indomethacin, diclofenac). **4. Quan Xie Jin Gu Tong; Xinhuang Pian; Jin Gu Feng Shi Kang Jiao Nang** The Hong Kong Department of Health advised consumers not to use these products after they were found to contain multiple prescription and non-prescription drugs that were not declared on their product label. (prednisone, piroxicam, diclofenac, indomethacin, naproxen).

Health Canada May/13 Two unauthorized health products — **"Stiff Nights" and "Stiff 4 Hours"** — were tested by Health Canada and were found to contain hidden ingredients (sildenafil and/or tadalafil) that may pose serious risks to the health of Canadians. The products were being sold at Saints N Sinners Ltd, 1715 Centre Street N.W., Calgary, Alberta.

Health Canada June/13 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Flutulang, Kapsul Gaut (Asam Urat), and True ProLife Vegrow** The Health Science Authority of Singapore advised consumers not to use these products after they were found to contain phenylbutazone, chlorpheniramine, dexamethasone, and a chemical compound similar to the prescription drug sildenafil. **2. Jinmaoshiwang tablets, Naturally Kouxan Best Slim capsules, and Majestic Slimming capsules** The Australian Therapeutic Goods Administration advised consumers not to use these products after they were found to contain sildenafil, sibutramine and phenolphthalein. **3. WOW, Super Power and SLIMDIA Revolution** The U.S. Food and Drugs Administration (FDA) warned consumers not to use these products after they were found to contain diclofenac sodium, methocarbamol, dexamethasone, sildenafil and sibutramine. **4. Libigrow XXXtreme, Blue Diamond, Blue Diamond Platinum, Mojo Nights Supreme, and Casanova** The U.S. Food and Drugs Administration warned consumers not to use these products after they were found to contain sildenafil, sulfoaildenafil and thioaildenafil.

Health Canada Aug/13 is advising Canadians not to use these foreign health products as they may pose a health risk. **1. Brazilian Slimming Coffee, Leisure 18 Slimming Coffee, 7 Days Slimming Coffee, Brazilian 7 Days Slimming Coffee, Beauty Secret Slimming Coffee, Body Beauty 5 Days Slimming Coffee, Leisure 18 Slimming Mango Juice, Leisure 18 Slimming Orange Juice, Authentic Leisure 18 Slimming Orange Juice, Super Slim Orange Juice, Coffee Fashion Slimming** The Hong Kong Department of Health has advised consumers not to use these products after they were found to contain the undeclared drug ingredients sibutramine and/or phenolphthalein. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34859a-eng.php **2. Steelman Capsules 2** The Hong Kong Department of Health has advised consumers not to use this product after it was found to contain undeclared aminotadalafil. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34861a-eng.php **3. CO Feng Shi Gu Tong Ning Jiao Nang** The Hong Kong Department of Health has advised consumers not to use this product after it was found to contain undeclared prednisone, diclofenac, ibuprofen, hydrochlorothiazide, metoclopramide and trimethoprim. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34861a-eng.php **4. Fu Fang Feng Shi Gu Kang Ling Jiao Nang** The Hong Kong Department of Health has advised consumers not to use this product after it was found to contain undeclared prednisone, diclofenac, ibuprofen, indomethacin, piroxicam and metoclopramide. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34861a-eng.php **5. Best Slim capsules, Meizi Evolution Botanical Slimming soft gel capsules** The Australian Therapeutic Goods Administration warned consumers not to use these products after they were found to contain the undeclared drug sibutramine. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34869a-eng.php **6. Libigirl capsules** The Australian Therapeutic Goods Administration warned consumers not to use this product after it was found to contain the undeclared prescription drugs sildenafil and tadalafil. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34869a-eng.php **7. Albuterex Xtreme Formula** The Australian Therapeutic Goods Administration has warned consumers not to use this product after it was found to contain undeclared theophylline, yohimbine and high amounts of undeclared caffeine. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34863a-eng.php **8. Albutarex Xtreme and Albutarex Femme Formula** The Australian Therapeutic Goods Administration has warned consumers not to use these products after they were found to contain undeclared theophylline and high amounts of undeclared caffeine. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34863a-eng.php

Health Canada Aug/13 **Prema G** (Granules packaged in tea packets, NPN: 80035944) was tested by Canada Border Services Agency and found to contain a hidden ingredient (hydroxyhomosildenafil thione).

Health Canada Oct/13 is warning consumers not to use unauthorized **Compound Danshen Dripping Pills** after it was associated with a Canadian case of methemoglobinemia, a rare but serious condition which may result in coma or death.

Health Canada Oct/13 Natural health product (**Spectrazyme**) recalled due to potential contamination with the antibiotic chloramphenicol. Metagenics Canada, in consultation with Health Canada, is voluntarily recalling its natural health product "Spectrazyme" – a digestive aid – due to a possible contamination with chloramphenicol, an antibiotic that may pose serious health risks to consumers.

Health Canada Oct/13 Natural health product (**Flora Essentials**) recalled due to potential contamination with the antibiotic chloramphenicol.

Health Canada Oct/13 Natural health products (**Kamizym-U and Kamizym+)** recalled due to potential contamination with the antibiotic chloramphenicol.

Health Canada Oct/13 wishes to inform Canadians that seized natural health products being sold by Lion King Health Enterprises Group Ltd., 1328-8368 Capstan Way, Richmond, BC. were tested and found to contain hidden ingredients and unauthorized substances similar to the prescription drug, sildenafil. (**North America Dami Ana 600mg, South America Maca 600mg, Ashwagandha 600mg, Optimusman 350mg, Superman 350mg, Innerget Instant Erection (NPN#80041194), Innerget Prolonged Performance (NPN#80041194), Innerget Everlasting Strength (NPN#80041194), Megaton 2080**.)

Health Canada Nov/13 is advising Canadians not to use these foreign health products as they may pose a health risk. These products have been found by regulators in other countries to contain drug ingredients or soy milk allergens that are not declared on the product labels, or a high level of microbial contamination. Prescription drugs should only be taken under the supervision of a healthcare professional. These products are not authorized for sale in Canada and have not been found on the Canadian market, but they may have been brought into the country by travellers or purchased over the Internet:

1. **Protein Extract and artiph**en http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36237a-eng.php ;
2. **Aisiyuan V26 Slimming Granules, AcaiBerry Living-XS, and 4C Cosmoslim** , http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36269a-eng.php ;
3. **MAXILOSS Weight Advanced** http://healthycanadians.gc.ca/recall-alert- rappel-avis/hc-sc/2013/36197a-eng.php;
4. **14 sexual enhancement products** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36233a-eng.php ;
5. **Ginseng Baji Gu Ci Wan, Tu Chong Ginseng Wan Le Seang and X-Tract Nature** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36359a-eng.php ;
6. **Ziyinzhuangyang tablets, Maxman III, and Mojo Risen** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36519a-eng.php ;
7. **Kyuwei** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36515a-eng.php ;
8. **ESV Extra Strong Version, MSV Strong Version, RL Rapid Loss, My Slimmer Me (MSM) soft gel capsules, Natural Miaotiaoyishen capsules, and Paiyouji Natural Slimming Capsules** http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36521a-eng.php.

Health Canada Dec/13 has updated the list of natural health products seized from **Lion King Health Enterprises Group** Ltd., 1328 - 8638 Capstan Way, Richmond, B.C. that have been tested and found to contain hidden ingredients and unauthorized substances similar to the prescription drug tadalafil.

Health Canada Dec/13 General Nutrition Centres Company (GNC), in consultation with Health Canada, is voluntarily recalling its natural health product "**Women's Phytoestrogen Formula**" – used for the relief of menopausal symptoms – due to possible contamination with chloramphenicol.

Health Canada Dec/13 testing of an unauthorized natural health product, **MaxHIMize**, found it to contain bacteria (Enterococcus durans and Bacillus spp) and undeclared caffeine that could present a risk to health. MaxHIMize is being promoted as a dietary supplement and for erectile dysfunction.

Health Canada Feb/14: 1. **Hairegenerator** The Hong Kong Department of Health warned consumers not to use this product after samples of the product were found to exceed the permissible limit for mercury. The level of mercury exceeds Health Canada's acceptable limits as well. 2. **Li Long Mei Guo Mo Bang, and Ginseng Tu chong Wan Lin Heong** The Singapore Health Sciences Authority warned consumers not to use this product after it was found to contain sildenafil, a drug ingredient that was not declared on the product label. 3. **Lightning 10.0+, LV Shou Reduces Fat, and STB Summit of the Thin Body S Woman Degreasing Burning Pill** The Hong Kong Department of Health warned consumers not to use this product after it was found to contain sibutramine, phenolphthalein, and indomethacin.

Health Canada Mar/14 is advising Canadians not to use these foreign health products as they may pose a health risk. 1. Xiang Gang Tian Long Sheng Wu Ke Ji Di Qi Dai Chi Jiu Zhan Shen http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/38599a-eng.php was found to contain **sildenafil**. 2. Various Sexual Enhancement Products http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/38577a-eng.php was found to have **sildenafil** and **tadalafil.** 3. Majestic Slim Perfect and Yixiu L-Carnitine Slimming Capsules http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/38609a-eng.php was found to contain **sildenafil** and **phenolphthalein.**

Health Canada Mar/14: **Zyrexin**, tested by Health Canada at the border was found to contain a hidden prescription drug ingredient **(Yohimbine)** .

Health Canada Apr/14 has seized the unauthorized drug, "**L-Showm Weight Loss Pills**", being sold at the U-Box store, located at 2809-4500 Kingsway, Burnaby, BC. Health Canada testing found that it contained an undisclosed ingredient, phenolphthalein.

Health Canada Apr/14: Four unauthorized drugs being sold at two SVN FUEL stores - one in Burnaby and one in Coquitlam, B.C. - were seized by Health Canada as they contain ingredients that are potentially dangerous to the health of consumers. The products, and the unapproved ingredients they contain, include **Jack3d** (DMAA (1, 3-dimethylamylamine), **Red Rockets** (ephedrine and caffeine), **West Pharm Therma Lean** (ephedrine and caffeine), and **OxyElite Pro** (1, 3-dimethylamylamine HCl and Yohimbe Bark extract). They were being promoted for weight management.

Health Canada Apr/14: 1) **San Xiao Ping Tang Jin Qi Jiao Nang**: The Hong Kong Department of Health warned consumers not to use this product after it was found to contain phenformin, pioglitazoneand glibenclamide**. 2) Volcano Male Enhancement** liquid & caps: The U.S. Food and Drug Administration warned consumers not to use these products after they were found to contain desmethyl carbodenafil, dimethylsildenafil and dapoxetine**. 3) Dr. Larry's Tranquility**: The U.S. Food and Drug Administration warned consumers not to use this product after it was found to contain undeclared doxepin and chlorpromazine.

Health Canada Apr/14: Nano Well-being Health Inc. issued a voluntary recall of **Super Arthgold**, 500 mg capsules to the consumer level. FDA laboratory analysis has found the product to contain chlorzoxazone, diclofenac and indomethacin, making it an unapproved new drug.

Health Canada May/14 **Blue Stinger** contains sulfoaildenafil**; 72 HP, Evil root and Pro Power Max** contains sildenafil**; Esbelin siloutte te, Esbelin Siloutte Herbal blend with L-Carnitine, Esbelder man**, **Esbelder fem, Esbelder siloutte** contains Sibutramine, N-Desmethylsibutramine, and N-di-Desmethylsibutramine; **Instant Slim** contains sibutramine and phenolphthalein; **Jack Rabbit** contains sildenafil and tadalafil**; Live Clinical 90 caps** contains milk, **Ortiga** contains diclofenac.

Health Canada May/14 One lot of **Lite Fit USA** (Lot Number 13165, Exp. 05/17) is being voluntarily recalled in the U.S. after analysis by the U.S. Food and Drug Administration revealed the lot contains the undeclared prescription drug sibutramine.

Health Canada May/14 has requested that Christmas Natural Foods Ltd. stop selling and recall its unauthorized health product, **Heartland Natural Wild Yam Moisturizing Cream**, after testing conducted by the Department identified a undisclosed prescription drug ingredient, progesterone.

Health Canada May/14: 1. **VitaliKOR**: FDA found vardenafil and tadalafil**;** 2. **Slim Fortune, Lidiy & Slim Expert** FDA found sibutramine**;** 3. **Vigor Tea sachets:** Australian Therapeutic Goods Administration found sulfoaildenafil**;** 4. **Prolifta capsules, PHUK and Virilis Pro:** FDA found **sildenafil;** 5. **Dr. Mao Slimming capsules, Perfect Body Solutions, Burn 7**: FDA found sibutramine; **Bella Vi Insane Amp'd Up, Be Inspired, Goodliness Fat Reducing capsules, Jimpness Beauty Fat Loss capsules**: FDA found sibutramine and phenolphthalein; 6. **Nature Most Laboratories Vanilla Almond, and Strawberry Banana Whey Power products**: FDA found undeclared milk, soy and almond allergens**;** 7. **Wood-E, Xzen Gold, Xzen XPress, XZen 1200, and XZone Premium**: FDA found Wood-E contains sildenafil, Xzen Gold and Xzen XPress contain sildenafil and tadalafil, & XZen 1200 contains tadalafil.

Health Canada June/14: **Bali Mojo & Vimax** contains tadalafil., **LOVher capsule**s contains tadalafil, sildenafil and diclofenac. **Erec-Bull,** contains yohimbine. **Best Whips & JINQIANGBUDOR Red Dragon** contains sildenafil. **Super Hard t**ablets contains sildenafil. **CONTROL All Natural Sexual Enhancement** contains sulfoaildenafil and dimethylsildenafil. **Phen Tabz contains dimethylamylamine (DMAA). Asset Extreme, Asset Extreme Plus, Meizitang Citrus, Slimming Diet Berry Plus, Citrus Fit Gold, Hot Detox, Thinogenics** contains sibutramine. **Tonic Life BP & Slimfast capsules** contains phenolphthalein . **Dr**. **Ming's Chinese Capsule**, **Magic Slim and Apple's Quic**k **Impact Weight Loss** contains sibutramine and phenolphthalein. **Pro ArthMax** contains diclofenac, ibuprofen, naproxen, indomethacin, chlorzoxazone. **Adipotrim XT** contains fluoxetine. **StemAlive** contains milk.

Health Canada July/14: **Wing Cheong Tong] Bak Feng Pill, [Yee On Tong] Bak Feng Pill, and Beijing Bak Feng Pill**: The Hong Kong Department of Health warned consumers not to use these products after they were found to contain excessive levels of lead. **Bella Vi Insane Bee Pollen Capsules, Bella Vi BTrim Ultimate Boost, Bella Vi BTrim Max, Bella Vi Extreme Accelerator**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and/or phenolphthalein. **Super Fat Burner capsules, Maxi Gold capsules, and Esmeralda softgels**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and phenolphthalein. **MME Naturally Maxman capsules, Blue Fantasy capsules, African Superman tablets, and MosKa** – energy for adults: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to containsildenafil. **Powerful leg-slimming capsules, Pink grain herbal slimming capsules, and Night fat-burning capsules**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain undeclared phenolphthalein and diclofenac. The product, Night fat-burning slimming capsules, was also found to contain undeclaredtheophylline. **Zi Xiu Tang Pollen capsule and Zi Xiu Tang Beauty Face and Figure capsule**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to contain undeclared sibutramine, phenolphthalein, diclofenac, and ibuprofen. The product, Zi Xiu Tang Beauty Face and Figure capsule, was also found to contain undeclared glibenclamide, and indomethacin.

Health Canada Aug/14 is informing healthcare professionals about a suspected drug interaction between **efavirenz (Sustiva) and ginkgo biloba**. The report is based on a 2012 published case report involving a Canadian patient with HIV infection.(1)

Heath Canada Aug/14: The United States Food and Drug Administration (FDA) warned consumers not to use the products **MV5 Days and S.W.A.G**., and the Australian Therapeutic Goods Administration (TGA) warned consumers not to use the product **Zhansheng Weige Cahoyue Xilishi tablets**, after they were found to contain sildenafil. The Australian Therapeutic Goods Administration (TGA) warned consumers not to use the product **Sanovera Starter capsules**, the Hong Kong Department of Health warned consumers not to use the product **Yanhee Slim** and the United States Food and Drug Administration (FDA) warned consumers not to use the products **Infinity, Asset Bee Pollen, Asset Bold, Slim Trim U, and Natural Body Solution**

after they were found to contain undeclared sibutramine. The Medicines and Healthcare Products Regulatory Agency (United Kingdom) warned consumers not to use the product **Shwasa Sanjeevani** and the Singapore Health Sciences Authority warned consumers not to use the product **Golden Dragon Linzi Dong Mai Dan** after they were found to contain dexamethasone. The Singapore Health Sciences Authority warned consumers not to use **Herbal Health Jointcare** after it was found to contain betamethasone-17-valerate, furosemide, piroxicam, chlorpheniramine and famotidine. The Australian Therapeutic Goods Administration (TGA) warned consumers not to use **Robust tablets** after it was found to contain aminotadalafil. The Australian Therapeutic Goods Administration (FDA) warned consumers not to use **3x Slimming Powder Capsules** after it was found to contain undeclared sibutramine and phenolphthalein. The Singapore Health Sciences Authority warned consumers not to use **Herbal Health RU Special Cream, Herbal Health YI Special Cream, Herbal Health JI Special Cream, and Herbal Health XIANG Special Cream** after they were found to contain chlorpheniramine, clotrimazole, miconazole and terbinafine. The Singapore Health Sciences Authority warned consumers not to use **Herbal Health V+** after it was found to contain sildenafil and tadalafil. The Singapore Health Sciences Authority warned consumers not to use **Herbal Health Backplus** 500mg after it was found to contain tadalafil.

Health Canada Sep/14: **La Jiao Shou Shen, B-Perfect, Diet Master, Super Slim, Slim Max**: The United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain undeclared sibutramine and phenolphthalein. **Sport Burner** :The United States Food and Drug Administration (FDA) warned consumers not to use the product Sport Burner after it was found to contain undeclared fluoxetine. Health Canada Sep/14: **Gold Vigra, Liu Bian Li, GoldReallas, Black Ant Strong, My Man His Enhancer 12 Pack, Top Man 3 and Vigour 800**: The United States Food and Drug Administration (FDA) warned consumers not to use the products **Gold Vigra, Liu Bian Li and GoldReallas**, and the Australian Therapeutic Goods Administration (TGA) warned consumers not to use the products **Black Ant Strong, My Man His Enhancer 12 Pack, Top Man 3 and Vigour 800**, after they were found to contain sildenafil.

Dick's Hard Up, P-Boost, and NatuRECT: United States Food and Drug Administration (FDA) warned consumers not to use these products after they were found to contain tadalafil. **3 Hard Knights**: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain sildenafil andthiosildenafil. **Germany Niubian**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use the product after it was found to contain sildenafil and zopiclone. **Alpha Male**: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain sildenafil,aminotadalafil, sulfosildenafil, sulfoaildenafil, hydroxythiohomosildenafil, and dimethylsildenafil. **REDDES (or REDDIES)** and **The Rock**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use these products after they were found to containsulfosildenafil and hydroxyhomothiosildenafil. **Full Throttle On Demand**: The United States Food and Drug Administration warned consumers not to use this product after it was found to contain propoxyphenyl sildenafil. **RezzRX**: The United States Food and Drug Administration warned consumers not to use this product after it was found to containhydroxythiohomosildenafil and/or aminotadalafil. **Play Hard for Men**: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use this product after it was found to contain yohimbine andhydroxyhomothiosildenafil. **Rhino 5 Plus, Maxtremezen, and Extenzone**: The United States Food and Drug Administration warned consumers not to use these products after they were found to contain desmethylcarbondenafil and dapoxetine. Health Canada Sep/14: **JIN LONG Snakes Bones Rheumatic Capsules**- The Singapore Health Sciences Authority warned consumers not to use this product after it was found to contain betamethasone, piroxicam,oxethazaine, paracetamol (also known as acetaminophen) and furosemide.

Health Canada Oct/14 is warning Canadians of the serious risks to health associated with use of the unauthorized drug product **Miracle Mineral Solution (MMS),** which was sold as a treatment for serious diseases such as cancer through the website www.buymms.biz. MMS contains sodium chlorite, which is a chemical used mainly as a textile bleaching agent and disinfectant and may pose serious risks to health if ingested. An alternate format of MMS, labelled as CDS, is also available for sale on the website and would pose a similar risk.

Health Canada Nov/14: An unauthorized health product, **Gra-MaxX Gold**, was seized by Health Canada as it contains an undeclared drug: N-Ethyl Tadalafil.

Health Canada Nov/14: A vendor in Atlantic Canada (www.health-recovery-info.com) is selling **Miracle Mineral Solution (MMS),** an unauthorized drug product (containing sodium chlorite) which Health Canada has previously warned may pose serious risks to health if ingested.

Health Canada Dec/14 is following up with Rapha Biotech Inc. **RAPHA Vitamin B1** (NPN: 80036493) -- undeclared ingredients: sibutramine, desmethyl sibutramine. **Gra-MaxX Gold** (yellow label) -- undeclared ingredient: N-ethyl tadalafil. **Rapha Diet** (700 mg, 270 Capsules) -- undeclared ingredient: caffeine. **Rapha Diet** (630 mg, 270 Capsules) -- undeclared ingredients: amphetamine, methamphetamine.

Health Canada Dec/14: "**Herberex**" (NPN 80041180) is being recalled nationwide after Health Canada testing confirmed it contains an undeclared drug: tadalafil.

Health Canada Dec/14: **Hydro-Lean** was seized from two Calgary stores because the label indicates it contains a combination of ingredients that can cause serious health risks (ephedrine and caffeine).

Health Canada Dec/14: "**Jetfuel Superburn**" is being recalled after Health Canada tests confirmed it contains two undeclared amphetamine-like drug substances that pose serious health risks (beta-methylphenethylamine and phenylpropylmethylamine).

Health Canada Dec/14: The United States Food and Drug Administration (FDA) warned consumers not to use the products **Lingzhi Cleansed Slim Tea, Trim-Fast Slimming Softgel, Sliming Diet By Pretty White, Lipo 8 Burn Slim, and Best Line Suplemento Alimenticio Capsules**. Tthe Hong Kong Department of Health warned consumers not to use the products **Slim Perfect Arm and Slim Perfect Legs** and the Australian Therapeutics Goods Administration (TGA) warned consumers not to use the product **Slyn Both Green capsules** after they were found to contain undeclaredsibutramine. The United States Food and Drug Administration (FDA) also warned consumers not to use the product **Mezo** after it was found to contain benzylsibutramine. **Mix Fruit Slimming**: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain undeclaredsibutramine and phenolphthalein.

Health Canada Dec/14: The Australian Therapeutic Goods Administration (TGA) warned consumers not to use the products **Zhansheng Weige Chaoyue Xilishi, Chong Cao Zhag Bian Bao, Night Man, and MMC Sex Men capsules** and the United Stated Food and Drug Administration (FDA) warned consumers not to use the product **O.M.G.** after they were found to contain sildenafil. **Arize**: The United Stated Food and Drug Administration (FDA) warned consumers not to use the product Arize after it was found to containsulfoaildenafil. **Herbal Vigor Quick Fix**: The United Stated Food and Drug Administration (FDA) warned consumers not to use the product **Herbal Vigor Quick Fix** after it was found to contain tadalafil.

Health Canada Dec/14: **LX1**: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain undeclared1,3-dimethylamylamine (DMAA).

Health Canada Dec/14: **Joint-Soft**: The Singapore Health Sciences Authority warned consumers not to use the product **JOINT-SOFT** after it was found to contain piroxicam anddexamethasone. The Singapore Health Sciences Authority warned consumers not to use the product **KEBIGUTAIJIAONANG** after it was found to containpiroxicam, hydrochlorothiazide, and prednisone. The Singapore Health Sciences Authority warned consumers not to use the product **Pil Raja Urat Asli** after it was found to contain piroxicam and indomethacin.

Health Canada Dec/14: **Bo Ying compound**: The United States Food and Drug Administration (FDA) warned consumers not to use this product after it was found to contain high levels of lead.

Health Canada Dec/14: "**Forta for Men**" (NPN 80045132) is being recalled after Health Canada testing confirmed it contains an undeclared drug: homosildenafil.

Health Canada Dec/14: Samson's Supplements stores in Calgary that pose a risk to health. **Nutrex Research Lipo6 Black, Nutrex Research Lipo6 Black Hers, Nutrex Research Lipo6 Unlimited, Nutrex Research Lipo6 Black Ultra Concentrate, West Pharm Yohimbe** Extract (bottle of 50 and 100 capsules), **West Pharm Yohimbe Extract** (bottle of 50 and 100 capsules), **NutraKey Yohimbine** HCl contains Yohimbine. **West Pharm Xtra Lean, West Pharm ThermaLean, West Pharm ThermoMAXXX** (bottle of 80 and 160 capsules), **Twinlab Ripped Fuel** contains Ephedrine and Caffeine. None of the products are approved for sale. The products are promoted for body building purposes, including for weight loss and increased energy, or for sexual enhancement.

Health Canada Jan/15: **Star Majestic Slimming**- Undeclared sibutramine & phenolphthalein via Australian Therapeutic Goods Administration. **Sit and Slim II**-Undeclared sibutramine & phenolphthalein via FDA.
Ginseng Kianpi Pil- Undeclared dexamethasone & chlorpheniramine via FDA. **Mayhem**- Undeclared dexamethasone & cyproheptadine via FDA.
Du Zhong Jin Gu Wan- Undeclared dexamethasone, chlorpheniramine & diclofenac via Singapore Health Sciences Authority.

Health Canada Jan/15 is reminding Canadians about the risks of purchasing unlicensed **home-use diagnostic** test kits following recent compliance and enforcement actions undertaken by the Department.

Health Canada Feb/15: Two unauthorized health products that may pose serious health risks were removed from sale by Health Canada. These products, "**MRM DHEA**" (labelled to contain DHEA) and "**Altimate Fat Burner Maximum Burn**" (labelled to contain DHEA, Yohimbe, caffeine and ephedrine) were being sold by Nature's Source, Unit #7, 2943 Major Mackenzie Drive, Vaughan, Ontario.

Health Canada Mar/15 advises- FDA Mar/15 **ABC Dophilus Powder**: undeclared fungus(Rhizopus oryzae). **Feng Shi Ling**: undeclared diclofenac & indomethacin. FDA Mar/15 **Bee Slim** & **Bee Thin** has undeclaried silbutramine.
FDA Mar/15 **Black Storm**: undeclared sildenafil. Australian Therapeutic Goods Administration **Max Hard**: undeclared sildenafil & aminotadalafil. **Rock Hard**: undeclared tadalafil. Singapore Health Sciences Authority Mar/15:
SPARTA X: undeclared hydroxyhomosildenafil & hydroxythiohomosildenafil. Singapore Health Sciences Authority Mar/15: **MAGIC PENIS** undeclared sildenafil. Singapore Health Sciences Authority Mar/15
MR ZACK POWERBRO: undeclared propoxyphenyl hydroxyhomosildenafil, propoxyphenyl aildenafil, propoxyphenyl thiohydroxyhomosildenafil & propoxyphenyl thioaildenafil. Singapore Health Sciences Authority Mar/15
Nutri Drops Grapefruit Diet: Undeclared sibutramine undeclared benzyl sibutramine & phenolphthalein.

Health Canada Mar/15 advisory regarding "**Altimate Fat Burner Maximum Burn**" being sold by Nature's Source in Vaughan, Ont., the Department received a complaint about the product also being sold at Nature's Source, 2391 Trafalgar Rd., Unit #6 in Oakville, Ont. Altimate Fat Burner Maximum Burn is an unauthorized health product labelled to contain DHEA, yohimbe, caffeine and ephedrine.

Health Canada Apr/15 testing has found that two unauthorized health products, "**Enhance**" and "**Natural-Power**," contain undeclared sildenafil.

Health Canada Apr/15: St. Francis Herb Farm "**Bulklax V**" and "**All Seasons Detox Kit**" recalled due to high levels of lead and/or arsenic.

Health Canada Apr/15 has suspended the licences of two natural health products containing the ingredient male fern (**Dryopteris filix-max**), "**Paranil**" and "**W.-W**. Safety information has raised potential concerns regarding effects of the specific ingredient at higher doses. Using the affected products may pose a serious health risk.

Health Canada Mar/15 is reminding Canadians that consuming a product sold as "**Miracle Mineral Solution**" (MMS) may pose serious health risks, following a Health Canada seizure of an MMS product from a vendor in Burin, Newfoundland on March 25, 2015.

Health Canada Apr/15 has suspended the licence of Filix Mas, a homeopathic product, because it contains the ingredient male fern (**Dryopteris filix-max**).

Health Canada May/15 **NaturaLyte Sodium Bicarbonate Liquid Concentrate** - Possible Bacterial Contamination - Fresenius Medical Care Canada, Inc.

Health Canada May/15 Recall of "**Galenic Health Ginger in Bentonite**" due to unacceptable levels of lead for children and adolescents.

Health Canada May/15 is warning consumers that an unauthorized drug, "**Stiff Rock**" promoted for male sexual performance enhancement was seized from Boutique Érotique 5ième avenue (also known as Boutique Érotique Liberté), 507 Gande-Île, Valleyfield, QC after Health Canada testing confirmed that the product contained drug ingredients: sildenafil; aminotadalafil; and hydroxythiohomosildenafil.

Health Canada Jun/15 is warning consumers that **Body Bentonite Unique Healing Powder** by Donna Pessin was found to contain high levels of metals

Health Canada Jun/15 requests quarantine of drugs linked to **Zhejiang Hisun Pharma** due to data integrity concerns.

Health Canada Jun/15: Three unauthorized health products that may pose serious risks to the health of Canadians were seized by Health Canada. The products, "**Sport X Ephedrine**", "**DHEA 25**" and "**Promatrix DHEA 25**" were being sold by S&H Health Foods, 2150 Burnhamthorpe Rd. W., Mississauga.

Health Canada Jul/15 is advising Canadians that it has received a serious domestic adverse reaction report of abnormal heart rhythms associated with the ingestion of "**Remogen**" (containing **ibogaine**), an unauthorized natural health product in Canada that may pose serious health risks. Canadians who have used this product and have concerns about their health should speak with their healthcare practitioner.

Health Canada Jul/15: Recall of Additional Lots of **NaturaLyte Sodium Bicarbonate** Liquid Concentrate due to Potential Bacterial Contamination.

Health Canada aug/15 is advising consumers that it is introducing label changes for certain homeopathic products that fall under the Natural Health Product Regulations (NHPR). More particularly, Health Canada is requesting the addition of statements on **homeopathic nosode products to make it clear that they are not vaccines or alternatives to vaccines** to improve the safe use of these products.

Health Canada Aug/15-Australian Therapeutic Goods Administration has **Golden Root Complex Capsules & Bushen Famous Men Capsules & Laopiaoke Capsules** with undeclared sildenafil.

Health Canada Aug/15-FDA has **Akttive Capsules & Zero Xtreme Capsules** with undeclared silbutramine.

Health Canada Nov/15:**Dragon Power**, an unauthorized product sold at The Herb Depot, 407-409 Dundas Street West, Toronto, Ontario, was found to contain an undeclared sildenafil.

Health Canada Nov/15: Various **Ayurvedic medicinal products** were found to contain high levels of heavy metals which may pose serious health risks. These products are not authorized for sale in Canada and have not been found on the Canadian market, but they may have been brought into the country by travellers or purchased over the Internet. (**Brahmi Vati Buddhivardhak; Bruhat Vata Chintamani Rasa; Chandraprabha Vati; Punarnavadi Mandoor; Yogaraja Guggulu**)

Health Canada Dec/15 informed Canadians that an unauthorized health product, **Natrol DHEA** 25 mg, was being sold on amazon.ca for hormonal management. This product may pose a serious risk to the health of Canadians.

Health Canada Dec/15: **Mega Power** contains tadalafil .

Health Canada Dec/15: **Biseptol 480** contains sulfamethoxazole & trimethoprim.

Health Canada Dec/15: **Naproxen E**mo contains naproxen.

Health Canada Dec/15: **Oxycort** contains oxytetracycline & hydrocortisone.

Health Canada Dec/15: **Herba Pini Syrop** contains codeine.

Health Canada Feb/16: "**Forta for Men**", is being recalled after testing confirmed one lot contains an undeclared drug: tadalafil.

Health Canada Feb/16 is advising Canadians who purchased **Novodalin B17**, an unauthorized natural health product claiming to treat cancer to stop using the product and contact their doctor for appropriate follow-up. No health products containing B17 or amygdalin have been authorized by Health Canada to treat cancer or any other condition. Novodalin B17 being sold online by cdnf.com also poses serious risks to health as it is labelled to contain apricot kernel extract. Apricot kernels may contain amygdalin, a compound derived from bitter apricot kernels that has the potential to release cyanide when ingested by humans

Health Canada Feb/16 is advising Canadians that a number of potentially dangerous unauthorized health products labelled as **B17/amygdalin/bitter apricot kernel** were available for sale in Canada.

Health Canada Mar/16: **Forta for Men Daily, Forta Xpload and Durazest For Men Volume**- may contain an undeclared drug: sildenafil.

Health Canada Mar/16 says S **Lion Juice Orange 10 gm** by Singapore Health Science Authority undeclared propoxyphenyl thioaidenafil.

Health Canada Mar/16 says **S Lion Juice 20 gm** by Singapore Health Science Authority undeclared thiodimethylsildenafil.

Health Canada Mar/16 says **S Lion Juice 10 gm** by Singapore Health Science Authority undeclared thiodimethylsildenafil and tadalafil.

Health Canada Mar/16 says **S Lion Juice 1** by Singapore Health Science Authority undeclared aminotadalafil and thiodimethylsildenafil

Health Canada Mar/16 says **Rhino 7 3000 & Rhino 7 Platinum 3000 Capsules** by FDA contains undeclared desmethyl carbondenafil and dapoxetine.

Health Canada Mar/16 says **Power Khan** by FDA contains undeclared sildenafil and thiosildenafil.

Health Canada Mar/16 says Australian Therapeutic Goods Administration: **Hongkong Tianli Biological 'Power' tablets, Longue Jambe Frères (Brother Long Legs) tablets** contains undeclared sildenafil.

Health Canada Mar/16 says Asia Black**, Black Widow 25, Burn Fat Now, Extreme Stack, Fataway Ultimate Stack, MaxOut Body, Metabolic Accelerator, Methyldrene Original 25 Dietary Supplements, ThermoFX, Thermogenic Fat Burner & Thin and Slim Naturally** by FDA contains undeclared salicylic acid.

Health Canada Mar/16 says **BASCHI Quick Slimming capsules** by Australian Therapeutic Goods Administration contains undeclared sibutramine.

Health Canada Mar/16 says **Basha Nut 100% Fruit Soft Gel Capsules**, **Ultimate Herbal Slimcap, Lishou Slimming Coffee, Meizi Super Power Fruits Herbal Slimming Formula, NATUREAL & Tip-Top Shape** by FDA contains undeclared sibutramine.

Health Canada Mar/16 says **Miracle Diet 30 & Xtreme Fat Burner Capsules** by FDA contains undeclared phenolphthalein.

Health Canada Mar/16 says **New Queen Slimming soft gel capsules** by Australian Therapeutic Goods Administration contains undeclared sibutramine.

Health Canada Mar/16 says **Perfect Slim Fast Track Slim & Slyn Both** by FDA contains undeclared fluoxetine

Health Canada Mar/16 says **Pink Bikini and Shorts on the Beach Blue Edition & Pink Bikini and Shorts on the Beach Blue Gold Edition** by FDA contains undeclared sibutramine and phenolphthalein.

Health Canada Mar/16 says **Super Herbs** by FDA contains undeclared sibutramine and desmethylsibutramine

Health Canada Mar/16 says **Baidyanath brand Agnitundi Bati, Baidyanath brand Arogyavardhini Bati, Baidyanath brand Brahmi Bati, Baidyanath brand Chitrakadi Bati, Baidyanath brand Gaisantak Bati, Baidyanath brand Marichyadi Bati, Baidyanath brand Rajahpravartini Bati, Baidyanath brand Saptamrit Lauh, Baidyanath brand Sarivadi Bati, Baidyanath brand Shankh Bati,** by FDA contains undeclared elevated levels of lead and mercury.

Health Canada seized six unauthorized products being promoted as dietary supplements from Herc's Nutrition, 175 Fletchers Creek Blvd., Brampton, Ontario.
(**RapidFire, Black Magic, China White & Lipo-Cuts** contains Yohimbine and ephedra. **Hydroxycut Hardcore Next Gen & Psychotic** contains Yohimbine.

Health Canada Mar/16: **Ejaculoid & Animal Test & Dust V2**: Yohimbine.

Health Canada Mar/16: **RSE7EN**: Desmethyl carbodenafil & dapoxetine, **Extreme Diamond 2000**: Desmethyl carbodenafil, **Master Zone 1500 & MV7 days 3500 or 2000**: Sildenafil & tadalafil, **Black Magic & Rock Hard Weekend**: Sildenafil, **Black Panther**: Sildenafil & desmethyl carbodenafil & dapoxetine, **Mamba is Hero**: Sildenafil & dimethyl carbodenafil & dapoxetine, **Black Mamba premium**: Desmethyl carbodenafil & dapoxetine,

Health Canada Apr/16: Australian Therapeutic Goods Administration says **100% healthy food for men tablets, & V-MAX Herbal Tablets** contains undeclared sildenafil.

Health Canada Apr/16: is advising Canadians that an unauthorized drug, **URX Bombshell**, labelled to contain prescription drug substances (yohimbine and rauwolfia), was being sold on Kijiji and at DiscountSupplementsCo.com

Health Canada Apr/16 seized seventeen unauthorized health products from the retailer, **Matrioshka Russian Delicatessen**, in Calgary, Alberta. Two unauthorized products were labelled with prescription drug ingredients (captopril and sulfanilamide).

Health Canada May/16 is warning Canadians not to purchase or use '**LifeGive'** health products to treat diseases such as cancer and dementia.

Health Canada May/16 seized an unauthorized product being promoted as a dietary supplement, **Animal Test**, from Supplement King, 1250 Brant Street, Unit 9a, Burlington, Ontario. This product contains yohimbine, a prescription drug ingredient.

Health Canada June/16: Australian Therapeutic Goods Administration-**Excellence Losing Weight capsules** contains undeclared silbutramine & Natural Model capsules contains undeclared sibutramine and phenolphthalein.

.Health Canada June/16: Singapore Health Sciences Authority-**Meizitang Botanical Slimming 100% Natural Soft Gel** contains undeclared diclofenac.

Health Canada June/16: FDA says **Boss Number #Six** contains undeclared tadalafil; **Bull & Bull's Genital** contains undeclared sildenafil; **Ginseng Power-X** contains undeclared sildenafil and sulfoaildenafil; **Golden Night** contains undeclared sildenafil and hydroxythiohomosildenafil; **Neophase Natural Sex Enhancer** contains undeclared hydroxyacetildenafil; **Weekend Prince** contains undeclared sildenafil; & **Wonder-Erect Male Gum** contains undeclared vardenafil.

Health Canada June/16: Australian Therapeutic Goods Administration- **Half Quite tablets** contains undeclared sildenafil; contains undeclared sildenafil and oxytetracycline; **Maxagra capsules** contains undeclared sildenafil and oxytetracycline; **Ninja-X** contains undeclared sildenafil and thiosildenafil; **Sextra capsules** contains Undeclared sildenafil and yohimbine & **Zhong Hua Niu Bian** tablets contains undeclared chloramphenicol and sildenafil.

Health Canada June/16: Australian Therapeutic Goods Administration-**Amazon Tonic III** contains undeclared oleandrin.

Health Canada June/16: FDA says **Bentonite Me Baby** contains elevated levels of lead, Crema Piel de Seda contains elevated levels of mercury, & Licorice Coughing Liquid contains undeclared morphine.

Health Canada June/16 is reminding Canadians about the serious risks posed by the unauthorized product "**Animal Test**,"after identifying additional retailers and a distributor selling the product which contained yohimbine.
Health Canada July/16: FDA says **Best Bentonite Clay** contains elevated levels of lead.
Health Canada July/16: FDA says **Sextra, & Zlimxter Capsules** contains undeclared sildenafil.
Health Canada July/16: FDA says **Dynamizm Capsules, ENVY BP, Propell Platinum, Xerophagy Capsules, & Sextra** contains undeclared sibutramine.
Health Canada July/16: FDA says **Salute Capsules** undeclared sildenafil, thiosildenafil, and sulfoaildenafil.
Health Canada July/16: FDA says **Eradicate Capsules** undeclared sibutramine and desmethylsibutramine.
Health Canada July/16: Australian Therapeutic Goods Administration says **Leisure Slimming capsules** contains undeclared sibutramine and phenolphthalein.
Health Canada July/16: Australian Therapeutic Goods Administration says **U Slimming and U Plus Slimming capsules** undeclared sibutramine, phenolphthalein, diclofenac, and lignocaine.
Health Canada July/16: Australian Therapeutic Goods Administration says **MMC Zang Ba Bao tablets, Super Bull 6000 Herbal capsules, & U.S. Black Gold tablets** undeclared sildenafil.
Health Canada July/16: **Wonderblue & B-Hard on Demand** has undeclared sildenafil as well as thiodimethylsildenafil and/or thiomethisosildenafil.
Health Canada Aug/16 is advising consumers not to use the weight loss product **AlgoSlim**, distributed via mail order by E Sélection. The package does not contain unauthorized AlgoSlim and instead contains an authorized product, Slite-T, from a lot that expired in June 2012.
Health Canada Jul/16 is informing Canadians that two unauthorized health products were seized from Next Level Fitness in Richmond and in Surrey,BC. The products **TRT (Testosterone Booster) and Freak'n Test (Testosterone Enhancer)** were labelled to contain a prescription drug substance (L-dopa) that may pose serious health risks to Canadians.
Health Canada July/16 **DR's Secret Bio Herbs Coffee** undeclared tadalafil
Health Canada July/16 **Exhilarate** undeclared sibutramine, desmethylsibutramine, phenolphthalein.
Health Canada July/16 **Ultimate Nutrition Amino Gold Capsules 1000mg, Ultimate Nutrition Amino Gold Tablets (1000mg) & Ultimate Nutrition Amino Gold Tablets (1500mg)** undeclared milk.
Health Canada Aug/16: Australian Therapeutic Goods Administration-King-**Wolf Tablets** undeclared sildenafil.
Health Canada Aug/16: Australian Therapeutic Goods Administration- **MAGNA-RX Capsules** undeclared sildenafil & acetaminophen.
Health Canada Aug/16: FDA-**My Steel Woody** undeclared sildenafil.
Health Canada Aug/16: Australian Therapeutic Goods Administration- **Black Storm tablets** undeclared sildenafil and vardenafil.
Health Canada Aug/16: FDA- **Dream Body Advanced + Acai Weight Loss & Cleanse, & Dream Body Extreme Gold** undeclared sibutramine, fluoxetine, and sildenafil.
Health Canada Aug/16: FDA- **Dream Body 450mg, Dream Body Original Formula, Dream Body Advanced 400mg, Extra Slim Plus Acai Berry Weight Loss Formula, Lose Weight Coffee & SBF Bee Pollen** undeclared silbutramine.
Health Canada Aug/16: Hong Kong Department of Health- **Lose Weight Coffee** undeclared silbutramine.
Health Canada Aug/16: Hong Kong Department of Health-TANGKE **TEGONGYIHAOJIAONANG** undeclared phenformin and glibenclamide.
Health Canada Aug/16: Hong Kong Department of Health-**4L Slimness and 4L Slimburn Plus** undeclared diclofenac.
Health Canada Sep/16 seized an unauthorized product called "**Black Orange**" from Keebo Sports Supplements at 2101 Quance St., Regina, Saskatchewan. The product is sold as a pre-workout stimulant and is labelled to contain ingredients that can pose serious health risks (yohimbine HCl, a prescription drug, and the combination of ephedrine and caffeine).
Health Canada Sep/16 is advising Canadians that Healthy Body Services Inc. has initiated a voluntary recall of two lots (G4016A and G4016) of Allmax-brand "**Rapidcuts Shredded**" capsules (NPN 80041658) because the product contains a prescription drug (yohimbine hydrochloride) not listed on the label.
Health Canada Sep/16 seized five unauthorized products promoted as workout or weight loss supplements from Keebo Sports Supplements at 1504 St. Mary's Road, Winnipeg, Manitoba. The products are labelled to contain various prescription and other drug substances that may pose serious risks to the health of Canadians. **Yohimbine** by Prime Nutrition contains Yohimbine HCl. **Diesel Fuel Stim** By Tokkyo Nutrition contains Rauwolfia Vomitoria Extract (std. min 90% alpha yohimbinw [sic]) (rootbark). **Amp-Stim** by Logan Carter contains Rauwolfia Vomitoria Extract (std. min 90% alpha yohimbine) (rootbark). **HydroxyElite** by Hi-Tech Pharmaceuticals, Inc. contains 1,3 Dimethyamylamine HCl. **Andro Quad** by Primeval Labs contains Epiandrosterone 4-androsterone.
Health Canada Sep/16 is informing Canadians that Healthy Body Services Inc. is expanding its voluntary recall of Allmax-brand "**Rapidcuts Shredded**" capsules (NPN 80041658). All lots are now being recalled as a precaution after certain lots were found to contain an undeclared prescription drug (yohimbine hydrochloride).
Health Canada Oct/16: **Anaconda Strong Formula, Boss-Rhino Gold X-tra Strength, De Guo Hei Bei (德国黑啤), Libigirl, Power Spring (XXX) Oral Liquid, Shangai Ultra X, Super Shangai, The Golden Root, Weili (一炮到天亮or Yi Pao Dao Tian Liang) , Ziyinzhuangyang**, -Undeclared sildenafil by United States Food and Drug Administration.
Health Canada Oct/16: **Ant Power tablets, Man King capsules**, -Undeclared sildenafil by Australian Therapeutic Goods Administration.
Health Canada Oct/16: **Golden Ant tablets**-Undeclared sildenafil and chloramphenicol byAustralian Therapeutic Goods Administration.
Health Canada Oct/16: **Xcelerated Weight Loss Ultra Max**- Undeclared phenolphthalein and sildenafil by United States Food and Drug Administration.
Health Canada Oct/16: **Adelganzantes R-II, Mang Luk Power Slim, Xcelerated Weight Loss Charged Up, & Xcelerated Weight Loss Turbo Charge**--Undeclared sibutramine by United States Food and Drug Administration.
Health Canada Oct/16: **B-finn**- Undeclared orlistat and 2-(diphenylmethyl)pyrrolidine (desoxy-D2PM)by Hong Kong Department of Health.
Health Canada Oct/16: **Citrus' Fit, Mang Luk Power Slim Detox, Slim Fit X, & Ultimate Lean** -Undeclared sibutramine and desmethylsibutramine by United States Food and Drug Administration.
Health Canada Oct/16: **Double S**- Undeclared sibutramine by Hong Kong Department of Health.
Health Canada Oct/16: **Maxx Easy**-Undeclared sibutramine and lorcaserin, and orlistat by United States Food and Drug Administration.
Health Canada Oct/16: **Mi Show Slimming capsules**- Undeclared sibutramine by Australian Therapeutic Goods Administration.
Health Canada Oct/16: **Xcelerated Weight Loss Ultra Max**- Undeclared phenolphthalein and sildenafil by United States Food and Drug Administration.
Health Canada Oct/16: **Zi Xiu Tang Beauty Face and Figure Capsule**- Undeclared phenolphthalein and fluoxetine by United States Food and Drug Administration.
Health Canada Oct/16 has requested that **SurThrival** voluntarily recall all lots of its colostrum products because they contain undeclared milk allergens, which may pose serious health risks to people who are allergic or hypersensitive to cow's milk.
Health Canada Oct/16 is informing Canadians that the product **Nature's Power Solutions Acidophilus Blend** contains undeclared milk allergens.
Health Canada Nov/16: **One More Knight 1750** has undeclared tadalafil and dapoxetine by the United States Food and Drug Administration.
Health Canada Nov/16: **Love4Long** has undeclared sildenafil by the United States Food and Drug Administration.
Health Canada Nov/16: **Kopi Jantan Tradisional Natural Herbs Coffee** has undeclared desmethyl carbodenafil by the United States Food and Drug Administration.
Health Canada Nov/16: **Natural Eruption** has undeclared sibutramine by the United States Food and Drug Administration.
Health Canada Nov/16: **DHZC-2 Tablet** has elevated levels of lead by the United States Food and Drug Administration.
Health Canada Nov/16: **Snake Powder Capsules** has undeclared dexamethasone, chloramphenicol, chlorpheniramine, ibuprofen, and tetracycline by the Singapore Health Sciences Authority.
Health Canada Nov/16: **JC Gold** has undeclared dexamethasone, dexchlorpheniramine, and frusemide (furosemide) by the Singapore Health Sciences Authority.
Health Canada Nov/16: **Tu Cho Pan Chi Pain** has undeclared dexamethasone, chlorpheniramine, and frusemide (furosemide) by the Singapore Health Sciences Authority.
Heallth Canada Nov/16: "**Phytovie Acore Vrai Calamus" herbal tea**, an unauthorized natural health product, is being recalled after Health Canada testing found it to contain excessive levels of beta-asarone.
Health Canada Dec/16 reports: Australian Therapeutic Goods Administration: **Bee Sexy Slimming capsules** undeclared sibutramine; Australian Therapeutic Goods Administration: **Biolo World Slimming capsules**-undeclared sibutramine and phenolphthalein; Hong Kong Department of Health: **ele Slim Shot**-undeclared orlistat; Singapore Health Sciences Authority: **LifeSparks 100% Natural PAIN RELIEF SUPPLEMENT**- undeclared chlorpheniramine, dexamethasone, diclofenac, paracetamol (acetaminophen), piroxicam, sulphamethoxazole; Singapore Health Sciences Authority: **LONGRED Oyster-x**-undeclared sildenafil; FDA: **Stiff Bull Herbal Coffee**-undeclared desmethyl carbodenafil; & Australian Therapeutic Goods Administration: **Wolfish Shark Viagra** tablets-undeclared sildenafil.

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Medicines and Healthcare products Regulatory Agency (MHRA) Dec/07 said: **Xiao Qin Long Wan**, a cold and flu medicine; pain reliever **Chuan Xiong Cha Tiao Wan**; **Bai Tou Weng Wan**, sold for stomach problems, and **Xie Gan Wan**, used to treat stress may contain Aristolochicia, which in unlicensed medicines was banned in UK in 1999
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MHRA Aug 2011 issues warning over traditional Chinese medicines containing **Lei Gong Teng (tripterygium wilfordii)**
MHRA Dec/11Health Sciences Authority in Singapore has issued a press release warning the public of four adulterated health products. **ATHRI-Eze** - is marketed as a traditional Chinese medicine and packaged in a bottle of 20 white capsules. **SEAR HEANG TIENCHI TU CHUNG WAN** - claims to treat rheumatic pain and backache and is sold in a bottle of 40 black pills with a red label. **CAP WIJAYA KUSUMA (AN KI IT)** and **WIKU JAHE KENCUR (AKUR MUJARAB)** - are promoted as Malay Jamu (postnatal) medicines, which are packed in foil sachets of brown powder and are labelled to treat rheumatoid and arthritic conditions.These four products have been found to contain undeclared pharmaceutical medicines. Ingredients found include: dexamethasone, furosemide, paracetamol, chlorpheniramine (also known as chlorphenamine), phenylbutazone, allopurinol & prednisolone.
MHRA Dec/11 In response to an urgent notice issued by MHRA, Bee Health Ltd has agreed to stop marketing FSC Black Cohosh 1000 mg due to concerns about the high dosage of black cohosh in the product. The MHRA advises consumers not to take the FSC Black Cohosh product as it equates to 50 times the dose approved for traditional herbal medicinal products used to relieve menopausal symptoms. It is not known what the risks or effects on the body could be associated with such a high level of Black Cohosh.
MHRA Jan/12 Consumers are advised not to take unlicensed **Butterbur (Petasites hybridus)** herbal remedies. Butterbur contains pyrrolizidine alkaloids (PAs) which studies have shown can result in serious liver damage and organ failure. PAs have also been shown to lead to cancer in animals. Butterbur is most commonly used to treat migraine and hayfever. Butterbur products have been associated with cases of liver toxicity; 40 cases have been reported in the literature. Of these cases, nine were of acute hepatitis and two of the nine cases resulted in liver failure requiring transplantation. The cases of liver toxicity appear to have occurred with extracts of Butterbur where the PAs had been removed and only small amounts remained. There is some evidence that other constituents found in Butterbur such as the sesquiterpene constituents for example petasin may be implicated in the liver toxicity.
MHRA Feb/12 Herbal sliming products found to contain potentially dangerous undeclared pharmaceuticals: **Expelling Grease Slimming Abdomen, V12 Fruit Slimming, 100% Natural Weight Loss Coffee, Leisure 18 Slimming Orange Juice, Fashion Slimming Milk Shake, Langli, Ya Buk & Fruit and vegetables lose weight**. MHRA has received advice from the Danish Medicines Agency that these unlicensed products have been tested and found to contain the Prescription Only Medicine Sibutramine.

MHRA Feb/12 has received advice from AGES PharmMed in Austria and the Danish Medicines Agency, warning that these unlicensed products have been tested and found to contain Tadalafil and/or Sildenafil: **AH Free/Reflexit, Stree Overlord, Man King, VigRX, Maxman, Maxman III, Viriya, & Imbiza for Men.**

MHRA Feb/12 Following a safety alert issued in October 2010 about slimming products containing Paiyouji the Agency has received a further complaint about a product called **'Paiyouji Plus - Fast Acting Slimming Tea'**. This product has been tested by the Agency and, as in the case of other Paiyouji products, found to contain sibutramine.

MHRA Mar/12 Traditional Chinese Medicine (TCM) **Anshen Bunao Pian** (Chung Lien Kulin Brand) has been found by the Department of Health in Hong Kong to contain 55 times the level of mercury permitted in China. Acute mercury poisoning can damage the neurological system and kidneys. The product is manufactured in mainland China and imported by Fung Wah (HK) Company.

MHRA July/12 Department of Health in Hong Kong have issued a warning asking members of the public not to buy or consume an oral product called '**Ling Zhi She Xiang Tong Mai Dan'**, as it may contain an undeclared pharmaceutical, dexamethasone.

MHRA Aug/12 **Echinacea should not be given to children under 12 years**: Oral herbal products containing echinacea should not be given to children under 12 years, the Medicines and Healthcare products Regulatory Agency (MHRA) has warned. http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON180627 [Accessed 24 October 2012].

MHRA: Austrian Sep/12 authorities have issued a warning for **Ramlostan Forte** manufactured by SC Parapharm, Romania. Ramlostan comes in white and blue packaging, with a picture of a ram at the top. Inside, there are ten blue capsules. The Austrian authority (AGES) has issued a warning for this product after finding it to contain Tadalafil.

MHRA Oct/12 The UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued a reminder about a potential adverse effect of liver problems when using **Black Cohosh** to relieve symptoms of the menopause. The MHRA has issued a press release reminding people about the risk of liver problems with Black Cohosh, following a serious case of liver failure resulting in a liver transplant suspected to have been caused by a herbal product containing Black Cohosh. The investigation of this case and of the product involved is ongoing. To date, the MHRA has received 53 reports of adverse reactions suspected to be associated with the use of Black Cohosh.

MHRA, Viridian Nutrition has agreed to recall stocks of **Black Cohosh** Root Capsules, as some batches of the product have been found to contain an undeclared plant species in addition to the declared plant species. The product is labelled as containing Black Cohosh, which is the common name of Cimicifuga racemosa, as specified in the European, British and American Pharmacopoeia. However tests carried out on the product have shown that the product also contains other Cimicifuga species, probably Cimicifuga foetida.

MHRA Nov/12 has received advice from the Danish Medicines Agency that this unlicensed product, **Ultra Slim** has been tested and found to contain the Prescription Only Medicine Sibutramine.

MHRA Nov/12 has received advice from the Ministry of Health, Jerusalem warning that this unlicensed product, **Shark Essence** has been tested and found to contain Tadalafil and Sildenafil.

MHRA Dec/12 Medicines and Healthcare products Regulatory Agency, 2012. Liver failure case highlights need to use **Black Cohosh** remedies carefully [online].

Available: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON199545

MHRA Feb/13 is advising consumers not to use the products specified below due to sibutramine content. Product names**: Fashion Slimming Coffee, L-Carnitine + P57, L-CarnitinL 360 Slimming Coffee, Brazil Potent Slimming Coffee sachets, Coffee 26 Original sachets, Coffee Nature Fashion Slimming sachets, Slender Capsule, Slim-1.**

MHRA Feb/13 Hong Kong Department of Health issues warnings about **Traditional Chinese Medicines (TCM) found to contain heavy** metals. Product names: [W.S.] Tian Ma Toutong Wan; Shi Hu Ye Guang Wan (Ye Guang Wan); Nai Chang Ming Yan Pills (Ming Yan Pills); [Fung Shing Pai] Tian-Ma Wan; Bak Foong Pills (11 products - see below for details).

MHRA Aug/13 has recently been made aware of several unlicensed herbal products which have been found to contain **heavy metals**: **Bak Foong Pills, Hairegenerator, Niu-Huang Chieh-tu-pien, Divya Kaishore Guggul, Chandraprabha Vati.**

MHRA May/14: Advising consumers not to use Ayurvedic Herbal Medicine **Shwasa Sanjeevani** as it has been found to contain dexamethasone. Hong Kong Department of Health found that samples of **Hairegenerator** exceeded the permissible limit for mercury. Singapore Health Sciences Department **Li Long Mei Guo Mo Bang** because it contains sildenafil & **Ginseng Tu chong Wan Lin Heong** contains dexamethasone.

MHRA Feb/16 Class 2 medicines recall: **Asda, St John's Wort, HRI Good Mood and Superdrug St John's Wort tablets** THR 02231/0002 because of product contamination.

Michel BA, Stucki G, Frey D, et al. **Chondroitins** 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. Arthritis Rheum 2005; 52:779-86.
(InfoPOEMs: After 2 years of treatment, chondroitin sulfate had no effect on comfort in patients with severe degenerative arthritis of the knee. Compared with placebo, however, it appears that chondroitin may have a small protective effect on the joint. The clinical relevance of this effect not known. (LOE = 1b))

Mills E, Singh R, Ross C, Ernst E. Sale of **kava** extract in some health food stores. CMAJ. 2003 Nov 25;169(11):1158-9. (January 2002, Health Canada issued an advisory, followed by a ban in August 2002, on the sale of herbal kava. One month after the advisory, 22 (67%) of 33 health food stores approached were selling kava. Two months after the ban, 17 (57%) of 30 stores continued to sell kava. These findings demonstrate that health food stores may need to be better informed about the sale of restricted natural health products.

Misaka S, Yatabe J, Müller F, et al. **Green tea** ingestion greatly reduces plasma concentrations of **nadolol** in healthy subjects. *Clin Pharmacol Ther* 2014.

Miyasaka LS, Atallah AN, Soares BG. **Valerian** for anxiety disorders. Cochrane Database Syst Rev 2006; 4:CD004515. This paper and [17**]

Miyasaka LS, Atallah AN, Soares BG. **Passiflora** for anxiety disorder. Cochrane Database Syst Rev 2007; 1:CD004518.

Mischoulon D. Update and critique of **natural remedies as antidepressant treatments**. Psychiatr Clin North Am 2007; 30:51-68.

Murphy RK, Ketzler L, Rice RD, et al. Oral **Glucosamine Supplements as a Possible Ocular Hypertensive Agent**. JAMA Ophthalmol. 2013 May 23:1-3.

Nahas R, Moher M. **Complementary and alternative medicine** for the treatment of type 2 diabetes. Can Fam Physician. 2009 Jun;55(6):591-6. Chromium, and possibly gymnema, appears to improve glycemic control. Fibre, green tea, and fenugreek have other benefits but there is little evidence that they substantially improve glycemic control. Further research on bitter melon and cinnamon is warranted. There is no complementary and alternative medicine research addressing microvascular or macrovascular clinical outcomes.

Nahas Richard, Sheikh Osmaan. **Complementary and alternative medicine** for the treatment of **major depressive disorder** Can Fam Physician June 2011 57: 659-663. (**St John's wort & exercise**)

Nahin RL, Pecha M, Welmerink DB, et al. Ginkgo Evaluation of Memory Study Investigators. Concomitant use of **prescription drugs and dietary supplements** in ambulatory elderly people. J Am Geriatr Soc. 2009 Jul;57(7):1197-205.

Nahin RL, Boineau R, Khalsa PS, et al. Evidence-Based Evaluation of **Complementary Health Approaches for Pain Management** in the United States. Mayo Clin Proc. 2016 Sep;91(9):1292-306

Nair KS, et al. **DHEA** in elderly **women** and **DHEA or testosterone** in elderly men. N Engl J Med. 2006 Oct 19;355(16):1647-59. (see also Pharmacist's Letter: Anti-aging Effects of DHEA. Dec/06)
(n= 2yr 87 males, 57 women) Men who received testosterone had a slight increase in fat-free mass, and men in both treatment groups had an increase in BMD at the femoral neck. Women who received DHEA had an increase in BMD at the ultradistal radius. Neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life. (InfoPOEMs: There is no evidence that supplementation with dehydroepiandrosterone (DHEA) or testosterone has any meaningful clinical benefit for older patients with low serum levels of those hormones. (LOE = 1b))

Navarro VJ, Barnhart H, Bonkovsky HL, et al. **Liver injury from herbals and dietary supplements** in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014 Jul 12.

Navarro V, Khan I, Björnsson E, et al. **Liver Injury from Herbal and Dietary Supplements**. Hepatology. 2016 Sep 27.

Neale C, Camfield D, et al. Cognitive effects of two nutraceuticals **Ginseng and Bacopa** benchmarked against modafinil: a review and comparison of effect sizes. Br J Clin Pharmacol. 2012 Oct 9.

Necyk C, Tsuyuki RT, Boon H, et al. **Pharmacy study of natural health product adverse reactions (SONAR):** a cross-sectional study using active surveillance in community pharmacies to detect adverse events associated with natural health products and assess causality. BMJ Open. 2014 Mar 28;4(3):e003431.

Newmaster SG, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. **DNA barcoding detects contamination and substitution** in North American herbal products. BMC Med. 2013;11:222.

Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms ofmenopausewith **black cohosh**, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med 2006;145:869–79.

Nicolai SP, Kruidenier LM, Bendermacher BL, et al. **Ginkgo biloba for intermittent claudication**. Cochrane Database Syst Rev. 2013 Jun 6;6:CD006888. doi: 10.1002/14651858.CD006888.pub3.
Overall, there is no evidence that Ginkgo biloba has a clinically significant benefit for patients with peripheral arterial disease.

Nieminen TH, Hagelberg NM, Saari TI, Neuvonen M, Laine K, Neuvonen PJ, Olkkola KT. **St John's wort greatly reduces the concentrations of oral oxycodone**. Eur J Pain. 2010 Jan 25.

Nightingale G, et al. A pharmacist-led medication assessment used to determine a more precise estimation of the **prevalence of complementary and alternative medication (CAM) use among ambulatory senior** adults with cancer. J Geriatr Oncol. 2015 Aug 12.

Ngo MQ, Nguyen NN, Shah SA. Oral **aloe vera** for treatment of diabetes mellitus and dyslipidemia. Am J Health Syst Pharm. 2010 Nov 1;67(21):1804, 1806, 1808.

Oct/13 The workout supplement marketed as "**Craze**" contains a potentially dangerous designer drug — a methamphetamine analog — according to an article in Drug Testing and Analysis. The analog, N,alpha-diethyl-phenylethylamine (N,alpha-DEPEA), was

found in three different samples of the product obtained from separate sources and analyzed by two labs. The product's label claims it contains phenylethylamines derived from dendrobium, but the authors say the component identified as N,alpha-DEPEA has never been identified in dendrobium. They say the amounts of N,alpha-DEPEA found "strongly suggest" that it's not a minor contaminant, adding that if their findings are confirmed, the FDA should "remove all N,alpha-DEPEA-containing supplements from the marketplace." The Boston Globe reports that another supplement, "**Detonate**," also contained N,alpha-DEPEA upon analysis.

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Ondrizek RR, Chan PJ, Patton WC, King A. Inhibition of human **sperm** motility by specific herbs used in alternative medicine (eg. St. John's Wort). J Assist Reprod Genet. 1999 Feb;16(2):87-91.

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Perri D, Dugoua JJ, Mills E, Koren G. Safety & efficacy of echinacea (E. angustafolia, purpurea & pallida) during pregnancy & lactation. Can J Clin Pharmacol.2006 Fall;13(3):e262-7.Epub 2006Nov3.

Perry, Rachel, Hunt, Katherine, Ernst, Edzard. Nutritional Supplements and Other Complementary Medicines for **Infantile Colic**: A Systematic Review. Pediatrics 2011 127: 720-733

Pharmacist's Letter: Health Benefits of Drinking **Green Tea.** Nov 2006.

Pharmacist's Letter. Is **Chondroitin** effective for Osteoarthritis. June 2007. (Best evidence is with glucosamine sulfate called DONA by Rotta Pharmaceuticals)

Pharmacist's Letter. **New Health Canada Rules Allow More Health Claims for Natural Products**. April 2008.

Pharmacist's Letter. **Hawthorn for Heart Failure**. April 2008.

Pharmacist's Letter. **Flaxseed**: Is It As Beneficial As Fish Oil? July 2009.

Pharmacist's Letter. **Supplements for Prevention and Treatment of Colds and Influenza**. Nov 2009.

Pittler MH, Ernst E. **Horse chestnut** seed extract for chronic venous insufficiency. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003230. The evidence presented implies that HCSE is an efficacious & safe short-term treatment for CVI. However, several caveats exist and more rigorous RCTs are required to confirm the efficacy of this treatment option.

Pittler MH, Ernst E. **Kava** extract for treating anxiety. Cochrane Database Syst Rev. 2003;(1):CD003383. CONCLUSIONS: Compared with placebo, kava extract appears to be an effective symptomatic treatment option for anxiety. The data available from the reviewed studies suggest that kava is relatively safe for short-term treatment (1 to 24 weeks), although more information is required. Further rigorous investigations, particularly into the long-term safety profile of kava are warranted.

Pittler MH, Ernst E. **Feverfew** for preventing migraine. Cochrane Database Syst Rev. 2004;(1):CD002286. CONCLUSIONS: There is insufficient evidence from randomised, double-blind trials to suggest an effect of feverfew over & above placebo for preventing migraine. It appears from the data reviewed that feverfew presents no major safety problems.

Pittler MH, Guo R, Ernst E. **Hawthorn extract** for treating chronic heart failure. Cochrane Database Syst Rev 2008; DOI: 10.1002/14651858.CD005312.pub2. (Not included in the review was the survival and Prognosis: Investigation of Crataegus Extract WS1442 in CHF (**SPICE**) trial, which was ongoing as Pittler et al were screening relevant trials. As reported by heartwire when the study was later presented at the American College of Cardiology 2007 Scientific Sessions, adding the herbal to ACE inhibitors, beta blockers, and other components of contemporary therapy failed to alter a composite primary end point that included sudden cardiac death, death due to progressive heart failure, fatal or nonfatal MI, and HF hospitalization at 24 months. The trial did support hawthorn extract's good safety record, however.)

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Qato DM, Wilder J, Schumm LP, et al. **Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States**, 2005 vs 2011. JAMA Intern Med. 2016 Apr 1

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Quinn JF.; Raman R,Thomas RG.; et al. **Docosahexaenoic Acid (DHA) Supplementation** and Cognitive Decline in Alzheimer Disease: A Randomized Trial. *JAMA*. 2010;304(17):1903-1911.

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Health Canada Apr/15: Methylphenidate Products – Risk of Priapism - Janssen Inc. - Novartis Pharmaceuticals - Purdue Pharma Inc. Prolonged and painful erections (priapism) have been very rarely reported in patients, including children, taking methylphenidate products. The prescribing information for these products has been updated to include this information.

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Online Extras – RxFiles Benzodiazepine Chart

BENZODIAZEPINE (BZ) COMPARISON CHART

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FDA July/15 is warning about a **counterfeit version of the anxiety drug diazepam** (e.g., Valium) being sold online. About 700 patients in Africa have taken haloperidol pills that were mislabeled as diazepam, according to the World Health Organization. The counterfeit tablets: are light yellow; bear the letters AGOG on one side; are scored across the center on the other side. Some patients who took them experienced face, neck, and tongue dystonia.

FDA Aug/16 review has found that the growing **combined use of opioid medicines with benzodiazepines** or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or **difficult breathing and deaths**.

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

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

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

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

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

Health Canada Aug/10 says **Fulda Unitang Herbs Sleep Plus**, an unauthorized product promoted as an herbal sleep aid, has been found to contain high levels of estazolam.

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💻 Bipolar Disorder: Online Extras

Previously Used Agents:

Gabapentin dose CrCl<60 **NEURONTIN**g (100,300,400 cap) (600$, 800$ mg tab ↑cost) ▼ Max of 4000mg/day	**Common**: somnolence, dizzy, ataxia, nystagmus, N/V, blurred vision,tremor,slurred speech,rash, behavioral changes in kids&↓WBC.**WEIGHT GAIN**=+(appears dose related), euphoria; ?akathisia on withdrawal	N/A **little effect as mood stabilizer**	√seizures; Option:Neuropathic pain &**Anxiolytic in severe PD& social phobia**,↓dose if ↓ renal fx, 3-25umol/l (? Significance/avail.)	Antacids ↓ by 20% absorption NO other sig. interactionsWith doses >600mg less is absorbed since mechanism is saturated	100mg hs (↑**100**-400mg/day increments) 3600mg/day	100mg po BID 300mg po BID **400mg po BID** 300mg po TID	27 50 **58** 70
Topiramate **TOPAMAX**g (25,50✗,100,200mg tab; 15, 25mg sprinkle cap) Hypospadias in male infants. Cleft	**Common**: nausea, dizzy, tremor, ataxia, somnolence, **cognitive dysfx**, headache, paresthesias, sedation, fatigue, diarrhea, metabolic acidosis, **nephrolithiasis & glaucoma** acute angle.stop Rx! **WEIGHT GAIN= loss possible** (seems dose & duration dependent &> in ♀)	CNS AE synergize with agents such as divalproex	Weight loss~**4kg** ?dose related May minimize weight gain induced by other psychotropics √seizures; 80% Renal elimination √migraine prophylaxis + dva→↓ platelet&↑**encephalopathy** **Renal stones**1.5% thus try to ↑**fluid intake**	**↓Topiramate level** by: **CBZ**& phenytoin (40%), valproate(15%) **↑ toxicity**of topiramate with: Ketogenic diet; Aceta-,dor-&metho-zolamide (topiramate has carbonic anhydrase inhib. properties) **Topiramate** >200mg/d**↓effectiveness** : **OCs** oral contraceptives	25mg hs ↑ only by **25-50mg/week** increments **250-400**mg/day	25mg po BID 50mg po BID **100mg po BID** 200mg po BID 400mg po hs Caution: ↓ **sweating** especially in children	79/298 148/566 140/536 207/780 207/780 generic/Trade

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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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RxFiles Related Documents:

Bipolar Disorder & Mood Stabilizer/Adjuvant Agent Comparison Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-psyc-moodstabalizers.pdf
Antipsychotic Comparison Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-Psyc-Neuroleptics.pdf
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Peri-Pregnancy Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Peri-Pregnancy-DrugTx.pdf
Q&A Are Antidepressants Safe during Pregnancy & Breastfeeding http://www.rxfiles.ca/rxfiles/uploads/documents/Antidepressants-PregnancyandBreastfeeding-QandA.pdf
Q&A Management of Bipolar Disorder during Pregnancy & Postpartum http://www.rxfiles.ca/rxfiles/uploads/documents/Bipolar-Pregnancy-QandA-Part-1-Text.pdf

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2008 (Annuls Int Med, Nov 2008) - Highlights

- Since all of the drugs are about equally effective, consider adverse-effect profiles, costs, and patient preferences when choosing among them.
- Assess the patient's status regularly, beginning within 2 weeks after starting therapy.
- Modify treatment if there's no response within 2 months.
- Successful treatments of first episodes of major depression should continue for about 6 months; patients with a history of two or more episodes should undergo treatment for much longer periods.

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FDA Dec/11 notified healthcare professionals and the public on the use of selective serotonin reuptake inhibitor (SSRI) antidepressants by women during pregnancy and the potential risk of a rare heart and lung condition known as **Persistent Pulmonary Hypertension of the Newborn** (PPHN). FDA has reviewed the additional new study results and has concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN.
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FDA: Aug/11 Antidepressant citalopram (Celexa, Forest Laboratories) should not be used in doses higher than 40 mg per day because of concerns that it can cause potentially fatal changes in heart rhythm.
FDA: Dec/11 Selective Serotonin Reuptake Inhibitor Antidepressants: Use During Pregnancy & Potential Risk of Persistent Pulmonary Hypertension of the Newborn http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm283696.htm
FDA Aug/13 Health and Beyond LLC is voluntarily recalling quantity lots of product **Tranquility**. The products have been found to contain a trace of Doxepin which is a pharmaceutical for sleep and Chlorpormazine for psychotic disorders.
FDA Jun/14 laboratory analysis confirmed that **Sport Burner & Toxin Discharged Tea** contains fluoxetine.
FDA Feb/15 laboratory analysis confirmed that **Botanical Slimming (Red), & Oxy ELITE Pro Super Thermogenic** (Lot# 216732, Exp. 04/17) contains fluoxetine.
FDA July 15:**Botanical Slimming (Red) & Xcel** contains Undeclared fluoxetine.
FDA July 15:**Natural Max Slimming** contains Undeclared sildenafil, fluoxetine, andsibutramine.

FDA Jul/15 is warning health care professionals and patients that reports of confusion between the antidepressant **Brintellix** and anti-blood clotting medication **Brilinta** have resulted in the wrong medication being prescribed.
FDA Nov/15 laboratory analysis confirmed that **Perfect Slim Fast Track Slim & Slyn Both** contains fluoxetine.
FDA May/16 has approved a brand name change for the antidepressant Brintellix (**vortioxetine**) to decrease the risk of prescribing and dispensing errors resulting from name confusion with the blood-thinning medicine Brilinta (ticagrelor). The new brand name of the drug will be **Trintellix**.
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Health Canada Feb/11 **Methylene blue injectable** in combination with serotonin reuptake inhibitors - Association with serotonin toxicity Cases of serotonin toxicity have been reported and published in association with the use of methylene blue injectable in patients exposed to drugs with serotonin reuptake inhibition properties.
Health Canada Jan/12: Lundbeck Canada, in collaboration with Health Canada, would like to inform you that the antidepressant **Celexa® (citalopram** hydrobromide; also marketed as generics), should no longer be used at doses greater than **40 mg per day** due to study results indicating a dose-dependent potential for QT prolongation.
Health Canada May/12 is informing Canadians of a labelling update for the prescription drug **Cipralex** (the brand name of the drug **escitalopram**) regarding a dose-related risk of abnormal heart rhythms. Cipralex is used to treat depression and belongs to a family of drugs known as Selective Serotonin Reuptake Inhibitors (SSRIs). 10 mg per day is the maximum recommended dose for patients who: are 65 years of age or older, or have liver problems, or are taking the heartburn drugs omeprazole or cimetidine which can increase the blood level of Cipralex. 20 mg per day is still the maximum recommended dose for most other patients.
Health Canada Mar/14: REMERON / **REMERON RD (mirtazapine**) – Abnormal Heart Rhythm - Merck Canada Inc. Cases of abnormal heart rhythm (eg. **QT** prolongation) have been reported with the antidepressant REMERON / REMERON RD (mirtazapine) mainly with drug overdose or when taking other drugs known to cause heart rhythm problems. The product information has been updated.
Health Canada June/14: **Adipotrim XT** contains fluoxetine.
Health Canada Sep/14: **Sport Burner** :The United States Food and Drug Administration (FDA) warned consumers not to use the product Sport Burner after it was found to contain undeclared fluoxetine.
Health Canada Mar/16 says **Perfect Slim Fast Track Slim & Slyn Both** by FDA contains undeclared fluoxetine
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nefazodone[3A4] SERZONE	carbamazepine ⑨⑥ cisapride ⑥②$_{cv}$ lovastatin ⑥$_{(rhabdo)}$ MAOI's ③ sibutramine ③ simvastatin ⑥$_{(rhabdo)}$ sumatriptan ③	alprazolam ⑥ atorvastatin ⑥ cyclosporin ⑥	digoxin ⑥, fentanyl ⑧ fluvastatin ⑥ grapefruit juice ⑧ haloperidol ⑥	indinavir/ritonavir ⑧ L-tryptophan ③ midazolam ⑥ paroxetine ③	phenytoin ⑨⑥ **pimozide** ⑥ cv pravastatin ⑥ quinidine ⑥②, ritonavir ⑧	**sedatives** ① tacrolimus ⑥② triazolam ⑥

CV=cardiovascular **HTN**=hypertension

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ANTIPSYCHOTIC COMPARISON CHART

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FDA Dec/14 is warning that the antipsychotic drug **ziprasidone** (marketed under the brand name, Geodon, and its generics) is associated with a rare but serious skin reaction that can progress to affect other parts of the body. A new warning has been added to the Geodon drug label to describe the serious condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
FDA May/16 is warning that **compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex** have been reported with the use of the antipsychotic drug **aripiprazole** (Abilify, Abilify Maintena, Aristada).
FDA May/16 is warning that the antipsychotic medicine **olanzapine** can cause a rare but serious skin reaction that can progress to affect other parts of the body. FDA is adding a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (**DRESS**).
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Health Canada June/11 Antipsychotic drugs: Labelling update regarding the risk of abnormal **muscle movements and withdrawal symptoms in newborns** exposed during pregnancy.

Health Canada Nov/13 **Risperidone- and paliperidone**-containing products are primarily prescribed for the treatment of schizophrenia; however, the risk of Intraoperative floppy iris syndrome (**IFIS**) applies to all patients undergoing cataract surgery, who have been exposed to these products, irrespective of indication.

Health Canada Feb/15 **Risperidone** - Restriction of the Dementia Indication - Janssen Inc. The indication for risperidone in dementia has been restricted to the **short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type**. The indication no longer includes the treatment of other types of dementia.

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Mukundan A, Faulkner G, Cohn T, Remington G. **Antipsychotic switching** for people with schizophrenia who have neuroleptic-induced **weight or metabolic problems**. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD006629. DOI: 10.1002/14651858.CD006629.pub2. Evidence from this review suggests that switching antipsychotic medication to one with lesser potential for causing weight gain or metabolic problems could be an effective way to manage these side effects, but the data were weak due to the limited number of trials in this area and small sample sizes. Poor reporting of data also hindered using some trials and outcomes. There was no difference in mental state, global state and other treatment related adverse events between switching to another medication and continuing on the previous one. When the three switching strategies were compared none of them had an advantage over the others in their effects on the primary outcomes considered in this review. Better designed trials with adequate power would provide more convincing evidence for using medication switching as an intervention strategy.
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SEDATIVE COMPARISON CHART

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FDA Jan/13 The recommendation applies to **zolpidem** products approved for bedtime use, marketed as generics and under the brand names *Ambien*, *Ambien CR*, *Edluar*, and *Zolpimist*. Data show the risk for morning impairment is highest with extended-release forms of these drugs, and **women** appear to be more susceptible to this effect because they eliminate zolpidem more slowly than men, a statement from the FDA notes.
FDA May/14 has notified health professionals and their medical care organizations of a new warning that the insomnia drug Lunesta (**eszopiclone**) can cause next-day impairment of driving and other activities that require alertness. FDA recommends a decreased starting dose of Lunesta to 1 mg at bedtime. Women and men are equally susceptible to impairment from **Lunesta**, so the recommended starting dose of 1 mg is the same for both.
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http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_127_e.html
Health Canada April/07is advising consumers not to use a product called **Eden Herbal Formulations Serenity Pills II** because it contains the undeclared drug **estazolam**.
Health Canada Dec/11 **Sublinox** is the first formulation of **zolpidem** in Canada. Internationally, it has been reported in association with **complex sleep behaviours**.
Health Canada May/12 **[Chung Lien Kulin Brand] Anshen Bunai Pian.** Hong Kong Department of Health warned that this traditional Chinese health product, used for insomnia, contains excessive levels of the heavy metal mercury.
Health Canada Jan/14 **Sublinox (zolpidem** tartrate) - New Dosage Recommendations to Minimize Risk of Next-Day Impairment in Both **Women and Men** - Valeant Canada. The recommended initial dose has been lowered to 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before awakening.
Health Canada Apr/14: **Dr. Larry's Tranquility**: The U.S. Food and Drug Administration warned consumers not to use this product after it was found to contain undeclared doxepin and chlorpromazine.
Health Canada Nov/14 **IMOVANE (zopiclone)** - New Dosage Recommendations to Minimize the Risk of Next-Day Impairment - sanofi-aventis Canada Inc. Patients who take IMOVANE and other medicines to help them sleep may experience **decreased ability to be alert the day after taking** the medicine, even if they feel fully awake. This can cause next-day impairment of driving or other activities that require full mental alertness.
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Cates CJ, Jaeschke R, Schmidt S, et al. Regular treatment with **salmeterol and inhaled steroids for chronic asthma: serious adverse events**. Cochrane Database Syst Rev. 2013 Mar 28;3:CD006922. doi: 10.1002/14651858.CD006922.pub3. We found no statistically significant differences in fatal or non-fatal serious adverse events in trials in which regular salmeterol was randomly allocated with ICS, in comparison to ICS alone at the same dose. Although 13,447 adults and 1862 children have now been included in trials, the frequency of adverse events is too low and the results are too imprecise to confidently rule out a relative increase in all cause mortality or non-fatal adverse events with salmeterol used in conjunction with ICS.

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Cates CJ, Jaeschke R, Schmidt S, et al. Regular treatment with **formoterol and inhaled steroids** for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2013 Jun 7;6:CD006924. doi: 10.1002/14651858.CD006924.pub3. From the evidence in this review, it is not possible to reassure people with asthma that regular use of inhaled corticosteroids with formoterol carries no risk of increasing mortality in comparison with use of inhaled corticosteroids alone. On the other hand, we have found no conclusive evidence of serious harm, and only one asthma-related death was registered during more than 4200 patient-years of observation with formoterol. In adults, no significant difference in all-cause non-fatal serious adverse events was noted with regular formoterol with inhaled corticosteroids, but a significant reduction in asthma-related serious adverse events was observed in comparison with inhaled corticosteroids alone. In children the number of events was too small, and consequently the results too imprecise, to allow determination of whether the increased risk of all-cause non-fatal serious adverse events found in a previous meta-analysis on regular formoterol alone is abolished by the additional use of inhaled corticosteroids.

Cates CJ, Welsh EJ, Rowe BH. **Holding chambers (spacers) versus nebulisers** for beta-agonist treatment of acute asthma.Cochrane Database Syst Rev. 2013 Sep 13;9:CD000052. Nebuliser delivery produced outcomes that were not significantly better than metered-dose inhalers delivered by spacer in adults or children, in trials where treatments were repeated and titrated to the response of the participant. Spacers may have some advantages compared to nebulisers for children with acute asthma.

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Chauhan BF, Chartrand C, Ducharme FM. **Intermittent versus daily inhaled corticosteroids** for persistent asthma in children and adults. Cochrane Database Syst Rev. 2013 Feb 28;2:CD009611. doi: 10.1002/14651858.CD009611.pub3. In children and adults with persistent asthma and in preschool children suspected of persistent asthma, there was low quality evidence that intermittent and daily ICS strategies were similarly effective in the use of rescue oral corticosteroids and the rate of severe adverse health events. The strength of the evidence means that we cannot currently assume equivalence between the two options.. Daily ICS was superior to intermittent ICS in several indicators of lung function, airway inflammation, asthma control and reliever use. Both treatments appeared safe, but a modest growth suppression was associated with daily, compared to intermittent, inhaled

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Chauhan BF, Ben Salah R, Ducharme FM. **Addition of anti-leukotriene agents to inhaled corticosteroids** in children with persistent asthma. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD009585. DOI: 10.1002/14651858.CD009585.pub2. The addition of anti-leukotrienes to ICS is not associatedwith a statistically significant reduction in the need for rescue oral corticosteroids or hospital admission compared to the same or an increased dose of ICS in children and adolescents with mild to moderate asthma.

Chauhan BF, Ducharme FM. Addition to **inhaled corticosteroids of long-acting beta-agonists versus antileukotrienes** for chronic asthma. Cochrane Database Syst Rev 2014;1:CD003137. In adults with asthma that is inadequately controlled by predominantly low-dose ICS with significant bronchodilator reversibility, the addition of LABA to ICS is modestly superior to the addition of LTRA in reducing oral corticosteroid-treated exacerbations, with an absolute reduction of two percentage points. Differences favouring LABA over LTRA as adjunct therapy were observed in lung function and, to a lesser extend, in rescue medication use, symptoms and quality of life. The lower overall withdrawal rate and the higher proportion of participants satisfied with their therapy indirectly favour the combination of LABA + ICS over LTRA + ICS. Evidence showed a slightly increased risk of SAE with LABA compared with LTRA, with an absolute increase of one percentage point. Our findings modestly support the use of a single inhaler for the delivery of both LABA and low- or medium-dose ICS. Because of the paucity of paediatric trials, we are unable to draw firm conclusions about the best adjunct therapy in children.

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(e.g. age and asthma severity including mild exacerbation and impending respiratory failure) and the treatment modalities (dose, intensity, and duration) associated with most benefit from anticholinergic use better.

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

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Health Canada Aug/09 is informing health care professionals and Canadians that it is conducting a safety review of the potential association between the asthma drug **Xolair** (the brand name for the drug omalizumab) and an increased risk of cardiovascular problems. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_129-eng.php

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Herath SC, Poole P. **Prophylactic antibiotic therapy** for chronic obstructive pulmonary disease (**COPD**). Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD009764. DOI: 10.1002/14651858.CD009764.pub2. Use of continuous prophylactic antibiotics results in a clinically significant benefit in reducing exacerbations in COPD patients. All trials of continuous antibiotics used macrolides hence the noted benefit applies only to the use of continuous macrolide antibiotics. The impact of pulsed antibiotics remains uncertain and requires further research. The trials in this review included patients who were frequent exacerbators and needed treatment with antibiotics or systemic steroids, or who were on supplemental oxygen. There were also older individuals with a mean age of 66 years. The results of these trials apply only to the group of patients who were studied in these trials and may not be generalisable to other groups. Because of concerns about antibiotic resistance and specific adverse effects, consideration of prophylactic antibiotic use should be mindful of the balance between benefits to individual patients and the potential harms to society created by antibiotic overuse.

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Karner C, Cates CJ. **Long-acting beta(2)-agonist in addition to tiotropium** versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Apr 18;4:CD008989. The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and long-acting beta(2)-agonist compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta(2)-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus long-acting beta(2)-agonist compared to long-acting beta(2)-agonist alone. There were insufficient data to make comparisons between the different long-acting beta(2)-agonists when used in addition to tiotropium.

Karner C, Cates CJ. Combination inhaled steroid and long-acting beta(2)-agonist in addition to **tiotropium versus tiotropium or combination** alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011 Mar 16;(3):CD008532.

Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease**.** Cochrane Database Syst Rev. 2012 Jul 11;7:CD009285. This review shows that tiotropium treatment was associated with a significant improvement in patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat to benefit (NNTB) of 16 to prevent one exacerbation. Tiotropium also reduced exacerbations leading to hospitalisation but no significant difference was found for hospitalisation of any cause or mortality. Thus, tiotropium appears to be a reasonable choice for the management of patients with stable COPD, as proposed in guidelines. The review however, shows that tiotropium delivered via the Respimat soft mist inhaler was associated with a significantly increased risk of mortality compared with placebo, which calls for caution with this device whilst awaiting the results of an ongoing head-to-head trial comparing tiotropium delivery devices and doses.

Karner C, Chong J, Poole P. **Tiotropium versus placebo** for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014 Jul 21;7:CD009285. This review shows that tiotropium treatment was associated with a significant improvement in patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat to benefit (NNTB) of 16 to prevent one exacerbation. Tiotropium also reduced exacerbations leading to hospitalisation but no significant difference was found for hospitalisation of any cause or mortality. Thus, tiotropium appears to be a reasonable choice for the management of patients with stable COPD, as proposed in guidelines. The trials included in this review showed a difference in the risk of mortality when compared with placebo depending on the type of tiotropium delivery device used. However, these results have not been confirmed in a recent trial when 2.5 mcg or 5 mcg of tiotropium via Respimat was used in a direct comparison to the 18 mcg Handihaler.

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

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Kenyon CC, Melvin PR, Chiang VW, et al. **Rehospitalization for Childhood Asthma**: Timing, Variation, and Opportunities for Intervention. J Pediatr. 2013 Nov 14.

Kenyon CC, Rubin DM, Zorc JJ, et al. Childhood Asthma **Hospital Discharge Medication Fills** and Risk of Subsequent **Readmission**. J Pediatr. 2015 Jan 29.

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Kerstjens HA, Disse B, Schroder-Babo W, et al. **Tiotropium** improves lung function in patients with severe uncontrolled **asthma**: a randomized controlled trial. J Allergy Clin Immunol. 2011 Aug;128(2):308-14.

Kerstjens HA, Engel M, Dahl R, et al. **Tiotropium in Asthma** Poorly Controlled with Standard Combination Therapy. N Engl J Med. 2012 Sep 2.

Kerstjens HA, Casale TB, Bleecker ER, et al. **Tiotropium or salmeterol** as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med. 2015 May;3(5):367-76.

Kew KM, Mavergames C, Walters JAE. **Long-acting beta2-agonists for chronic obstructive pulmonary disease**. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD010177. Moderate-quality evidence from 26 studies showed that inhaled long-acting beta2-agonists are effective over the medium and long term for patients with moderate to severe COPD. Their use is associated with improved quality of life and reduced exacerbations, including those requiring hospitalisation. Overall, findings showed that inhaled LABAs did not significantly reduce mortality or serious adverse events.

Kew KM, Karner C, Mindus SM, et al. **Combination formoterol and budesonide** as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults

and children. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD009019. DOI: 10.1002/14651858.CD009019.pub2. SiT reduces the number of people having asthma exacerbations requiring oral steroids and the number requiring hospitalisation or an ER visit compared with fixed-dose combination inhalers. Evidence for serious adverse events was unclear. The mean daily dose of inhaled corticosteroids (ICS) in SiT, including the total dose administered with reliever use, was always lower than that of the other combination groups. This suggests that the flexibility in steroid administration that is possible with SiT might be more effective than a standard fixed-dose combination by increasing the dose only when needed and keeping it low during stable stages of the disease. Data for hospitalisations alone could not be obtained, and no studies have yet addressed this question in children younger than age 12.

Kew KM, Seniukovich A. **Inhaled steroids and risk of pneumonia** for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD010115. DOI: 10.1002/14651858.CD010115.pub2. Budesonide and fluticasone, delivered alone or in combination with a LABA, are associated with increased risk of serious adverse pneumonia events, but neither significantly affected mortality compared with controls. The safety concerns highlighted in this review should be balanced with recent cohort data and established randomised evidence of efficacy regarding exacerbations and quality of life. Comparison of the two drugs revealed no statistically significant difference in serious pneumonias, mortality or serious adverse events. Fluticasone was associated with higher risk of any pneumonia when compared with budesonide (i.e. less serious cases dealt with in the community), but variation in the definitions used by the respectivemanufacturers is a potential confounding factor in their comparison.

Kew KM, Dias S, Cates CJ. **Long-acting inhaled therapy** (beta-agonists, anticholinergics and steroids) for **COPD**: a network meta-analysis.CochraneDatabase of SystematicReviews 2014, Issue 3.Art.No.:CD010844.DOI: 10.1002/14651858.CD010844.pub2. This network meta-analysis compares four different classes of long-acting inhalers for people with COPD who need more than shortacting bronchodilators. Quality of life and lung function were improved most on combination inhalers (LABA and ICS) and least on ICS alone at 6 and at 12 months. Overall LAMA and LABA inhalers had similar effects, particularly at 12 months. The network has demonstrated the benefit of ICS when added to LABA for these outcomes in participants who largely had an FEV1 that was less than 50% predicted, but the additional expense of combination inhalers and any potential for increased adverse events (which has been established by other reviews) require consideration. Our findings are in keeping with current National Institute for Health and Care Excellence (NICE) guidelines.

Kew KM, Kirtchuk L, Michell CI. **Intravenous magnesium** sulfate for treating adults with acute asthma in the emergency department. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD010909. DOI: 10.1002/14651858.CD010909.pub2

Kew KM, Beggs S, Ahmad S. **Stopping long-acting beta2-agonists (LABA) for children with asthma well controlled on LABA and inhaled corticosteroids**. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD011316. DOI: 10.1002/14651858.CD011316.pub2. There is currently no evidence from randomised trials to inform the discontinuation of LABAs in children once asthma control is achieved with ICS plus LABA. It is disappointing that such an important issue has not been studied, and a randomised double-blind trial recruiting children who are controlled on ICS plus LABA is warranted. The study should be large enough to assess children of different ages, and to measure the important safety and efficacy outcomes suggested in this review over at least six months. The only randomised evidence for stopping LABA has been conducted in adults; it will be summarised in a separate review.

Kew KM, Undela K, Kotortsi I, et al. **Macrolides for chronic asthma**. Cochrane Database Syst Rev. 2015 Sep 15;9:CD002997. Existing evidence does not show macrolides to be better than placebo for the majority of clinical outcomes. However, they may have a benefit on some measures of lung function, and we cannot rule out the possibility of other benefits or harms because the evidence is of very low quality due to heterogeneity among patients and interventions, imprecision and reporting biases.The review highlights the need for researchers to report clinically relevant outcomes accurately and completely using guideline definitions of exacerbations and validated scales. The possible benefit of macrolides in patients with non-eosinophilic asthma based on subgroup analyses in two of the included studies may require further investigation.

Kew KM, Dahri K. Long-acting muscarinic antagonists **(LAMA) added to combination long-acting beta-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS** for adults with asthma. Cochrane Database Syst Rev. 2016 Jan 21;1:CD011721. Tiotropium add-on may have additional benefits over LABA/ICS alone in reducing the need for rescue oral steroids in people with severe asthma. The effect was imprecise, and there was no evidence for other LAMA preparations. Possible benefits on quality of life were negligible, and evidence for the effect on serious adverse events was inconsistent. There are likely to be small added benefits for tiotropium Respimat 5 µg daily on lung function and asthma control over LABA/ICS alone and fewer non-serious adverse events. The benefit of tiotropium add-on on the frequency of hospital admission is still unknown, despite year-long trials.Ongoing and future trials should clearly describe participants' background medications to help clinicians judge how the findings relate to stepwise care. If studies test LAMAs other than tiotropium Respimat for asthma, they should be at least six months long and use accepted and validated outcomes to allow comparisons of the safety and effectiveness between different preparations.

Kew KM, Cates CJ. **Remote versus face-to-face check-ups** for asthma. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD011715. DOI: 10.1002/14651858.CD011715.pub2. Current randomised evidence does not demonstrate any important differences between face-to-face and remote asthma check-ups in terms of exacerbations, asthma control or quality of life. There is insufficient information to rule out differences in efficacy, or to say whether or not remote asthma check-ups are a safe alternative to being seen face-to-face.

Kew KM, Quinn M, Quon BS, et al. **Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma** in adults and children. Cochrane Database Syst Rev. 2016 Jun 7;6:CD007524. Current evidence does not support increasing the dose of ICS as part of a self initiated action plan to treat exacerbations in adults and children with mild to moderate asthma. Increased ICS dose is not associated with a statistically significant reduction in the odds of requiring rescue oral corticosteroids for the exacerbation, or of having adverse events, compared with a stable ICS dose. Wide confidence intervals for several outcomes mean we cannot rule out possible benefits of this approach.

Kew KM, Nashed M, Dulay V, et al. **Cognitive behavioural therapy (CBT) for adults and adolescents with asthma**. Cochrane Database Syst Rev. 2016 Sep 21;9:CD011818. For adults with persistent asthma, CBT may improve quality of life, asthma control, and anxiety levels compared with usual care. Risks of bias, imprecision of effects, and inconsistency between results reduced our confidence in the results to low, and evidence was lacking regarding the effect of CBT on asthma exacerbations, unscheduled contacts, depression, and medication adherence. There was much variation between studies in how CBT was delivered and what constituted usual care, meaning the most optimal method of CBT delivery, format, and target population requires further investigation. There is currently no evidence for the use of CBT in adolescents with asthma.

Khorfan FM, Smith P, Watt S, Barber KR. Effects of **nebulized bronchodilator** therapy on heart rate and arrhythmias in critically ill adult patients. Chest. 2011 Dec;140(6):1466-72. In critically ill adult patients, nebulized albuterol and ipratropium does not cause significant tachycardia or tachyarrhythmias. Substitution of levalbuterol for albuterol (salbutamol) to avoid tachycardia and tachyarrhythmias is unwarranted.

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

Kiljander TO, Junghard O, Beckman O, Lind T. Effect of **Esomeprazole** 40 mg Once or Twice Daily on Asthma: A Randomized, Placebo-controlled Study. Am J Respir Crit Care Med. 2010 Jan 28.

Kim V, Criner GJ. **Chronic bronchitis and chronic obstructive pulmonary disease**. Am J Respir Crit Care Med. 2013 Feb 1;187(3):228-37.

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Kloepfer KM, Olenec JP, Lee WM, et al. Increased **H1N1 Infection Rate** in Children with Asthma. Am J Respir Crit Care Med. 2012 Jun 15;185(12):1275-9.

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

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

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Krieger J, Song L, Philby M. Community Health Worker **Home Visits** for Adults With Uncontrolled Asthma: The **HomeBASE** Trial Randomized Clinical Trial. JAMA Intern Med. 2014 Nov 24.
Krug N, Hohlfeld JM, Kirsten A-M, et al. Allergen-induced asthmatic responses modified by a **GATA3-specific DNAzyme**. N Engl J Med 2015;372:1987-95.
Kruis AL, Smidt N, Assendelft WJ, et al. **Integrated disease management interventions for patients with chronic obstructive pulmonary disease.** Cochrane Database Syst Rev. 2013 Oct 10;10:CD009437. In these COPD participants, IDM not only improved disease-specific QoL and exercise capacity, but also reduced hospital admissions and hospital days per person.
Kruis AL, Smidt N, Assendelft WJ, et al. Cochrane corner: is **integrated disease management** for patients with **COPD** effective?. Thorax. 2014 Jan 14.
Kruis AL, Boland MR, Assendelft WJ, et al. Effectiveness of **integrated disease management for primary care chronic obstructive** pulmonary disease patients: results of cluster randomised trial. BMJ. 2014 Sep 10;349:g5392.
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Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined **corticosteroid and long-acting** beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006829. Combination therapy was more effective than long-acting beta-agonists in reducing COPD exacerbation rates, although the evidence for the effects on hospitalisations was mixed, and requires further exploration. No significant impact on mortality was found even with additional information from the TORCH trial. The superiority of combination inhalers should be viewed against the increased risk of side-effects, particularly pneumonia.

Nannini LJ, Lasserson TJ, Poole P. **Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists** for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Sep 12;9:CD006829. doi: 10.1002/14651858.CD006829.pub2. Concerns over the analysis and availability of data from the studies bring into question the superiority of ICS/LABA over LABA alone in preventing exacerbations. The effects on hospitalisations were inconsistent and require further exploration. There was moderate quality evidence of an increased risk of pneumonia with ICS/LABA. There was moderate quality evidence that treatments had similar effects on mortality. Quality of life, symptoms score, rescue medication use and FEV(1) improved more on ICS/LABA than on LABA, but the average differences were probably not clinically significant for these outcomes. To an individual patient the increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations.

Nannini LJ, Poole P, Milan SJ, et al. **Combined corticosteroid and long-acting beta2-agonist** in one inhaler **versus inhaled corticosteroids** alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013 Aug 30;8:CD006826. doi: 10.1002/14651858.CD006826.pub2. Combination ICS and LABA offer some clinical benefits in COPD compared with ICS alone, especially for reduction in exacerbations. This review does not support the use of ICS alone when LABAs are available. Adverse events were not significantly different between treatments.

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both.Currently, the available data are insufficient and of very low quality in comparisons of the efficacy of aclidinium versus tiotropium. The efficacy of aclidinium versus LABAs cannot be assessed due to inaccurate data. Thus additional trials are recommended to assess the efficacy and safety of aclidinium compared to other LAMAs or LABAs.

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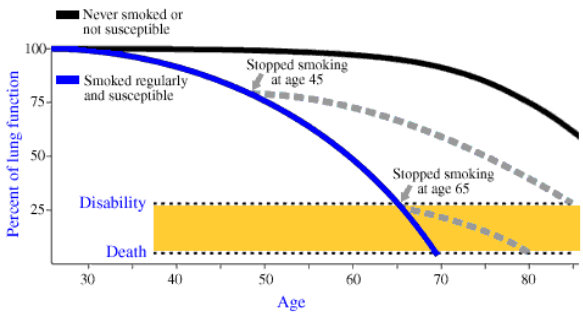

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Asthma UK www.asthma.org.uk; Allergy UK www.allergyuk.org; Lung & Asthma Information Agency www.laia.ac.uk.
Canadian Asthma Consensus Guidelines web site http://www.asthmaguidelines.com
Canadian Network For Asthma Care (CNAC) http://www.cnac.net?english/clinics.html
Global Initiative for Asthma (GINA) http://www.ginasthma.com

Additional benefit of pharmacotherapy[24-26]

Current therapy	Escalate to …	Change in Exacerbations	Change in Hospitalizations	Change in Quality of Life	Additional $
SAMA	LAMA	Risk of having one or more exacerbation: OR 0.71; 95% CI 0.52-0.95	Risk of being hospitalized (for any cause): OR 0.34; 95% CI 0.15-0.70	Average change in SGRQ of -3.30; 95% CI -5.63 to -0.97	$40-50
LAMA	LAMA + LABA	Risk of having an exacerbation leading to hospitalization: OR 1.07 (0.63-1.81)	Risk of being hospitalized (for any cause): OR 1.01; 95% CI 0.63-1.61	Average change in SGRQ of -1.61; 95% CI -2.9 to -0.29	$10-30
LAMA + LABA	LAMA + LABA + ICS	Risk of having one or more exacerbation over 1 year: OR 0.81; 95% CI 0.51 to 1.30	Risk of being hospitalized (for any cause) over 1 year: OR 0.91; 95% CI 0.53 to 1.58	Average change in SGRQ of -1.02; 95% CI -5.10 to 3.06	$30-140

SGRQ: St. George's Respiratory Questionnaire. Measures quality of life. A decrease of at least 4 points (on a scale of 0 to 100) is the minimum clinically important difference to indicate an improvement in quality of life.

Evidence for escalating therapy from a SAMA to a LAMA is of good quality and reaches both statistical and clinical significance. Evidence for dual and triple therapy does not reach clinical or statistical significance, but is based on few, relatively low quality trials.

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Karner C, Chong J, Poole P. **Tiotropium versus placebo** for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014 Jul 21;7:CD009285. This review shows that tiotropium treatment was associated with a significant improvement in patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat to benefit (NNTB) of 16 to prevent one exacerbation. Tiotropium also reduced exacerbations leading to hospitalisation but no significant difference was found for hospitalisation of any cause or mortality. Thus, tiotropium appears to be a reasonable choice for the management of patients with stable COPD, as proposed in guidelines. The trials included in this review showed a difference in the risk of mortality when compared with placebo depending on the type of tiotropium delivery device used. However, these results have not been confirmed in a recent trial when 2.5 mcg or 5 mcg of tiotropium via Respimat was used in a direct comparison to the 18 mcg Handihaler.

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Kew KM, Seniukovich A. **Inhaled steroids and risk of pneumonia** for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD010115. DOI: 10.1002/14651858.CD010115.pub2. Budesonide and fluticasone, delivered alone or in combination with a LABA, are associated with increased risk of serious adverse pneumonia events, but neither significantly affected mortality compared with controls. The safety concerns highlighted in this review should be balanced with recent cohort data and established randomised evidence of efficacy regarding exacerbations and quality of life. Comparison of the two drugs revealed no statistically significant difference in serious pneumonias, mortality or serious adverse events. Fluticasone was associated with higher risk of any pneumonia when compared with budesonide (i.e. less serious cases dealt with in the community), but variation in the definitions used by the respectivemanufacturers is a potential confounding factor in their comparison.

Kew KM, Dias S, Cates CJ. **Long-acting inhaled therapy** (beta-agonists, anticholinergics and steroids) for **COPD**: a network meta-analysis.CochraneDatabase of SystematicReviews 2014, Issue 3.Art.No.:CD010844.DOI: 10.1002/14651858.CD010844.pub2. This network meta-analysis compares four different classes of long-acting inhalers for people with COPD who need more than shortacting bronchodilators. Quality of life and lung function were improved most on combination inhalers (LABA and ICS) and least on ICS alone at 6 and at 12 months. Overall LAMA and LABA inhalers had similar effects, particularly at 12 months. The network has demonstrated the benefit of ICS when added to LABA for these outcomes in participants who largely had an FEV1 that was less than 50% predicted, but the additional expense of combination inhalers and any potential for increased adverse events (which has been established by other reviews) require consideration. Our findings are in keeping with current National Institute for Health and Care Excellence (NICE) guidelines.

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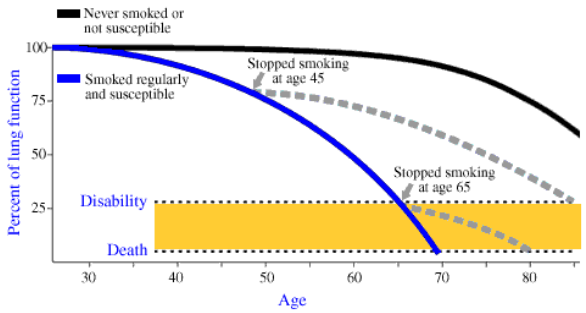

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Online Extras for ASTHMA AND COPD INHALATION DEVICES CHART:

Milk allergies and lactose inhalers Most DPIs contain lactose. This lactose is often derived from milk; trace amounts of residual milk protein has caused allergies in a few case reports. Lactose-free: **BRICANYL** Turbuhaler; **PULMICORT** Turbuhaler; all MDIs; all Respimats. Note: lactose-intolerant patients can still use a lactose-containing inhaler.

▼ covered by NIHB

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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.[8] 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. [30]
12. Other references of interest: [31,32,33,34,35,36,37,38,39,40,41]; Tools to assess dependence. E.g. Fagerstrom Tolerance Scale [42]

CHAMPIX / Varenicline – for Smoking Cessation

Perspective – at 52wks

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

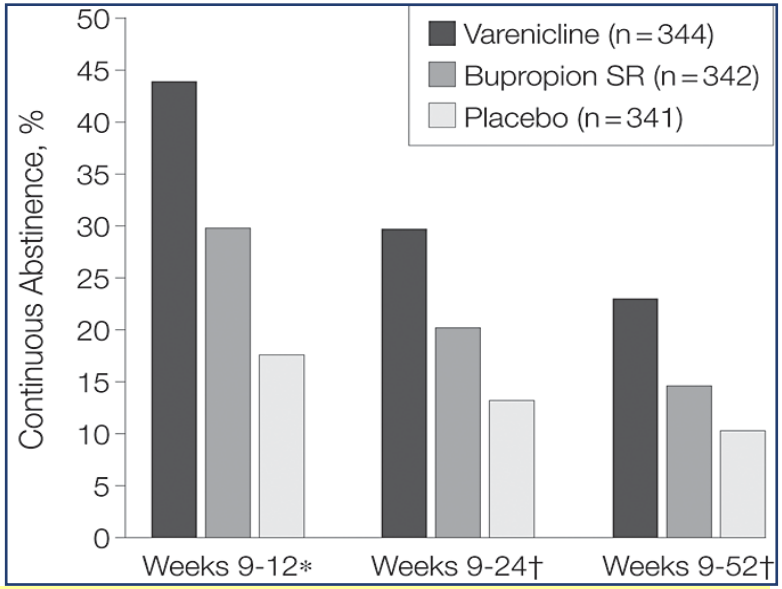
- 2.8x better than Placebo
- NNT= 8 (95% CI: 6, 11)

- 1.6x better than Bupropion (Zyban)
- NNT= 14 (95% CI: 9, 34)

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

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

Jorenby, D. E. et al. JAMA 2006;296:56-63.



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

Advantages: - one extra person successfully quitting at 1 year for every 14 patients treated. based on 2 RCTs

Disadvantages: - more nausea, weight gain, and potentially mood/behavior changes; ?? ↑ CV events (FDA 2011)
- relatively new drug with some potential unknowns (in terms of adverse reactions, drug interactions, etc)
- $200 more per person (not bad for 1/14 who might get extra benefit, but not good for the other 13 people.)

Qualifier: - above based on studies, all funded by the manufacturer with the potential for associated bias

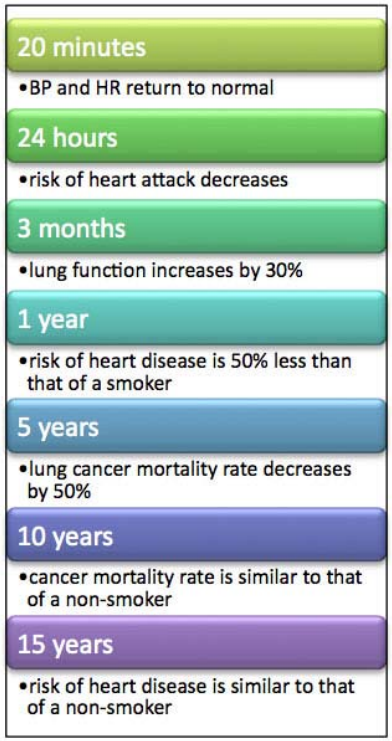
Cochrane 2012 – Nicotine receptor partial agonists: Evidence for some ↑long-term efficacy of varenicline over a) placebo RR=2.27 @6 mo, b) NRT RR= 1.13 non-significant, c) bupropion RR=1.52 @1 yr but ↑serious adverse events RR 1.3. Post marketing concerns being assessed.

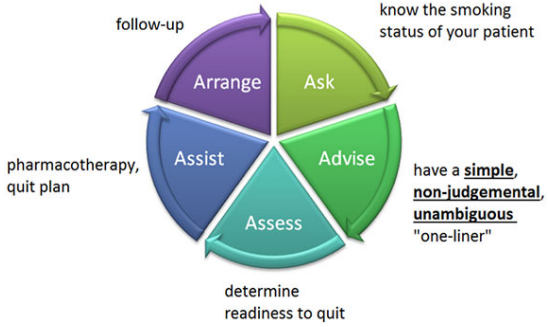
Extras: **Rimonabant ACOMPLIA** –(not in Canada) cannabinoid receptor 1 blocker; 36% complete smoking cessation in final 4 wks of a 10 wk trial Dose: 20mg/d SE: nausea, **depression**, anxiety & ↓ weight. [xliii,xliv,xlv] ??Clonidine use
Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch Gen Psychiatry. 2009 Nov;66(11):1253-62. {Nicotine lozenge, bupropion, and bupropion plus lozenge produced effects that were comparable with those reported in previous research, the nicotine patch plus lozenge produced the greatest benefit relative to placebo for smoking cessation.}

e-Cigaretes: 1) nicotine containing electronic cigarettes (misnomer as aerosolizing delivery device + cartridge). They are illegal in Canada. Current controversies with regulation in the USA. Counsel patients to avoid; alternate products/approaches available for smoking cessation.
2) Concerns: a) risk becoming starter product & skirt smoke free laws, b) potential toxicities, c) lack evidence for benefit as smoking cessation aid & strong potential to ↑ addiction, d) diversion of devices for use in delivering alternate drugs of abuse. e) short term use found to have adverse physiological effects, increased flow resistance and decreased FeNO. f.) toxic and carcinogenic compounds still delivered in e-cigarettes but in lower concentration than traditional cigarettes (Medical Letter Nov 2012.)

Cytisine: Derived from an extract of golden rain acacia seeds; (1.5 mg oral tablets) in 740 adults who smoked ≥ 10 cigarettes/day and were willing to attempt to stop smoking permanently. Patients were randomized to cytisine vs. placebo for 25 days. The dose was 6 tablets for the first 3 days, followed by 5 tablets/day on days 4-12, 4 tablets/day on days 13-16, 3 tablets/day on days 17-20, and finally 2 tablets/day on days 21-25. All patients received minimal counseling during 4 clinical visits and 3 telephone calls over 12 months. Cytisine is currently available in Russia and Poland (at the equivalent of $6 to $15 per course). [West 2011]

Benefits from stopping smoking:





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Modified Fagerström Test for Nicotine Dependence

1. How soon after you wake up do you smoke your first cigarette?
Within 5 minutes (3 points)
5 to 30 minutes (2 points)
31 to 60 minutes (1 point)
After 60 minutes (0 points)

2. Do you find it difficult not to smoke in places where you shouldn't, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?
Yes (1 point)
No (0 points)

3. Which cigarette would you most hate to give up; which cigarette do you treasure the most?
The first one in the morning (1 point)
Any other one (0 points)

4. How many cigarettes do you smoke each day?
10 or fewer (0 points)
11 to 20 (1 point)
21 to 30 (2 points)
31 or more (3 points)

5. Do you smoke more during the first few hours after waking up than during the rest of the day?
Yes (1 point)
No (0 points)

6. Do you still smoke if you are so sick that you are in bed most of the day, or if you have a cold or the flu and have trouble breathing?
Yes (1 point)
No (0 points)

Scoring: 7 to 10 points = highly dependent; 4 to 6 points = moderately dependent; less than 4 points = minimally dependent.

FIGURE 1. Modified Fagerström test for evaluating intensity of physical dependence on nicotine.
Adapted with permission from Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86:1119-27.

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FDA Chantix/**Champix** Warning Feb/2008: 491 **suicide** reports; **39 completed**. **Canada**: **46 psychiatric** adverse reactions reported from April 1-Nov23/07

FDA and Public Health Experts Warn About **Electronic Cigarettes** July,2009 Laboratory analysis of electronic cigarette samples has found that they contain carcinogens and toxic chemicals such as diethylene glycol, an ingredient used in antifreeze. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm

FDA Aug, 2009 — Announced the launch of a new division, the **Center for Tobacco Products**, "in an historic effort to curb the hundreds of thousands of deaths caused by those products each year." The new center will oversee the Family Smoking Prevention and Tobacco Control Act, signed into law by President Barack Obama in June 2009.

FDA May/11 has decided to oversee **electronic cigarettes** the same way it does tobacco products.

FDA June/11 drug safety communication: **Chantix (varenicline) may increase the risk of certain cardiovascular adverse events** in patients with cardiovascular disease.

FDA Quit Smoking package **images** 2011 http://www.fda.gov/downloads/TobaccoProducts/Labeling/UCM259401.pdf

FDA July/11 has approved an updated drug label for the smoking cessation aid Chantix (**varenicline**) to include information about the efficacy and safety of the drug in two patient populations who may benefit greatly from giving up smoking—those with cardiovascular disease and those with chronic obstructive pulmonary disease (COPD).

FDAOct/11 has reviewed the results from two FDA-sponsored epidemiological studies that evaluated the risk of **neuropsychiatric adverse** events associated with the smoking cessation drug **Chantix (varenicline).** Neither study found a difference in risk of neuropsychiatric hospitalizations between Chantix and nicotine replacement therapy (NRT; e.g., NicoDerm patches). However, both studies had a number of study design limitations, including only assessing neuropsychiatric events that resulted in hospitalization, and not having a large enough sample size to detect rare adverse events (see 10/24/2011 Drug Safety Communication below for more information). Healthcare professionals and patients should continue to follow the recommendations in the physician label and the patient Medication Guide, and to monitor for neuropsychiatric symptoms when prescribing or using Chantix. The drug manufacturer is conducting a large safety clinical trial of Chantix to assess neuropsychiatric adverse events, and results from this study are expected in 2017.

FDA Dec/12 is informing the public about the results of a large, combined analysis (called a meta-analysis) of clinical trials that compared patients who received the smoking cessation drug **Chantix (varenicline)** to patients who received a placebo (an inactive treatment). A higher occurrence of major adverse cardiovascular events (a combined outcome of cardiovascular-related death, nonfatal heart attack, and nonfatal stroke) was observed in patients using Chantix compared to placebo. These events were uncommon in both the Chantix and placebo groups, and the increased risk was not statistically significant, which means it is uncertain whether the excess risk for the Chantix group was due to the drug or due to chance.

FDA Apr/13 is allowing makers of **nicotine-replacement products to change their labeling "to allow some flexibility on how they are used and for how long**," the agency announced. Almost 30 years' experience with the products shows that they "do not appear to have significant potential for abuse or dependence," according to the FDA. Nor are there safety concerns about people using the products even while continuing to smoke or using two products simultaneously. In addition, the agency says if smokers believe they need to use a product longer than the recommended 2 to 3 months in order to quit, "it is safe to do so in most cases."

FDA Mar/15 is warning that the prescription smoking cessation medicine **Chantix (varenicline) can change the way people react to alcohol**. Interactions between alcohol and Chantix have resulted in some patients experiencing increased intoxicating effects of alcohol, sometimes associated with aggressive behavior and/or amnesia. In addition, rare accounts of seizures in patients treated with Chantix have been reported. FDA has approved changes to the Chantix label to warn about these risks.

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

Health Canada Mar/09 is advising Canadians not to purchase or use **electronic smoking products**, as these products may pose health risks and have not been fully evaluated for safety, quality and efficacy by Health Canada.
http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_53-eng.php (FDA and Public Health Experts Warn About Electronic Cigarettes http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm)

Health Canada June/10 **CHAMPIX** (varenicline tartrate) - Changes to the Canadian Product Monograph - Pfizer Canada Inc. Changes include: 1- a boxed warning highlighting recommendations about neuropsychiatric adverse events, 2- a warning about rare reports of serious allergic and skin reactions, 3- a guidance for prescribers about information to be shared with their patients prior to and during treatment, and 4- an additional dosing option for CHAMPIX.

Health Canada Jan/12 is informing Canadians that our **review of Champix** is now complete and the label has been updated with new information with respect to cardiovascular safety. Champix (brand name for varenicline tartrate) is a prescription drug used to help patients quit smoking in combination with supportive counselling. Health Canada evaluated data from a quit-smoking clinical trial involving 700 smokers with cardiovascular disease (approximately 350 who received Champix and 350 who received a placebo or "sugar pills"). Cardiovascular disease is a broad term for any condition that affects the heart and/or blood vessels, including heart attack and stroke. Although a slightly increased number of patients experienced serious heart-related events in the group treated with Champix compared to the group treated with placebo, the study was not adequately designed to be able to test the cardiovascular safety of Champix. The small study size combined with other study design weaknesses make it impossible to draw conclusions based on these data. The possibility of an increased risk of heart attack or stroke in patients with cardiovascular disease can neither be confirmed nor ruled out at this time.

Health Canada May/13 CHAMPIX (**varenicline** tartrate) and ZYBAN (**buproprion** hydrochloride) - Revision to the Consumer Information of Non-Nicotine Smoking Cessation Aids - Pfizer Canada Inc. and Valeant Canada LP. The revised product monographs indicate that thorough consideration should be given to the option of **nicotine replacement therapy**, prior to a decision to prescribe a non-nicotine treatment.

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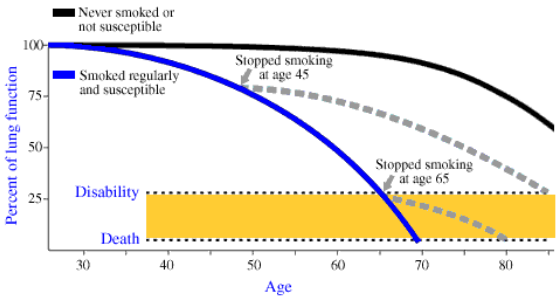

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Cannabinoids: Online Extras 💻

Links for Prescribing of Medical Marijuana

1. Medical documentation (complete minimum of once per year, but may authorize for shorter durations): www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/med-eng.pdf
2. List of Licensed Producers: www.hc-sc.gc.ca/dhp-mps/marihuana/info/list-eng.php
3. Application to grow marijuana at home: healthycanadians.gc.ca/drugs-products-medicaments-produits/buying-using-achat-utilisation/cannabis-medical/access-acces/personal-production-personnelle/index-eng.php
4. See College Bylaws below for Saskatchewan - must complete marijuana treatment agreement form (sample below). For other provinces, refer to here for guidance https://www.cmpa-acpm.ca/-/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors

College of Physicians & Surgeons of Saskatchewan: The College's bylaw 2014-

The College's bylaw which regulates physician authorization of medical marihuana is now in effect. A summary of the bylaw follows:

1. The bylaw begins with a statement that there has not been sufficient scientific or clinical assessment to provide evidence about the safety and efficacy of marihuana for medical purposes. The bylaw begins with an acknowledgement that federal government regulations have authorized the use of marihuana for medical purposes.

2. A physician cannot authorize the use of marihuana for a patient unless the physician is also the treating physician
for the condition for which the patient is authorized to use marihuana. For example, if a patient is to be authorized to use medical marihuana to deal with symptoms of MS, the physician must also be the treating physician for the patient's MS.

3. A physician must review the patient's medical history, review relevant records pertaining to the condition for which the use of marihuana is authorized and conduct an appropriate physical examination before authorizing the patient's use of marihuana.

4. The patient must sign a written treatment agreement which contains the following:

A) A statement from the patient that the patient will not seek a prescription for marihuana from any other physician during the period for which the marihuana is prescribed;
B) A statement by the patient that the patient will utilize the marihuana as prescribed, and will not use the marihuana in larger amounts or more frequently than is prescribed;
C) A statement by the patient that the patient will not give or sell the prescribed marihuana to anyone else, including family members;
D) A statement by the patient that the patient will store the marihuana in a safe place;

5. The physician's record for the patient must include the requirements for all medical records and, in addition, contain the following:

A) The treatment agreement signed by the patient;
B) The diagnosis for which the patient was authorized to purchase marihuana;
C) A statement of what other treatments have been attempted for the condition for which the use of marihuana was prescribed and the effect of such treatments;
D) A statement of what, if anything, the patient has been advised about the risks of the use of marihuana;
E) A statement that in the physician's medical opinion the patient is likely to receive therapeutic or palliative benefit from the use of marihuana to treat the patient's condition.

6. The physician must retain a single record, separate from other patient records, which can be inspected by the College, and which contains:

A) The patient's name, health services number and date of birth;
B) The quantity and duration for which marihuana was prescribed;
C) The medical condition for which marihuana was prescribed;
D) The name of the licensed producer from which the marihuana will be obtained, if known to the physician.

7. Physicians who prescribe marihuana will be required to provide the College with the information referenced in paragraph 6:

A) Every twelve months if the physician has prescribed marihuana to fewer than 20 patients in the preceding 12 months;
B) Every six months if the physician has prescribed marihuana to 20 or more patients in the preceding 12 months.

8. The bylaw prohibits physicians from diagnosing or treating patients at the premises of a licensed producer;

9. The bylaw prohibits physicians who prescribe marihuana from having an economic or management interest in a licensed producer;

10. The bylaw prohibits physicians from storing or dispensing marihuana from any location where the physician practices medicine.

The bylaw is numbered Bylaw 19.2 of the regulatory bylaws of the College and is available at the College's website.

Sample treatment agreement to comply with the College Bylaw

I _____ understand that I will be receiving a medical document from Dr. _____ which will authorize me to purchase marihuana for a medical purpose. I agree to the following:

A) I will not seek to obtain a medical document to authorize me to purchase marihuana from any other physician during the period for which the marihuana is authorized;
B) I will utilize the marihuana as authorized in the medical document and I will not use the marihuana in larger amounts or more frequently than is authorized in the document;
C) I will not give or sell the prescribed marihuana to anyone else, including family members;
D) I will store the marihuana in a safe place;
E) I understand that if I break any of these conditions, Dr. _____ may refuse to provide any future medical authorization to purchase marihuana.

_____ _____
Patient's signature Date

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

Link to – Health Canada - Medical Marihuana: How to Apply: http://www.hc-sc.gc.ca/dhp-mps/marihuana/how-comment/applicant-demandeur/index-eng.php
Link to CFPC: http://www.cfpc.ca/Dried_Cannabis_Prelim_Guidance/

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    Marijuana Stakeholder statistics from Health Canada: http://www.hc-sc.gc.ca/dhp-mps/marihuana/stat/index-eng.php
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clinical trials showing that using **ESAs to target a hemoglobin level of greater than 11 g/dL in patients with CKD provides no additional benefit** than lower target levels, and increases the risk of experiencing serious adverse cardiovascular events, such as heart attack or stroke. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm260641.htm
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Addional information about Mircera (Web-only)

Methoxy polyethylene glycol-epoetin beta **MIRCERA** [13] Single-dose **vials** (solution): 50, 100, 200, 300, 400, 600, 1000 µg/mL Single-dose **pre-filled syringes:** 50µg/0.3mL, 75µg/0.3mL, 100µg/0.3mL, 150µg/0.3mL, 200µg/0.3mL, 250µg/0.3mL, 400µg/0.6mL, 600µg/0.6mL	✓ **Tx of anemia with CKD** Pre-filled syringes: sterile & do not contain preservatives. Store in fridge at 2-8°. (Do not freeze) Keep in original package to protect from light. Stable at room temperature ≤ 25° C for up to 1 month Allow to reach room temp. before inj.		SC in ND-CKD & PD-CKD; **IV** or SC in HD-CKD Not currently on ESA tx: 0.6 mcg/kg every 2 weeks as a single IV or SQ inj Pts on ESA: can convert to MIRCERA given once a month as a single IV or SQ inj. Monthly Mircera starting IV or SQ dose mcg/monthly: 120 if <40 Aranesp or <8,000 Eprex; 200 if <40-80 Aranesp or 8-16,000 Eprex; 360 if >80 Aranesp or >16,000 Eprex (Aranesp in mcg/week, Eprex in IU/week) Equivalent with IV or SQ. If Hgb target is reached, may give once monthly using a dose equal to twice the previous every two week dose.	✗ ⊗ Not on formulary. Not yet avail. in Canada, but NOC received Mar 2008

Erythropoiesis Stimulating Agents (ESA) in Anemia of Chronic Kidney Disease (CKD): Therapeutic Alternatives

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FDA June/11 notified healthcare professionals that new, modified recommendations for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) have been approved to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The new dosing recommendations are based on clinical trials showing that **ESAs to target a hemoglobin level of greater than 11 g/dL in patients with CKD provides no additional benefit** than lower target levels, and increases the risk of experiencing serious adverse cardiovascular events, such as heart attack or stroke. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm260641.htm

FDA: Feb/13 All lots of **peginesatide (Omontys)** — an anemia drug approved less than a year ago for adults on dialysis — are being recalled due to reports of serious and sometimes **fatal adverse hypersensitivity reactions**, including anaphylaxis. Approximately 0.02% of patients had a fatal reaction within 30 minutes of receiving a peginesatide injection, according to postmarketing data. About 0.2% of patients overall had reactions; about a third of these were serious (i.e., requiring immediate medical attention). Some 25,000 patients have received the drug since it was launched, the FDA says.

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Extras for Iron Management:

New FDA: Ferric carboxymaltose Injectafer for IDA if poor response to oral/ND-CKD, 750mg/15ml IV x 2 doses 1 week apart;. SE: nausea, dizzy, hypertension hypophosphatemia, anaphylaxis.
Ferric pyrophosphate citrate Triferic IV solution for iron replacement with CKD & on dialysis.

Oct/11 The FDA has granted accelerated approval for **deferiprone (Ferriprox)** to treat transfusion-related iron overload in patients with thalassemia who do not respond to prior chelation therapy. The drug, an oral iron chelator, is the first new treatment approved for this disorder since 2005, according to the agency. Agranulocytosis was noted in about 2% of patients in clinical studies. Other adverse effects included nausea, arthralgia, vomiting, neutropenia, and increased alanine aminotransferase levels.

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FERAHEME should now only be given by infusion of the diluted product into a vein over a minimum period of 15 minutes. FERAHEME should no longer be used in patients with any known history of drug allergy.
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Red Flags for calciphylaxis?

Natural Products Database Search on phosphate-containing products:

Enemol Sodium Phosphate Enema (Dominion Pharmacal): Each 60 ml serving contains: Sodium Phosphate dibasic, heptahydrate 6 g. • Sodium Phosphate monobasic, anhydrous 16 g. Other Ingredients: Benzalkonium Chloride, Edetate Disodium, Purified Water. NPN 02096900.

Enema (HJ Sutton): Each 30 mL serving contains: Dibasic Sodium Phosphate 7 g (118 mL) • Monobasic Sodium Phosphate 19 g (118 mL). Other Ingredients: Benzalkonium Chloride, Disodium EDTA, Purified Water. NPN 02231170.

Kali Phosphoricum 6x (Thompson's Homeopathic Supplies Ltd): For 'stress and tension'. Potassium Phosphate 6X. Other Ingredients: Ground Corn Starch, Lactose. DIN-HM 00190101
Magnesia Phosphorica 6x tabs (Thompson's Homeopathic Supplies Ltd): Oral Laxative. Magnesium Phosphate 6X. Other Ingredients: Ground Corn Starch, Lactose. DIN-HM 00189995.

Natrum Phosphoricum 6x tabs (Thompson's Homeopathic Supplies Ltd.): Oral laxative. Each tablet contains: Sodium Phosphate 6X. Other Ingredients: Corn Starch, Lactose. DIN-HM 00190160

Naturally Sourced Calcium from Milk with Vit D and Magnesium (Immunotec Inc): Oral Laxative. Two tablets contain: Calcium Phosphate 250 mg • Magnesium 15 mg • Vitamin D (D3) 100 IU. Other Ingredients: Acacia Gum, Carnauba Wax, Croscarmellose Sodium, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Purified Water. NPN 02243453
New Era Biochemic Tissue Salt 10, 2, 6, 8 (Seven Seas Limited): Each tablet contains: Sodium Phosphate 6x 0.07 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 0016935.

New Era Combination F Biochemic Tissue Salts (Seven Seas Limited): Each tablet contains: Magnesium Phosphate 6x 0.0175 mcg • Potassium Phosphate 6x 0.0175 mcg • Silicon Dioxide 6x 0.0175 mcg • Sodium Chloride 6x 0.0175 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 00147028

New Era Combination G Biochemic Tissue Salts (Seven Seas Limited): Each tablet contains: Calcium Fluoride 6x 0.0175 mcg • Calcium Phosphate 6x 0.0175 mcg • Potassium Phosphate 6x 0.0175 mcg • Sodium Chloride 6x 0.0175 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 00147036

New Era Combination N Biochemic Tissue Salts (Seven Seas Limited): Oral Laxative. Each tablet contains: Calcium Phosphate 6x 0.0175 mcg • Magnesium Phosphate 6x 0.0175 mcg • Potassium Chloride 6x 0.0175 mcg • Potassium Phosphate 6x 0.0175 mcg. Other Ingredients: Acacia Gum, Lactose Monohydrate. DIN-HM 00534862
Oral Laxative (HJ Sutton Industries): Each 1 tsp serving contains: Dibasic Sodium Phosphate 0.9 g. Other Ingredients: Glycerin, Sodium Saccharin, Sodium Benzoate, Purified Water. NPN 80003212

Phoslax: Oral Laxative (Odan Laboratories Ltd): Each one tsp serving contains: Dibasic Sodium Phosphate 0.9 g. • Monobasic Sodium Phosphate 2.4 g. Other Ingredients: Glycerin, Natural Ginger Flavour, Natural Lemon Flavour, Sodium Benzoate, Purified Water. NPN 80000689

Schuessler Tissue Salts General Debility Comb B (Martin & Pleasance): Oral Laxative. Each tablet contains: Calcium Phosphate 6.0 X • Ferrum Phosphoricum 6.0 X • Kali Phosphoricum 6.0 X. Other Ingredients: Anhydrous Calcium Hydrogen Phosphate, Lactose, Magnesium Stearate. DIN-HM 80003543

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💻 Drug Interactions: Online Extras

Drug Interaction Descriptions

Pharmacodynamic Interactions	
Additive/Synergistic	• Occurs when drugs exhibit the same pharmacologic effect and/or the same adverse effect (e.g. ibuprofen + citalopram → increased bleed risk)
Antagonistic	• Occurs when drugs exhibit opposing pharmacologic actions (e.g. oxybutynin + donepezil → competing anticholinergic/cholinergic effects)
Pharmacokinetic Interaction – Absorption	
Changes in GI pH	• Decreasing pH can decrease absorption of some drugs (e.g. PPI therapy decreases calcium absorption)
Adsorption/Chelation/Complexing	• Certain drugs bind together, reducing absorption (e.g. cholestyramine binds to valproic acid → decreased absorption of valproic acid)
Changes in GI Motility	• Changing the rate that the stomach empties can change the rate and/or extent of absorption (e.g. metoclopramide + atovaquone→ metoclopramide speeds up gastric emptying → decreased absorption of atovaquone)
Pharmacokinetic Interaction – Distribution	
Protein Binding	• Drug displacement from serum proteins causes transient increases in unbound drug concentration. Rarely of clinical significance. Primarily of clinical concern for drugs with both a narrow therapeutic range AND high protein binding (e.g. valproic acid started in patient already on phenytoin → displacement of phenytoin from serum proteins). If displacement is suspected, monitor <u>unbound</u> concentration to make dose changes.
P-glycoprotein	• P-gp efflux pump – drug transporter protein which pumps drug **out of** cells so it is not absorbed or distributed (e.g. clarithromycin + digoxin → clarithromycin inhibits P-gp → increased absorption & level of digoxin)
Organic Anion Transporting Polypeptides	• OATP influx pump – drug transporter protein which pumps drug **into** cells, often to be excreted (e.g. cyclosporine + rosuvastatin→ cyclosporine inhibits OATP →decreased excretion & ↑level of rosuvastatin).
Pharmacokinetic Interaction – Metabolism	
Enzyme Induction	• Increasing enzyme expression will increase metabolism of a drug. Typically this means ↓ therapeutic effects (e.g. carbamazepine is an enzyme inducer which increases metabolism of tacrolimus→ decreased level of tacrolimus). Note: with prodrugs (metabolite is active drug) there will be ↑ therapeutic effects from enzyme induction. • May take 1 week or more before reaching maximum effect of drug interaction.
Enzyme Inhibition	• Decreasing enzyme activity will decrease metabolism of a drug. Typically this means ↑ therapeutic effects (e.g. ritonavir is an enzyme inhibitor which decreases metabolism of lovastatin → increased level of lovastatin). • Enzyme inhibition is typically faster than induction (i.e. max effect within 24 hours). • Drugs that are metabolized by several enzymes are less likely to be affected by inhibition as metabolism can be diverted to other pathways.
Enterohepatic Recycling	• Some medications are "recycled" by intestinal bacteria and re-absorbed. Interrupting this cycle can cause ↓ therapeutic effects (e.g. mycophenolate + metronidazole → metronidazole destroys bacteria needed to recycle mycophenolate → decreased mycophenolate levels and ↑ risk of organ rejection).
Pharmacokinetic Interaction – Excretion	
Renal & Biliary Mechanisms	• An uncommon mechanism. A change in urine pH may affect tubular reabsorption (though this is typically not clinically significant). A change in renal tubular secretion may be caused through an OATP or P-gp interaction as above. A change in renal blood flow may reduce excretion (e.g. ibuprofen + lithium → ibuprofen reduces renal blood flow → increased lithium levels).

More Management of Common/Important DIs

Medications Involved			Mechanism / Management / Comments
Vasodilators nitrates, PDE5Is (sildenafil, etc.), alpha-blockers			PDE5 inhibitors enhance the vasodilating effects of nitrates, causing severe hypotension (case reports of death). Nitrates should only be given 24hrs after sildenafil or vardenafil, & 48hrs after tadalafil. If using alpha-blockers with PDE5Is, use low doses of each drug and separate by >6hrs. Tamsulosin and extended release alfuzosin seem safe with PDE5Is.
fluroquinolones	+	corticosteroids	Both classes increase risk of tendon rupture (through different mechanisms). Counsel patients to avoid excessive tendon stress.
triptans	+	ergot derivatives	Combination contraindicated due to risk of additive vasoconstriction / coronary vasospasm. Space triptans and ergot derivatives at least 24hrs apart.
clonidine	+	TCAs	The mechanism is unclear, but combining TCAs with clonidine has led to large increases in blood pressure. If no alternatives, monitor BP and titrate doses slowly.
cefuroxime; itraconazole; ketoconazole; ledipasvir; mycophenolate; others	+	PPIs; H2RAs; antacids	These medications require stomach acid for proper absorption; reducing acid can ↓efficacy. Enteric-coated mycophenolate does not have this issue. Where possible, management is often to use antacids/H2RAs prn & taken >2hrs after the interacting med, until tx complete.
clarithromycin	+	atorva-, lova-, simva-statin	Hold high-doses of atorva-, lova-, or simvastatin for a few days while on clarithromycin (3A4 Θ) to prevent rhabdomyolysis. Other statins: no interaction.
cholestyramine	+	numerous meds	Cholestyramine resin can bind to (↓ absorption of) many medications in the gut, including amiodarone, digoxin, fat-soluble vitamins (ADEK), leflunomide, mycophenolate, & phenobarb. Spacing administration times can sometimes prevent an interaction (2 hours before or six hours after the binding resin).
gemfibrozil	+	statins	Gemfibrozil is a CYP inhibitor which can increase levels of potentially all statins. Case reports of rhabdomyolysis have been documented. In general, use a different fibrate (e.g. fenofibrate) if combination statin and fibrate therapy is necessary. See RxFiles Q & A on Statin Intolerance.
risperidone in older adults	+	furosemide	Furosemide can ↑ risperidone AE. This combo has been associated with ↑ mortality in dementia patients. Ensure adequate hydration; avoid combo if possible.
valproic acid	+	carbapenems	Carbapenems ↓ valproate levels, likely through ↑ metabolism. Use a different antibiotic when possible; ↑ valproate dose if necessary until carbapenem tx done.
alpha-blockers (e.g. doxazocin)	+	loop diuretics (e.g. furosemide)	This combination in elderly women can increase incontinence. Avoid where possible.

Warfarin Interactions - Mnemonic

The 8A's – Warfarin Interactions + Bleed Risk[14]:

↑ INR (increased bleed risk)	**A**cetaminophen **A**lternative remedies e.g. gingko, dong quai, fenugreek, chamomile **A**miodarone **A**ntibiotics esp. cotrimoxazole, metronidazole, macrolides, fluoroquinolones **A**ntidepressants e.g. SSRIs **A**ntifungals e.g. fluconazole
↓ INR (decreased efficacy)	**A**lternative remedies e.g. St. John's Wort, ↑vit K intake, tobacco **A**nti-epileptics e.g. phenobarbital, CBZ, phenytoin **A**ntithyroid medications e.g. PTU

→ Increased bleed risk without changing INR:
Antiplatelets e.g. ASA, clopidogrel, prasugrel
Anti-inflammatory agents e.g. NSAIDs, COXIBs

Warfarin interacts with many medications; this is not a full list!
Management: Check INR in 4-6 days if combination is used. Monitor for signs of bleeding.

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Academic Detailing:

Canada

- **BC CDUP: http://www.cdup.org/**
- **Dalhousie: http://cme.medicine.dal.ca/ADS.htm**

Non-Canadian

- **Academic Detailing – National Resource Centre for Academic Detailing (USA): http://www.narcad.org/**
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Management Of Substance Abuse In Emergency

{To contact poison centre in your Canadian province: http://capcc.ca/provcentres/centres.html }

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

Assessment & Management issues:

- **Infections**: soft tissue; other (endocarditis, HIV, hepatitis, etc.)
- **Overdose vs Intoxication vs Withdrawal vs Other**
  {Other e.g. subdural hematoma from fight, stroke, infectious component}
- **Consider detailed assessment if:**
  - Acknowledgment of drug use
  - Physical signs e.g. track marks, nasal septrum atrophy
  - Urine drug screen +ve {Note: emergency drug screen is unlikely to significantly affect impact upon management in the ER.}[50]
- **Approach for engagement**
  - Accept patient autonomy
  - Non-judgemental approach
  - Collaborative approach with patient
  - Confidentiality
  - Proactive discussion on meds and behaviours
- **Managing Potentially Violent Patient**[51]**:**
  - Have a staff & public safety plan!
  - Maintain autonomy & dignity of users, intervene early, approach patients with caution, don't startle, avoid provocation, be aware of your own demeanour, use calm language, don't make promises, provide options and choice, remove dangerous objects from your person, know exits, don't turn back on patient, role for distraction, be firm & compassionate, depersonalize issue; avoid confronting, but if necessary maintain distance, avoid corners/cornering, explain intension, ask for facts & encourage reasoning, ask for weapons to be put down not handed over, know how to call for help.

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

Intoxication: Common Presentations – Possible Causes [52,53]

- **Unresponsive**: hypoglycemics, narcotics, alcohol, cyanide, carbon monoxide, tranquilizers, hydrocarbons, barbiturates
- **Seizures**: hypoglycemics, amphetamines, cocaine, hallucinogens, anticonvulsants, TCAs, PCP, mescaline; benzodiazepine withdrawal especially high dose ; alcohol withdrawal tremors/seizures
- **Hyperthermia**: salicylates, Ecstasy, atropine, amphotericin B, phenytoin
- **Hypothermia**: ethanol, narcotics, sedatives/hypnotics, TCAs, barbiturates, carbon monoxide.
- **If mixed presentation consider possibility of mixed ingestion!**

For table outlining Toxic Syndromes or "toxidromes", see Goldfrank's Toxicologic Emergencies

Intoxication Management - [Primary assessment **ABCs**: airway, breathing, circulation]

Opioids BP: ↓ HR: ↓ RR: ↓ Temp: ↓ Pupil$_{size}$: ↓ Diaphoreis - & depressed, hyporeflexia	Intoxication {coma, lethargy, stupor; constipation, N&V; flushing, pruritis; hypotension; miosis; resp depression} ◆ supportive tx; regular assessment of cardio/respiratory safety ◆airway protection; ◆correction of hypoxia ⇨ naloxone option: short term duration; balance reversal of resp depression with opioid withdrawal (naloxone can be considered if opioid toxicity suspected). ◆consider type of opioid for duration of risk & naloxone effect ◆consider N-acetyl-para-aminophenol level if overdose cause unknown (r/o acetaminophen as possible agent). CAUTION: depending on timing, a "non-toxic" level can become toxic; consult poison centre
Stimulant BP: ↑ HR: ↑ RR: ↑ Temp: ↑ Pupil$_{size}$: ↑ Diaphoreis ↑ agitated/confused, tremor/seizure	Supportive tx {agitation, diaphoresis, hypertension, hyperthermia, mydriasis, psychosis, seizures, ↑HR} - oral diazepam for agitation & hypertension e.g cocaine inuced - IV diazepam or midazolam short acting if severe agitation/anxiety - Optional: sedating antipsychotic - Monitor: hyperthermia, hypothermia, cardiac, electrolytes - HTN: benzodiazepines; alternatively nitroprusside, NTG - α-blockers. {generally avoid β-blockers as will result in unopposed α constriction}
Alcohol	Supportive tx {immediate life-threatening complications in kids are respiratory depression & hypoglycaemia} ◆airway; ◆IV access (fluid management); correct hypoglycaemia with dextrose soln & electrolytes; ◆thiamine

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

When to Discharge? ◆ Consider time from last ingestion. ◆ Can they walk unaided?

Extras (RxFiles - Substance Abuse)

- if using cocaine/other stimulants then detox is the only option. Rapid detox is not recommended during pregnancy.
- Patients should only be "nodding" (falling asleep on methadone) if the dose is too high, they are a new start, or if they using BZD's at the same time – may consider a tox screen to assess if patient is also using any other drugs
- In Saskatoon methadone doses goes up by 10mg increments and down by 5mg increments for dose adjustments with some physicians.
- Using both oral LA morphine (Kadian) in addition to methadone when starting patients is sometime done to prevent acute withdrawal & allow for methadone titration (e.g. a few weeks of dual treatment); controversial.
- IV drug abusers: considerations see reference [54]
- Other substances of abuse: volatile inhalants, Listerine mouthwash
- Be weary of illegitimate on-line pharmacies which supply controlled substances without a prescription.[55]

Acute Alcohol Intoxication[56,57]

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

Management of Cocaine Body Packers[58]:

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

Lifespan Spectrum of Complications: *Pregnancy* - obstetrical complications, fetal distress, stillbirth, low birth weight; *adolescent & young adult* – self inflicted injuries, homicides, premature morbidity; *Later life* - ↑ decline. {Associate health problems: non-fatal overdose, ↑ infections IV and NIDU (HCV; Hepatitis A, B); liver fibrosis cannabis, periodontis cannabis; psychiatric (psychosis, anxiety, depression) various, cannabis; long-term ↓ cognitive performance.}[59]

Substance Abuse in Older Adults[60]: 2005 USA data on treatment programs: Alcohol only (48%), alcohol + 2nd illicit substance (52%); 2nd substance cocaine 40%, marijuana 29%, opiates 16%, stimulants 5%, other 10%.

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

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

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Quotes

- "it takes more than 2½ minutes to assess a patient for a possible opioid prescription" ; a challenge, especially for busy walk-in and minor emergency types of practice
- "it takes only 30 minutes to argue, but only 30 seconds to write a Rx"; reflecting the realities and frustrations of everyday practice.
- "Its OK to say 'No'"
- "I didn't realize how big a problem Rx opioids were on the street"

UK Study Ranking - most harmful drugs: overall, to individual and to society.

- Nutt DJ, King LA, Phillips LD; on behalf of the Independent Scientific Committee on Drugs. Lancet. 2010 Oct 29. Drug harms in the UK: a multicriteria decision analysis.
- BACKGROUND: Proper assessment of the harms caused by the misuse of drugs can inform policy makers in health, policing, and social care. We aimed to apply multicriteria decision analysis (MCDA) modelling to a range of drug harms in the UK. METHODS: Members of the Independent Scientific Committee on Drugs, including two invited specialists, met in a 1-day interactive workshop to score 20 drugs on 16 criteria: nine related to the harms that a drug produces in the individual and seven to the harms to others. Drugs were scored out of 100 points, and the criteria were weighted to indicate their relative importance. FINDINGS: MCDA modelling showed that heroin, crack cocaine, and metamfetamine were the most harmful drugs to individuals (part scores 34, 37, and 32, respectively), whereas alcohol, heroin, and crack cocaine were the most harmful to others (46, 21, and 17, respectively). Overall, alcohol was the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places. INTERPRETATION: These findings lend support to previous work assessing drug harms, and show how the improved scoring and weighting approach of MCDA increases the differentiation between the most and least harmful drugs. However, the findings correlate poorly with present UK drug classification, which is not based simply on considerations of harm. FUNDING: Centre for Crime and Justice Studies (UK).

Salvia leaves (magic mint, diviner's sage, sally D, purple sticky)

- Member of mint family, smoked or chewed. Contains salvinorin A, a selective kappa opioid receptor antagonist; does not bind to $5HT_{2A}$ receptors like other hallucinogens. Halucinogen effects rapid & last <30min. SE: dysphoria, diuresis, chills, headache, insomnia, exhaustion, loss of control, impaired coordination & judgement (= DANGEROUS!). Sensationalized in SK by Saskatoon media DJ who smoked herb on live broadcast in Dec 2010.

Angel's Trumpet: (Angel's tears, Apple of Peru, Green Dragon, Devil's trumpet)

- Alkaloid (atropine, scopolamine) containing flowers & stem. Each flower contains 0.2mg atropine & 0.65mg scopolamine; 3-6 flowers causes hallucinations; 9+ flowers can be life-threatening. Commonly ingested by making a tea. Effects in 1-4hrs; duration 24+hrs. SE: mydriasis, dry mouth, tachycardia, fever, erythema, constipation, ↑↑ thirst, retrograde amnesia & anxiety; arrhythmias & CV collapse / respiratory failure in high doses. (= DANGEROUS!)

"Bath Salts" PABS for abuse: are actually designer stimulants (e.g. methylenedioxpyrovalerone-MDPV, NRG-1; mephedrone-M-Cat, Meow, 4-MMC, Bubbles; methylone-methylenedioxymethcathinone, bk-MDMA,M1, Explosion) being sold in shops & online. *Cloud 9, Ivory Wave, Vanilla Sky, Purple Wave, Blizzard, Blue Silk*, etc.
Common in UK, now USA via New Orleans, India, China.
Similar effects (↑HR, paranoia, psychosis) & tx as stimulants. May/11 CDC: MMWR- Emergency Department Visits After Use of a Drug Sold as "Bath Salts" --- Michigan, November 13, 2010--March 31, 2011 http://www.cdc.gov/mmwr/pdf/wk/mm60e0518.pdf
Two common ingredients: MDPV (a dopamine & norepinephrine (NE) reuptake inhibitor ➔ stimulant); mephedporone: MAOI effects that ↑ 5HT, NE, & DA at neuronal synapses (AEs: agitation, aggression, anxiety, bruxism, chest pain, confusion, diaphoresis, headache, hyperreflexia, ↑BP, N&V, palpitations, periopheral vasoconstriction, pareshtesia, psychosis, seizure, ↑HR.)
Sep/11: DEA invoked its emergency authority necessary to protect the public & will make Schedule 1 substances in 30 days from now.
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National Institute on Drug Abuse (NIDA) http://www.drugabuse.gov/publications/drugfacts/synthetic-cathinones-bath-salts

Spice – ("legal highs"): a range of synthetic drugs; combustable vegetable material sprayed with a variety of chemicals, each slightly different; often mixed with tobacco & smoked; effect (heightened awareness acoustics; imagination; potential for panic & violence; blackouts).

- The most extreme of effects often subside in 15min. Signs: acrid breath smell; higher voice pitch. Withdrawal: cramping, sweating, twitching. Other cautions: Low moods & self harm common. "Not for human comsuption!"

Miscellaneous Other Drug Considerations / Cautions

- Salbutamol: sometimes used to enhance effect of crack cocaine
- Benzodiazepines: calming effect
- Bupropion: sometimes messed with & snorted for high
- Quetiapine: may enhance heroin effects & risk

Harm reduction recommendations for substance abusers at risk of HIV, HCV & other harms (CATIE). Link: http://www.catie.ca/en/programming/best-practices-harm-reduction

Oxymorphone OPANA ER Abuse

- Thrombotic thrombocytopenic purpura (TTP) strongly associated with injection drug abuse of OPANA ER.

Buprenorphine/naloxone (ZUBSOLVE), 1.4mg/0.36mg – new SL tab formulation (available in USA); ↑bioavailability & may taste better than Suboxone. (Achieves plasma concentrations = 2/0.5mg and 8/2mg strengths of other Brand tabs.)

Synthetic Cannabinoids – common in herbal incense products

- Full agonists of CB1 & therefore ↑potential for overdose & toxicity
- ↑ association with seeking medical attention. AEs: agitation, altered time perception, anxiety, dysphoria, ↑BP, listlessness, hallucinations/psychosis, nausea, paranoia, seizures, tachycardia.
- Marijuana extraction/concentration ⇨ production of very highly concentrated levels (80-90%) called "Shatter"; easily over consumed resulting in overdose / emergency visits

Videos – informational related to teen drug recreational drug use (for teens, by teens) - Canada

- **Unwasted - 4 videos by teens regarding gambling, alcohol, marijuana, opioids/oxycontin: http://unwasted.ca/; or http://unwasted.ca/the-pressures (★★★★★)**
- **Mixing prescription drugs and alcohol. http://itdoesntmix.ca/**
- **Your when moment (videos from Nova Scotians): http://changingtheculture.ns.ca/**

Videos – other

- **Addressing the risk of diversion of Rx drugs; secure storage of medications. Powerful.** http://www.youtube.com/watch?v=-sunbJDZe1whttp://www.youtube.com/watch?v=-sunbJDZe1w

Guidelines of interest:
Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline CAMH: http://www.cpso.on.ca/uploadedFiles/policies/guidelines/office/buprenorphine_naloxone_gdlns2011.pdf

Other Links of Interest:
http://addictionlibrary.org/

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Health Canada Mar/11 Salvia divinorum (S. divinorum) is a species of sage belonging to the mint family. Some street names for S. divinorum include: Sally D, Lady Sally, Maria pastora, ska Maria pastora, ska pastora, diviner's sage, magic mint, puff, incense special, and salvia. Canadians are cautioned against the use of products containing S. divinorum and/or salvinorin A because these products are known to cause hallucinations and little is known about the long-term effects of these substances on the brain and body.
Health Canada May/13 has been made aware of three products ("Rochefort", "Rush" and "Amsterdam Special"), commonly known as "poppers", labelled to contain alkyl nitrites . These products, labelled as leather cleaners and/or liquid incense, are known to be used by consumers to get "high" and may pose serious risks to health if they are inhaled or swallowed.
Health Canada Jun/13 Eight products labelled as leather cleaners or liquid incense contain, or allege to contain, alkyl nitrites were being sold by Saints N Sinners Ltd, 1715 Centre Street N.W., Calgary, Alberta. These products, commonly known as "poppers" are used by consumers to get "high" and may pose serious risks to health if they are inhaled or swallowed
Health Canada Dec/14 is following up with Rapha Biotech Inc. Rapha Diet (630 mg, 270 Capsules) -- undeclared ingredients: amphetamine, methamphetamine.
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Organ Transplant Facts:

Canada: There were 2,083 solid organ transplants in Canada, as compared with 2,188 in 2007, according to Canadian Organ Replacement Register statistics (http://cihi.ca /cihiweb/dispPage.jsp?cw_page=AR3230_E&cw_topic=3230). The total number of organ donors also decreased, to 1038 from 1046 in 2007.
Roughly 4380 Canadians were on waiting lists for transplants as of Dec. 31, 2008. — Sabrina Doyle, Ottawa, Ont. http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=media_20091222_e

Organ Donor Activity in Canada, 1999 to 2008 http://secure.cihi.ca/cihiweb/products/CORR_AiB_EN_20091222_rev20100106.pdf

During the past decade, the number of organ donors in Canada increased from 812 to 1,038 per year; living donors accounted for 69% of this increase. While there were increases in organ donation during the past decade, the demand for organs also grew. For example, in the case of kidneys, the incidence rate of end-stage renal disease increased from 149 to 168 per million population. The availability of donated organs in Canada rose by more than one-quarter (28%) over the past decade, but this increase is not keeping pace with demand. More than 1,000 Canadians donated organs in 2008, up from 812 in 1999, according to a new study released today by the Canadian Institute for Health Information (CIHI). With an increase in the number of Canadians with organ failure, combined with medical advancements that are keeping these patients alive longer, the results show an increase in the demand for organs. Last year, about 215 Canadians died while waiting for an organ transplant. A national paired exchange program has been launched for donor and recipient pairs who do not match as an initiatives to maximize the number of live-donor organs available at http://www.ccdt.ca/english/ldpe/index.htm called the Living Donor Paired Exchange Registry (LDPE).

According to the Canadian Organ Replacement Registry's 2008 annual report, there were an estimated 33,832 people with end-stage renal disease in Canada at the end of 2006, an increase of 69.7% since 1997. Of these, 20,465 were on dialysis and 13,367 were living with a functioning kidney transplant.

US Dept of Health and Human Services: Organ Procurement and Transplantation Network (OPTN) Data reports: http://optn.transplant.hrsa.gov/latestData/viewDataReports.asp

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